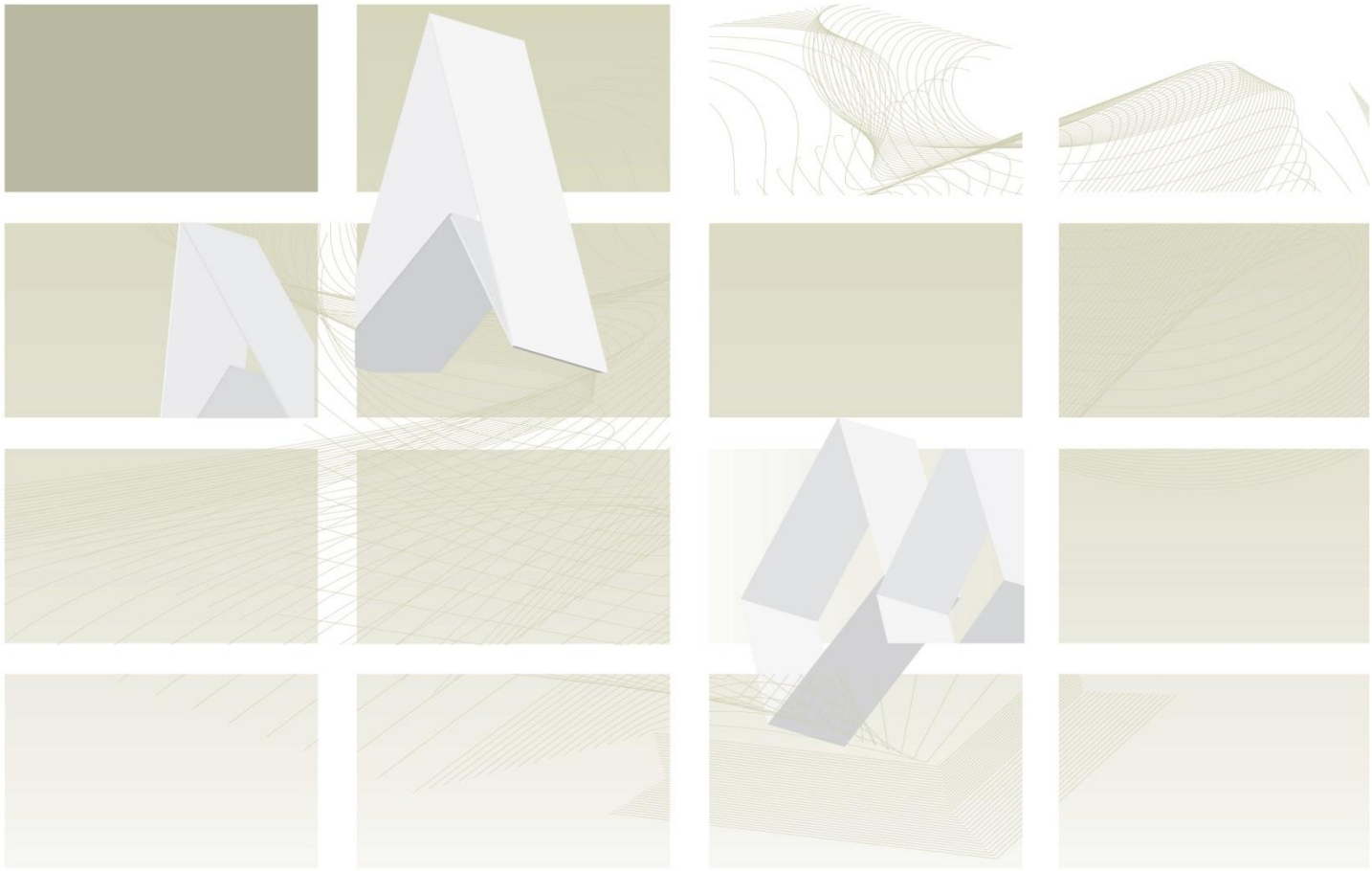
Public Health England

NHS

UK Standards for Microbiology Investigations

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

V 53 Screening and monitoring for hepatitis E infection



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"NICE has renewed accreditation of the process used by **Public Health England (PHE)** to produce **UK Standards for Microbiology Investigations**. The renewed accreditation is valid until **30 June 2021** and applies to guidance produced using the processes described in **UK standards for microbiology investigations (UKSMIs) Development process, S9365', 2016**. The original accreditation term began in **July 2011.**"

