UK Health Security Agency

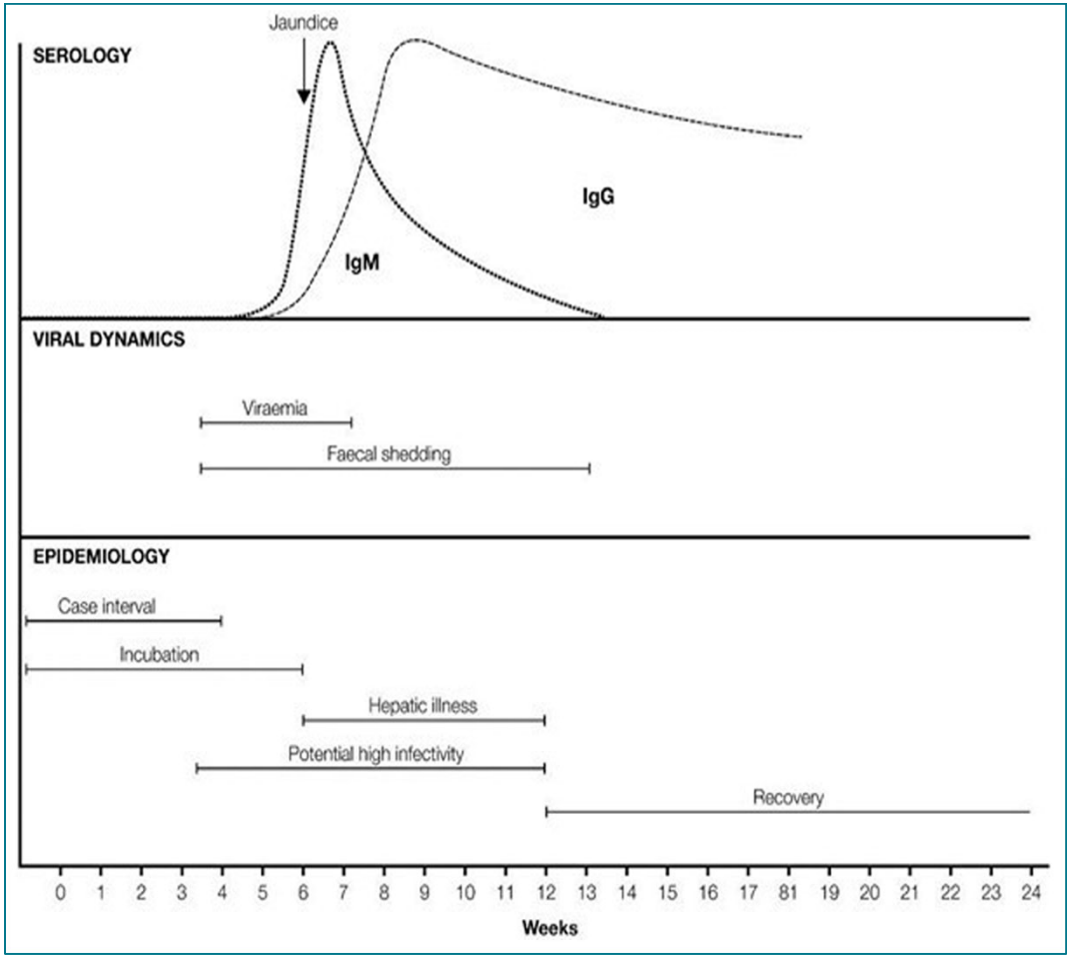
Hepatitis A virus testing and diagnostics: opportunities and challenges

Dr Sema Mandal, Consultant Epidemiologist & Deputy Director
Blood Safety, Hepatitis, STI and HIV Division

Presented on behalf of Dr Siew Lin Ngui & Dr Samreen Ijaz,
Virus Reference Department