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

First consultation: 20/08/2015 – 17/09/2015

Version of document consulted on: V 53dn+

Proposal for changes

Comment number	1		
Date received	20/08/2015	**Laboratory/Professional body**	Royal Cornwall Hospital
Section	Scope PAGE 8		
Comment			
The draft guidance suggests that an ALT value of 100 IU/ml be used to determine whether HEV serology is worth doing in the investigation of possible hepatitis but does not cite any supporting evidence. In our experience the peak ALT has to be much higher than this. A study of performed in our centre suggests that a peak value of 300 IU/ml is more appropriate. This study will shortly be submitted for publication.			
Evidence			
See answer to section 5.			
Financial barriers			
Cost would increase significantly if ALT>100 cut off was adopted.			
Health benefits			
HEV disease is underdiagnosed in UK and has significant consequences especially in those with pre-existing liver disease and immunocompromised. Antiviral treatment and immune modification can reduce some of these (eg chronic hepatitis E leading to serious liver disease) in the latter group. Guidance which increases appropriate testing for HEV infection will both provide a better understanding of locally acquired disease and better treatment of patients at risk of serious infection.			
Recommended action	**NONE** It was felt by the group that if a cut off of ALT >300 was used a significant number of cases would be missed. A cut off of ALT >100 is supported by Harvala et al (J Clin Virol. 2014 Mar;59(3):184-7).		

Comment number	2		
Date received	20/08/2015	**Laboratory/Professional body**	PHE Public Health Laboratory
Section	Algorithms and Footnotes (see below)		
Comment			
a. Immunocompetent: HEV NAAT Not reactive Report. HEV RNA not detected. No evidence of recent infection. The problem with this comment is that it fits with cases			

of low IgM reactivity / IgM not reactive but in cases where both the IgG & IgM were reactive (and you have already reported it as consistent with recent infection), the HEV RNA can be negative if the patient did not present quickly enough, ie viraemia disappears once you have an immune response. b. Immunocompetent: Under HEV NAAT reactive report, why is there a b footnote asking for a repeat sample in 7 -10 days? c. Immunocompromised: general comment. Referral labs and local clinics do not specify if the patient is immunocompromised and according to the algorithm all immunocompromised patients need a HEV NAAT. d. Immunocompromised: HEV RNA NAAT not reactive report: However HIV infection cannot be excluded - this is not helpful at all since by far the majority of pts would have neg HEV serology, neg NAAT and yet the lab will not be able to tell them whether HEV has been excluded. Surely if you have no antibodies and negative HEV NAAT you should state the person doesn't have HEV? Also in cases where you have both HEV IgG and IgM without HEV RNA it could indicate a recent infection which the person cleared. e. Immunocompromised: HEV RNA NAAT reactive report: Should you not ask for a repeat sample (? Time period) to see if HEV viraemia has cleared? f. Footnotes b: What are appropriate symptoms and LFT pattern? Should it also not read: 'send a second sample within 7-10 days if HEV hepatitis is still suspected'? Is there adequate evidence, as with HIV, that the HEV serology will evolve sufficiently in 7 days to make a positive diagnosis of acute HEV? How do you interpret repeat serology in terms of the algorithm and what should the appropriate comments be? g. General comment: HEV IgG and IgM should be tested for concurrently.	
Financial barriers	
No.	
Recommended action	a. **ACCEPT** Algorithm updated. Text replaced with ‘compatible with recent acute HEV infection’. b. **ACCEPT** Footnote ‘b’ not appropriate. Text removed. c. **NONE** The requirement for patient information and the necessity of knowing a patient’s immune status when undertaking this particular test should be highlighted in the laboratory user manual. d. **ACCEPT** Algorithm updated. Text replaced with ‘no evidence of HEV infection’. e. **ACCEPT** Algorithm updated. HEV to be monitored for 3 months. f. **ACCEPT**

	The document has been amended. g. **ACCEPT** Algorithm updated.

Comment number	3		
Date received	26/08/2015	**Laboratory/Professional body**	Nottingham University Hospitals
Section	Testing Immunocompetent		
Comment			
Despite HEV IgM and IgG positive, if NAAT negative, wouldn't report it as 'no evidence of HEV' as viraemia doesn't last as long as the IgM.			
Financial barriers			
The sheer number of 'acute hepatitis' screens and the finances to fund including HEV into the routine screening of all of those samples.			
Health benefits			
Certainly a lot of benefit, considering HEV at the moment is currently underdiagnosed. Covering all possibilities is going to be tricky. Especially if at the same time need to be cost-effective.			
Recommended action	**ACCEPT** Algorithm updated. Text replaced with 'compatible with recent acute HEV infection'.		