Hepatitis A virus (HAV) diagnostic tests

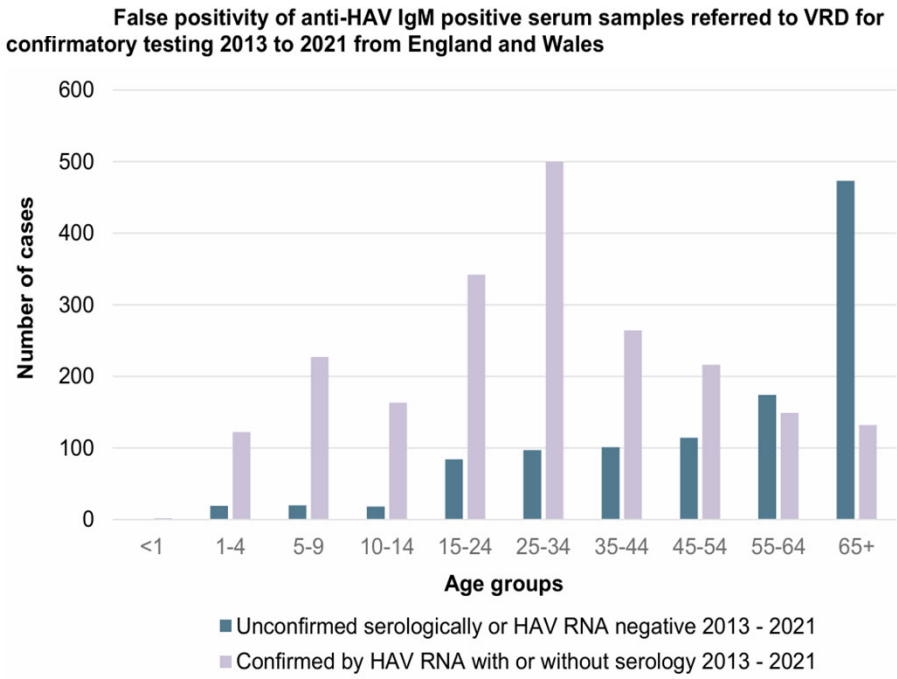
- **Anti-HAV IgM Antibody Test (EIA):** detects active or recent hepatitis A infection.
  - Appears around the onset of symptoms and lasts for several months
  - False positive results are common if weak reactivity
- **Anti-HAV IgG Antibody Test:** detects past infection or immunity from previous vaccination
  - Desirable at same time as IgM as can help interpretation
- **HAV RNA Testing:** confirms active infection
  - Used in complex or uncertain cases (such as pregnancy or atypical presentations)
  - Mostly only available in specialist reference laboratories
- Testing done on commercial platforms at UKHSA



[Hepatitis A infection: prevention and control guidance - GOV.UK]

Challenges with serology: false positive IgM

- Testing of anti-HAV IgG at the same time as IgM is preferred
  - IgM reactivity in the absence of detectable anti-HAV IgG should raise doubts over the specificity of the IgM reactivity.
  - High IgG reactivity together with a moderate level of IgM indicates HAV infection in the recent past rather than current acute infection
  - IgM results may be negative if tested in the early stages of infection (< 5 days from onset of illness) so repeat samples may be needed
- Interpretation of laboratory results requires clinical details e.g. the date of onset of jaundice, other liver function tests, together with information on the age of the patient



Hepatitis A infection: prevention and control guidance - GOV.UK

Hepatitis A in England and role of diagnostics

- HAV is a **notifiable** disease and organism
  - Local serological testing for IgM (+/- IgG) at NHS labs
  - Clinician or lab (via SGSS) must report HAV to the national public health agency
  - Enhanced molecular surveillance: questionnaire and submission of positive samples to national reference laboratory
  - **Lab diagnostics: confirm case via HAV RNA and serology**

- Public health management of cases and close contacts to control spread
  - **Post exposure** vaccination: vaccine (+/- HNIG if fully susceptible and elderly / CLD / immunosuppressed
  - **Lab diagnostics: identify vulnerable close contacts and inform wider control measures**

- UK is a non endemic country for hepatitis A virus (HAV) infection
  - Cases linked to **travel** or imported / contaminated food from endemic countries
  - Recent outbreaks associated with food vehicles and men who have sex with men
  - **Lab diagnostics: molecular typing to detect and characterise transmission events and outbreaks**