Comment number	4		
Date received	03/09/2015	**Laboratory/Professional body**	Nottingham
Section	Scope, HEV in immunocompromised		
Comment			
a. Page 8 2/3rds down - you refer to a patent - I think you mean patient. b. HEV infection in the immunocompromised page 12. Not sure I understand the logic of beginning with IgG and IgM testing when surely the primary diagnostic test is HEV RNA? You acknowledge as much in footnote f, so why not start with RNA testing? c. I am intrigued to know how we are supposed to converse with our clinical colleagues in the circumstance where HEV RNA is not detected, and yet we are supposed to issue a report saying HEV infection cannot be excluded. So the clinician rings me up and asks how can we exclude HEV infection? To which I reply .....? If the definition of HEV infection in an immunocompromised host is dependent upon demonstration of HEV RNA, and HEV RNA is not present, then why can we not exclude HEV			

infection? Why is this different in an immunocompromised host as compared to an immunocompetent one, where we are encouraged to issue a report HEV RNA not detected. No evidence of recent infection in this circumstance, even when IgM and IgG positive!?	
Recommended action	a. **ACCEPT** Text updated. b. **ACCEPT** Algorithm updated. c. **ACCEPT** Algorithm updated. Text replaced with 'no evidence of HEV infection'.

Comment number	5		
Date received	03/09/2015	**Laboratory/Professional body**	Luton & Dunstable University hospital
Section	Page 12		
Comment			
The algorithm states that even when IgG and IgM and viral PCR is NOT detected Hep E cannot be excluded. How would one go about excluding Hep E infection in this instance?			
Recommended action	**ACCEPT** Algorithm updated. Text replaced with 'no evidence of HEV infection'.		

Comment number	6		
Date received	04/09/2015	**Laboratory/Professional body**	Dundee
Section	Various (see below)		
Comment			
a. Criteria for defining an acute HEV infection in a patent with acute hepatitis. 'The presence of HEV RNA (with or without detectable HEV antibodies), or both anti-HEV IgG and IgM antibody.' This seems to contradict the first algorithm which has IgG and IgM reactive but PCR neg samples being reported as 'HEV RNA not detected. No evidence of recent infection.' Even though at the IgM and IgG pos stage they are reported as 'Consistent with recent HEV infection.' HEV RNA to follow. b. I note also that we are notifying at the IgM and IgG pos stage (footnote d) and not waiting for the RNA result.			

c. If we are saying in the immunocompromised that RNA neg does not exclude infection, why are we saying different in the immunocompetent who will typically have lower viral loads? I think we need to clear up these discrepancies. d. Footnote c is out of sequence on the diagrams. e. Borne is miss-spelled in reference 4.	
Financial barriers	
We currently do this testing via a ref lab and unless they suddenly start charging, no. Can't afford to bring in house.	
Health benefits	
No.	
Recommended action	a. **ACCEPT** Algorithm updated to reflect the definition of acute. b. **ACCEPT** This has been moved to the report stage following RNA testing. c. **ACCEPT** Algorithm updated. Text replaced with 'no evidence of HEV infection'. d. **ACCEPT** Algorithm updated. e. **ACCEPT** Text updated.

Comment number	7		
Date received	11/09/2015	**Laboratory/Professional body**	British HIV Association (BHIVA)
Section			
Comment			
Thank you for the opportunity to comment on the PHE guidance on 'Screening for Hepatitis E Infection'. HEV is an under-recognised cause of both acute hepatitis and also of chronic liver disease in immune-compromised individuals, including people living with HIV; this guideline highlights the importance of considering HEV early and provides clear, easy to follow algorithms for testing. a. We strongly support the recommendation to test HEV RNA, regardless of serology, in immunocompromised (including HIV). Although a definition of chronic HEV is included there is a lack of advice about when to consider chronic HEV. b. HEV is also an under-recognised cause of neurological presentations including brachial neuritis and peripheral neuropathy so it may be worth adding a sentence to			

this effect it would be helpful so have a short summary box of 'When to test for HEV' eg. As part of the 1st line investigation of acute hepatitis; as part of the 2nd line investigation of unexplained chronic hepatitis, particularly in immunocompromised individuals; in individuals with acute neurological presentations consistent with HEV. c. Clearly, as an SMI, the guidelines focus on the microbiological aspects of HEV but we would suggest that when finalised the guideline is promoted through the appropriate clinical speciality organisations (including infectious disease, HIV, immunology, acute medicine, hepatology and any speciality utilising immunosuppressive therapies) in order to improve awareness.	
Recommended action	a. **ACCEPT** The document has been amended. b. **ACCEPT** Text regarding neurological presentations added to the introduction and referenced. c. **ACCEPT** Specialist organisations will be alerted once the document is issued.