- Selective (targeted) immunisation for those at risk e.g. MSM, people travelling to endemic countries
  - No universal childhood vaccination programme
  - **Lab diagnostics: serial serosurveys and monitor impact of vaccination programme**
  - But do not recommend testing pre-exposure vaccination

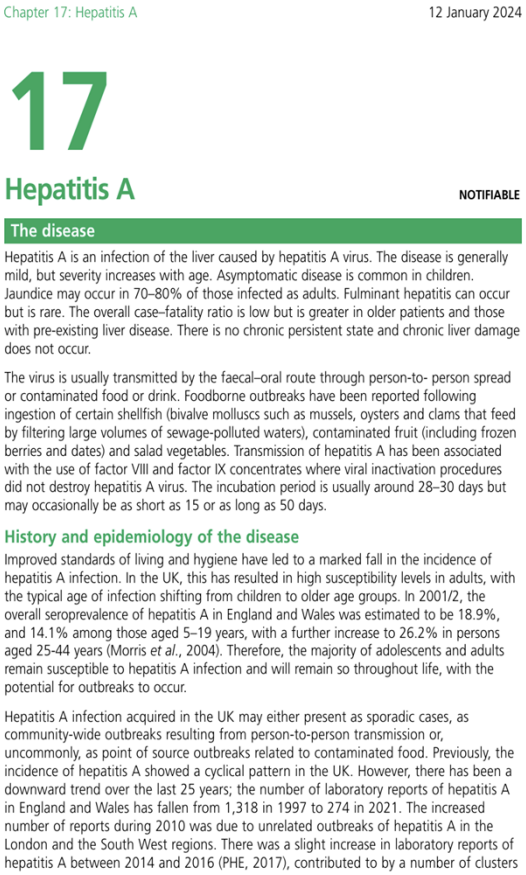
UKHSA Hepatitis A guidance and vaccination resources

UK Health Security Agency

Public health control and management of hepatitis A

2024 updated guidance



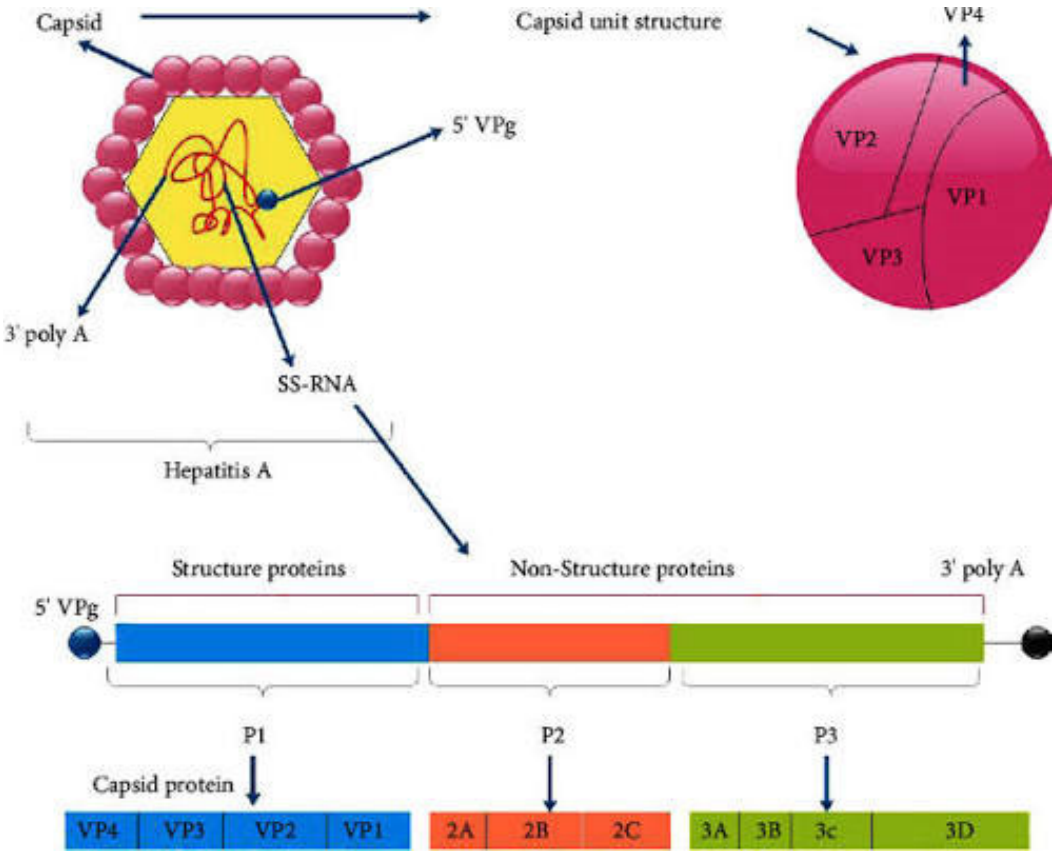


[Hepatitis A infection: prevention and control guidance - GOV.UK]

[Hepatitis A: the green book, chapter 17 - GOV.UK]

HAV PCR for RNA detection, sequencing and phylogenetic analysis

- Molecular typing is a reference laboratory capability
- The genome of HAV consists of a 7500-nucleotide linear, positive-stranded RNA
- Sequencing method based on PCR amplification across the HAV **VP1/2PA region**
- The VP1/2PA junction region encompasses the C-terminus end of the VP1 capsid protein and the N-terminus of the 2A non-structural protein
- The fragment UKHSA sequence is 551 bp
- This region is **highly variable** making it ideal for phylogenetic analysis and cluster identification
- The region sequenced allows for direct comparison across other laboratories making it informative for multi-national cluster/transmission analysis
- There is helpful exchange of information across countries through EpiPulse and HAVNet



Phylogenetics: identification and monitoring of multinational HAV outbreaks amongst MSM

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Rapid communication

Open Acces

Outbreak of hepatitis A associated with men who have sex with men (MSM), England, July 2016 to January 2017

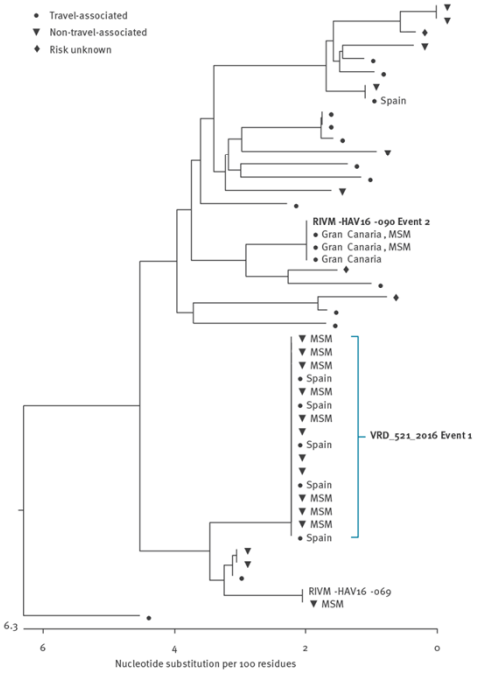
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Kazim Beebeejaun[1], Srilaxmi Degala[2], Koye Balogun[1], Ian Simms[3], Sarah Charlotte Woodhall[3], Ellen Heinsbroek[4], Paul David Crook[4], Ishani Kar-Purkayastha[5], Juli Treacy[5], Kate Wedgwood[6], Kate Jordan[7], Sema Mandal[1], Siew Lin Ngui[8], Michael Edelstein[1]

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Epidemiological update: Hepatitis A outbreak in the EU/EEA mostly affecting men who have sex with men

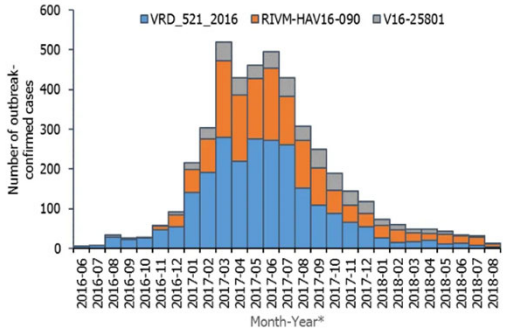
Epidemiological update | Archived

12 September 2018

As of 7 September 2018, the number of outbreak-confirmed cases reported in 22 EU/EEA countries since 1 June 2016 is 4 475.