Comment number	8		
Date received	17/09/2015	**Laboratory/Professional body**	Portsmouth Hospitals NHS Trust
Section	Various (see below)		
Comment			
a. **Guidance:** Within the scope of document there is a suggestion to use of ALT for limiting number of patients for testing, the example given suggests a level of ALT >100 IU/mL **Comments:** Agree that using ALT is a reasonable method for limiting number of samples screened. The level of ALT suggested indicating testing is lower than expected. Is there any data to support this? Data from a local PHT audit from January 2013 – December 2014 (24 months) summarised below. <u>Local testing at PHT</u> Between January 2013 and – December 2014 there were requests for HEV testing on 339 patients. Clinical requests for HEV and acute hepatitis are evaluated by the microbiology team to determine if HEV testing indicated. HEV testing was considered indicated if patients had a recent ALT >300 (immunocompetent patients), abnormal LFTs (immunocompromised patient including those with alcoholic liver disease) with no other identified cause and symptoms consistent with HEV infection. Using these testing strategies 279 patients were tested for HEV (80% of requests). Of the 279 patients tested 21 (7.5%) had evidence of acute HEV infection (HEV IgM and IgG positive or HEV PCR positive). The demographic of the patients with evidence of acute HEV infection:			

Mean age 63.71 (range 38 to 86)

Male : female ratio = 3.2 : 1

In the immunocompetent patients with evidence of acute HEV infection (n=15) the peak in ALT occurred on average 2.4 days before testing (Range of 9 days before - 2 days after). The average peak in ALT observed was 1737, with the lowest peak observed being 437 and the highest peak observed 5090. Supporting the currently used cut off for tested of ALT>300.

In immunocompromised patients with evidence of recent/active HEV infection (n=6) an ALT response was also observed. The average peak in ALT observed was 1379, with the lowest peak being 117 and the highest being 2732. The timing of the peak in immunocompromised patients is more complex, due to host factors and chronic/prolonged HEV infections. However all positives had raised ALT (>97) on day of testing.

PHT Suggests: based on the data above suggest using a cut off of ALT >300 to target appropriate HEV testing in immunocompetent patients. In an immunocompromised patient any unexplained abnormal ALT should warrant HEV PCR +/- HEV serology to exclude HEV infection.

b. **Guidance:** Within the scope of the document there is a paragraph that highlights the difference in severity of infection based on genotype during infection and suggests testing to determine genotype to identify patients at risk of severe infection.

   Comments: Does genotyping change patient management? Would pregnant women with G1 be managed differently to those with G2 /G3? E.g. increased benefit of antivirals (e.g. Ribavirin) vs the risk of treating in G1 infections compared to other genotypes? What is the current turnaround time of genotyping? Can it be performed rapidly enough to impact upon clinical management?

   PHT suggests: Clarify the purpose, turnaround time and impact of genotyping in context to support suggestion.

c. **Guidance:** In the laboratory diagnosis section there is mention of commercial systems for solid phase IgM and IgG being based on antigens from HEV G1 and G2.

   Comments: Is this solely to raise awareness for limitations of available assays or is PHE suggesting a particular assay type covering G3 should be used in local laboratories? As numbers of samples being tested increase laboratories will look to bring this test in house.

   PHT suggests: Clarify if there are requirements for local assays being introduced including coverage of genotypes and sensitivity / specificity.

d. **Guidance:** The point is raised in the laboratory diagnosis section that the detection of HEV IgM alone is not diagnostic of HEV infection and that HEV IgM AND IgG, IgG seroconverson or HEV PCR positive is required to confirm an acute diagnosis.

   Comments: The causes of stand-alone IgM positive results are well established to be either recent/active infection or non-specific cross reaction in an assay.
   If the clinical picture is unclear then there is a role for confirmation of the IgM results by further serology or PCR.

   However if the result match the clinical picture, and other causes of symptoms have been excluded it is difficult to see the added benefit to the patient of further sample testing (IgG and PCR) or repeating patients serology for rising titres/seroconversion. Performing additional testing on all IgM positive patients will incur an increased

laboratory cost at no clear benefit to the patient.

In the PHE document UK standards for Microbiological investigations: investigation of hepatitis the criteria for diagnosis of hepatitis A states “Diagnosis of acute infection requires demonstration of anti-HAV IgM antibodies or seroconversion”. Given the similarity between these two viruses why are the criteria for defining acute hepatitis E “the presence of HEV RNA or both anti-HEV IgG and IgM antibodies”?

Guidance on up to date for HEV detection states “The diagnosis of hepatitis E virus (HEV) is based upon the detection HEV in serum or stool by polymerase chain reaction (PCR) or by the detection of IgM antibodies to HEV” based on the following paper “Simultaneous detection of immunoglobulin A (IgA) and IgM antibodies against hepatitis E virus (HEV) Is highly specific for diagnosis of acute HEV infection.” Takahashi M, Kusakai S, Mizuo H, Suzuki K, Fujimura K, Masuko K, Sugai Y, Aikawa T, Nishizawa T, Okamoto H SO J Clin Microbiol. 2005;43(1):49

PHT suggests: Reconsider testing strategies including definitions of a positive case compared to current HAV guidance and papers or provide evidence for the strategies stated in the guidance.

e. **Guidance:** Within the HEV infection in the immunocompetent protocol there are several comments on interpretation and further testing strategies.

Comment: As per points above on testing strategies reconsider algorithm and comments.

PHT Suggests: IgM positive, IgG negative comment “serology consistent with recent HEV infection; however isolated IgM result may be a non-specific cross reaction in assay. Consider sending a repeat sample in 7-10 days to clarify”
The comments regarding HEV RNA state “evidence of recent infection” should this be “active” rather than “recent”.

f. **Guidance**: The HEV infection in the immunocompromised protocol

Comments: The need for antibodies AND PCR is clearer in this group given that antibody testing can be unreliable in immunocompromised patient.
The RNA not detected comments could be clarified e.g. “no evidence of active infection” instead of “HEV RNA not detected, however HEV infection cannot be excluded”. Is the HEV infection cannot be excluded in reference to intermittent absence of viraemia? Is this comment valid in all sets of serology results?
The RNA detected comment. Should this mention the possibility of chronic infection in immunosuppressed patients? Would a comment about monitoring for clearance of RNA in 3 months be sensible in this patient group?

PHT Suggests: consider changes to protocol as discussed in comment section

g. **Guidance:** Molecular characterisation is suggested on all PCR positives

Comments: Is molecular characterisation for clinical or epidemiological purposes? If this is epidemiological will the cost of transport and testing be covered by PHE? If this is clinical what is the impact on patient management of knowing the genotype?

PHT suggests: Clarify purpose, impact and benefit of molecular characterisation and who will incur the costs of testing.

Recommended action	a. **NONE** It was felt by the group that if a cut off of ALT >300 was used a significant number of cases would be missed. A cut

	off of ALT >100 is supported by Harvala et al (J Clin Virol. 2014 Mar;59(3):184-7). b. **ACCEPT** Document amended. c. **NONE** Solid phase IgM and IgG no longer mentioned in the text. d. **ACCEPT** This has been amended in the document. e. **ACCEPT** The algorithm and report text has been amended. It is now stated that IgM reactivity alone is not diagnostic of recent HEV infection and RNA testing must be undertaken. A footnote has been added to request a repeat sample. Where RNA is detected the report comment has been amended to 'compatible with early acute HEV infection'. f. **ACCEPT** The algorithm and report comments have been updated. Serology and PCR testing is recommended concurrently. Where IgM negative, IgG positive and RNA is not detected the report has been amended to 'no evidence of active HEV infection. Where IgG and IgM are both negative and RNA is not detected the report has been amended to 'no evidence of HEV infection'. A section on monitoring following RNA detection (for up to three months) has been added to the algorithm. g. **NONE** This recommendation was removed during the re-write of the document.

Comment number	9		
Date received	17/09/2015	**Laboratory/Professional body**	Public Health Wales
Section	Flow chart. Page 11 and 12		
Comment			
a. Page 11: Your Interim Report when IgM reactive/IgG reactive stating 'Consistent with recent HEV infection. HEV RNA to follow'. You then report the further not detected RNA result as 'HEV RNA not detected. No evidence of recent infection'. These results are in opposition. How long does the RNA last for in relation to the IgM? A further explanation on the RNA result is required. b. Page 11: Your Interim Report when the IgM is reactive but the IgG is not reactive states 'Consistent with relatively recent infection or false negative result' should you put acute (in view of the negative IgG), and also consider the possibility of a false			

positive IgM? Why are you suggesting to notify at this stage? c. Work flow page 12: Report comment on negative HEV NAAT. You state that HEV infection cannot be excluded- may be more useful to have a comment regarding clearance in stool in immunocompromised individuals (if previously found to be RNA detected) as an explanation for this comment.	
Financial barriers	
No.	
Health benefits	
No.	
Recommended action	a. **ACCEPT** The algorithm had been updated to address this. Where IgG and IgM are reactive, the report is 'compatible with acute HEV infection', When tested, and HEV RNA is not detected, the comment has been amended to 'compatible with recent acute HEV infection'. Further clarification will be sought regarding the length of time that RNA is detectable in relation to IgM. b. **ACCEPT** Algorithm updated. This point of the algorithm now states that IgM reactivity alone is not diagnostic of recent HEV infection. RNA testing must be carried out. A footnote has been added to the algorithm to request a second sample investigate the possibility of an initial IgM false positive. c. **ACCEPT** The algorithm has been updated and the report comments (for when RNA is not detected) have been amended. A section has also been added to the algorithm which refers to monitoring RNA levels for up to three months following a positive RNA result.

Comment number	10		
Date received	17/09/2015	**Laboratory/Professional body**	PHE Colindale
Section	Testing in the immunocompetent and immunocompromised		
Comment			
In the immunocompetent figure IgG and IgM testing should be carried out at the same time.			
Financial barriers			
N/A			

Health benefits	
N/A	
Recommended action	**ACCEPT** The algorithm has been updated.

Targeted questions:

Does your laboratory currently include hepatitis E as part of an initial hepatitis screen? Please comment.		
Date received	**Laboratory/Professional body**	**Comment**
20/08/2015	Royal Cornwall Hospital	Yes. We screen with a rapid HEV IgM test and refer reactive samples for HEV IgG/M confirmation.
20/08/2015	PHE Public Health Laboratory	No, only if asked for. Reason not: hospitals do not want to pay for it.
26/08/2015	Nottingham University Hospitals	No.
31/08/2015	Manchester Royal Infirmary/Manchester PHL	Yes.
03/09/2015	Nottingham	For patients with an ALT > 100 IU/ml.
03/09/2015	Luton & Dunstable University hospital	Yes.
04/09/2015	Dundee	We do include it but we get the test done at another lab.

Do you currently test for IgG and IgM concurrently in immunocompetent patients?		
Date received	**Laboratory/Professional body**	**Comment**
20/08/2015	Royal Cornwall Hospital	Yes. We perform rapid IgM on-site and refer all samples for PCR.
20/08/2015	PHE Public Health Laboratory	Yes.
26/08/2015	Nottingham University	Yes.

	Hospitals	
31/08/2015	Manchester Royal Infirmary/Manchester PHL	IgM only.
03/09/2015	Nottingham	We currently send samples to Colindale, so presumably samples are tested according to Colindale's algorithm. We have been intending to bring this in-house for some time.
03/09/2015	Luton & Dunstable University hospital	No but will commence shortly.
04/09/2015	Dundee	We get these tests done but also ask for PCR.

What do you think are the advantages/disadvantages of testing for IgG and IgM concurrently in immunocompetent patients?		
Date received	**Laboratory/Professional body**	**Comment**
20/08/2015	Royal Cornwall Hospital	Not sure what is to be gained if all these patients are tested by PCR anyway.
20/08/2015	PHE Public Health Laboratory	Saves time, helps to interpret IgM, if you use a EIA with not that high IgM sensitivity then sometimes you can have a very high IgG with a false neg. IgM.
26/08/2015	Nottingham University Hospitals	Advantages, IgM can be false positive, if IgG negative prompts NAAT testing. Disadvantages: If IgM negative don't need to do the IgG as may not be clinically relevant to know that this is indeed past HEV.
31/08/2015	Manchester Royal Infirmary/PHL	No real drawbacks if assessing early infection rather than immunity in UK patients likely to be infected with G3, but may miss reinfections in other groups.
03/09/2015	Nottingham	Disadvantage - cost. Screen first for IgM.
04/09/2015	Dundee	We get the antibody result earlier. We may get occasional false positives on the IgM.
17/09/2015	PHE Colindale	Testing concurrently is essential, diagnosis cannot be made on the bases of a single antibody test.

Do you think that it would be useful to include information regarding the scenarios where IgM is negative in immunocompetent patients, but IgG may be positive?		
Date received	**Laboratory/Professional body**	**Comment**
20/08/2015	Royal Cornwall Hospital	Not sure what is to be gained if all these patients are tested by PCR anyway.
20/08/2015	PHE Public Health Laboratory	Yes.
26/08/2015	Nottingham University Hospitals	Yes.
31/08/2015	Manchester Royal Infirmary/ PHL	Yes.
03/09/2015	Nottingham	Yes - was wondering why you would need an IgG if IgM negative in an immunocompetent patient.
04/09/2015	Dundee	Footnote is fine.
17/09/2015	PHE Colindale	Yes, my understanding is that Richard Tedder has drafted a new testing algorithm to replace the current draft.

Do you use faecal antigen tests in immunocompromised patients? Please comment.		
Date received	**Laboratory/Professional body**	**Comment**
20/08/2015	Royal Cornwall Hospital	No.
20/08/2015	PHE Public Health Laboratory	No.
26/08/2015	Nottingham University Hospitals	No, just HEV RNA in stool samples.
31/08/2015	Manchester Royal Infirmary/Manchester PHL	No - would rely on PCR on blood.
03/09/2015	Nottingham	No.
03/09/2015	Luton & Dunstable	No.

	University hospital	
04/09/2015	Dundee	No.

Second consultation: 02/02/2018 – 16/02/2018

Version of document consulted on: V 53dzw+

Proposal for changes

Comment number	1		
Date received	02/02/2018	**Laboratory/Professional body**	Public Health England
Section	Page 14		
Comment			
The draft SMI is well-written and clear. I don't think that an HEV IgM reactive, HEV IgG reactive result should be interpreted as serological evidence of recent HEV infection without qualification if HEV RNA testing has not been done or is negative. This is because the specificity of IgM testing is low, even in IgG positive samples. I would prefer something like; "Consistent with recent HEV infection, although a non-specific IgM result is also possible." It may be relevant to refer to separate guidance from NHSBT on HEV screening of donors.			
Evidence			
We have observed several HEV IgG and HEV IgM positive samples where results of other IgM/PCR tests indicate an alternative diagnosis, e.g. Hepatitis A, EBV.			
Financial barriers			
Not completed.			
Health benefits			
Not completed.			
Recommended action	**ACCEPT** Document updated and a reference to SABTO added.		

Comment number	2		
Date received	05/02/2018	**Laboratory/Professional body**	Laboratory
Section	Report comment		
Comment			

In immunocompetent individual, SMI V53 considers HEV IgG as an important marker for confirming acute HEV infection. This should only be in the context of compatible symptoms and other causes of hepatitis has been excluded. HEV RNA, though has its limitation, should be advocated as the confirmatory test, as a positive HEV RNA result not only confirm the diagnosis, but also inform management. In the flow chart, the HEV IgG arm almost invariably lead to HEV RNA testing, so in itself is an unnecessary step.
Evidence
We have seen many patients with borderline deranged LFT who has a low level reactive HEV IgM and reactive HEV IgG labelled as acute HEV infection. Since non-specific IgM reaction is common and patients could have past exposure to HEV (particularly those from abroad). It is not reliable to diagnose acute HEV based on a combination of positive HEV IgG and IgM result. The level of positivity, the clinical context, exclusion of other causes need to be taken into account.
Financial barriers
None.
Health benefits
None.

Recommended action	**ACCEPT** The foot notes have been amended to take account of this point.

Comment number	3		
Date received	08/02/2018	**Laboratory/Professional body**	Professional body
Section	Page 9 Laboratory diagnosis		

Comment
Suggest Acute viral screen should also include serology for CMV & EBV infection.
Evidence
Clinical experience.
Financial barriers
No.
Health benefits
No.

Recommended action	**ACCEPT** The UK SMI has been updated.

Comment number	4		
Date received	08/02/2018	**Laboratory/Professional body**	North Cumbria University Hospitals
Section	Report comments		
Comment			
Interpretative table uses different words to describe similar results - it is not obvious why this occurs and is potentially confusing. Example: IgM reactive, IgG not reactive, RNA detected = *Diagnostic* of acute HEV infection IgM reactive, IgG reactive, RNA detected = *Compatible with* current acute HEV infection If this is the suggested wording then it deserves some explanation why one result is diagnostic of HEV infection and the other is merely compatible with it.			
Evidence			
N/A			
Financial barriers			
None.			
Health benefits			
Not completed.			
Recommended action	**ACCEPT** The document has been amended.		

Comment number	5		
Date received	09/02/2018	**Laboratory/Professional body**	NHS Lothian
Section	Immunocompetent algorithm		
Comment			
a. The algorithm is very good. Just has IgG in 2 places. I can see why as some people will have more ready access to IgG and would do at the same time as sending away for PCR. Perhaps there can be a pointer that don't need to do IgG twice once before PCR and once when PCR is neg. Can you have box on the algorithm to make that clear. b. Can put a note about testing of organ donors by PCR –somewhere.			
Evidence			
No real evidence - just don't think you need to do IgG twice.			
Financial barriers			
None.			

Health benefits	
None.	
Recommended action	a. **NONE** The working group feel that the algorithm is clear. b. **ACCEPT** A reference to SABTO will be added.

Comment number	6		
Date received	12/02/2018	**Laboratory/Professional body**	North Bristol NHS Trust
Section	All		
Comment			
Overall very good, and much needed. Reference base helpful. Comments have been tracked onto a word version sent separately. The main points are: interpretative comments in table do not match those in the algorithm; rationale is needed around urgent genotyping in pregnancy associated infections.			
Evidence			
Professional opinion.			
Financial barriers			
Consider impact of mandating quantitative NAAT for screening n immunocompromised.			
Health benefits			
It should improve the diagnosis and management of HEV, notably in the immunocompromised.			
Recommended action	**ACCEPT** The main points have been accepted. For reasons of openness and transparency comments need to be on the standard form as opposed to track changes.		

Comment number	7		
Date received	15/02/2018	**Laboratory/Professional body**	Professional body
Section			
Comment			
The British Infection Association supports these guidelines. One typo was spotted- page 10 after reference 18 there are 2 full stops rather than 1.			

Evidence	
Not completed.	
Financial barriers	
Not completed.	
Health benefits	
Benefits are likely in improved recognition and uptake of testing.	
Recommended action	**ACCEPT** The document has been updated.

Comment number	8		
Date received	15/02/2018	**Laboratory/Professional body**	Public Health England
Section	Page numbers outlined in comment box below		
Comment			
a. Hepatitis E – ensure use lower case ‘h’ throughout b. Pg.9 first use of ALT – define c. Pg.10 amend double full-stop in first paragraph under ‘HEV infection in immunocompromised’ d. Flow-charts; please ensure consistency, where appropriate, in the ‘Report:…’ boxes e.g. on pg.14 the third box along and the sixth box are both essentially RNA+ but one reads ‘Report: compatible with acute HEV infection’ and the other ‘Report: compatible with early acute HEV infection’ e. Also on pg.20 the heading is ‘Report Comments’ but within the tables the column heading is ‘Interpretative comments’ and these are different from the report comments in the flow chart. Please could there be consistency of wording between and within the tables and flowcharts for clarity?			
Evidence			
Not completed.			
Financial barriers			
No.			
Health benefits			
No.			
Recommended action	a. **ACCEPT** b. **ACCEPT** c. **ACCEPT**		

	d. **ACCEPT** e. **ACCEPT**

Comment number	9		
Date received	16/02/2018	**Laboratory/Professional body**	Public Health England
Section	p14 HEV in the immunocompetent		
Comment			
I don't see the harm of doing HEV IgG at the same time as IgM so I don't understand why the algorithm suggests doing IgM on its own in the first instance. Establishing the IgG status can be useful. If a patient has been unwell for some time and has recovered/presented late/no longer jaundiced etc. Then to find him/her IgG not detected is useful information. In addition, if no other viral hepatitides have been found, one could repeat the HEV serology to look for IgG seroconversion. The finding of an equivocal IgG/IgG close to cut-off could also raise suspicions of HEV as the causative organism. The UK SMI describes the limitations of IgM e.g. short-lived (p10), so to omit IgG seems to be questionable. The text describing HEV infection in the immunocompetent (p9/10) seems incongruous with the algorithm on p14. If the omission of HEV IgG in step 1 of the algorithm is cost-driven, I think this is a false economy.			
Evidence			
Not completed.			
Financial barriers			
Most NHS microbiology labs do not have HEV RNA PCR, so will rely on PHE/NHS virology labs, increasing TAT +/- cost.			
Health benefits			
No.			
Recommended action	**ACCEPT** The algorithm has been amended.		

Comment number	10		
Date received	16/02/2018	**Laboratory/Professional body**	SfAM
Section			
Comment			
Perhaps consider moving the algorithms from the middle of the document to the front or back, so they may be referenced more quickly.			

Evidence	
Not completed.	
Financial barriers	
Not completed.	
Health benefits	
Not completed.	
Recommended action	**NONE** This will be considered when the template styles are reviewed.

Comment number	11		
Date received	16/02/2018	**Laboratory/Professional body**	Laboratory
Section	Pg 9 Laboratory diagnosis		
Comment			
Our local policy is to screen to HEV infection on patients with ALT >300 IU/L.			
Evidence			
Not completed.			
Financial barriers			
Not completed.			
Health benefits			
Not completed.			
Recommended action	**ACCEPT** Amended to eg in the document.		

Comment number	12		
Date received	16/02/2018	**Laboratory/Professional body**	Newcastle upon Tyne Hospitals NHS Foundation Trust
Section	a. Flowchart p14 and footnote a p15 b. Flowchart p16 and footnote 'a' p17		
Comment			
a. Flowchart p14 and footnote a p15 Left-hand and centre boxes. These suggest			

reporting cases positive for HEV IgM and IgG without detectable viral RNA as 'serological evidence of recent HEV infection'. We suggest the comment says 'serology compatible with recent HEV infection'. In practice many of these cases reflect non-specific IgM reactivity. Careful review of the presentation and clinical and the IgM index is required for interpretation. We suggest this is reflected in a footnote. b. Flowchart p16 and footnote 'a' p17 Top box and footnote a suggest that HEV RNA testing for the initial diagnosis of HEV infection in the immunocompromised should be by a quantitative assay. While accepting this is true for the monitoring of treatment in chronic infection, and that many laboratories would therefore chose to use a quantitative assay for all testing, for a diagnostic test a qualitative assay of the required sensitivity should be sufficient. We suggest this is reflected in the footnote.	
Evidence	
Not completed.	
Financial barriers	
Not completed.	
Health benefits	
Not completed.	
Recommended action	a. **ACCEPT** The document has been updated. b. **ACCEPT** The document has been updated.

Respondents indicating they were happy with the contents of the document

Overall number of comments: 1			
Date received	04/09/2015	**Laboratory/Professional body**	Aberdeen Royal Infirmary