Since the last epidemiological update on this multi-country hepatitis A outbreak published on 23 March 2018, 19 European Union/European Economic Area (EU/EEA) countries (Austria, Belgium, Croatia, Denmark, Estonia, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Malta, the Netherlands, Portugal, Slovenia, Spain, Sweden and the United Kingdom) have reported 364 new outbreak-confirmed cases. Outbreak-confirmed cases are EU/EEA residents with laboratory-confirmed hepatitis A virus (HAV) genotype IA and a sequence with ≥99.3% homology to one of the three HAV genotype IA outbreak strains (VRD_521_2016; RIVM-HAV16-090; and V16-25801) based on overlapping fragments at the VP1-2a region.

As of 7 September 2018, the number of outbreak-confirmed cases reported in 22 EU/EEA countries since 1 June 2016 is 4 475 (Figure 1). For 4 411 of these cases, information on gender is available, with a male-to-female (M/F) ratio of 6.8. A sharp reduction in the M/F ratio observed after May 2017, when it reached 11.8. The M/F ratio for the cases reported from May to August 2018 was 4.0. No other strains have been reported to be widely circulating among men who have sex with men (MSM) apart from the three outbreak strains and their close variants (Figure 1).



RAPID COMMUNICATION

Ongoing outbreak of hepatitis A associated with sexual transmission among men who have sex with men, Portugal, October 2023 to April 2024

Ebba Rosendal[1,2,*], Sebastian von Schreeb[3,4,5,*], Alexandre Gomes[4], Sara Lino[7], Berta Grau-Pujol[1,4,5], Sara Magalhães[7], Vasco Ricoca Peixoto[4], Carla Roque[3], Joana Moreno[3], Fernando Maltez[7], Fernando Almeida[8], Rita Sá Machado[9], Rui Tato Marinho[10,*], Paula Vasconcelos[4], Rita de Sousa[4,7], João Vieira Martins[1,**]

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Article received on 06 May 2024 / Accepted on 23 May 2024 / Published on 23 May 2024

An outbreak of hepatitis A is ongoing in Portugal, with 71 confirmed cases from 7 October 2023 to 24 April 2024. Most cases are male, aged 18–44 years, with many identifying as men who have sex with men (MSM) and reported as suspected sexual transmission. Phylogenetic analysis identified the subgenotype IA, VRD 521–2016 strain, last observed in an MSM-associated multi-country outbreak in 2016 to 2018. We wish to alert colleagues in other countries to investigate potential similar spread.

Portugal is classified as a very low-endemicity country for hepatitis A [1,2]. Since 2007, 10–82 cases have been reported annually, with the exception of a global multi-country outbreak in 2016 to 2018 that largely affected men who have sex with men (MSM) [3,4]. In early 2024, an increase in hepatitis A cases was detected, and

Outbreak detection and case definition

Through the national surveillance system, an unusually high number of hepatitis A cases was reported with symptom onset in mid-January 2024 (Figure), between five and six cases per week compared with an average of 0.5 cases per week during the previous 4 years. Concurrently, clinical reports and early investigations suggested that many cases were MSM, while also raising concern of sexual transmission. Molecular surveillance identified several cases with the same subgenotype IA HAV strain (VRD 521–2016), indicating a linked outbreak within this community. As the high number of cases persisted in the following week, an alert was issued on the European Centre for Disease Prevention and Control (ECDC) EpiPulse platform on 28 February 2024, followed by a public health warning from the Directorate-General of Health (DGS) on 12

Phylogenetics: identification and monitoring of multinational HAV outbreaks

RAPID COMMUNICATION

Hepatitis A outbreak associated with consumption of dates, England and Wales, January 2021 to April 2021

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Investigators: The investigators are listed at the end of the article

Citation style for this article:
Garcia Vilaplana Tatiana, Leeman David, Balogun Koye, Ngui Siew Lin, Phipps Emily, Khan Wazirzada M, Incident Team, Balasegaram Sooria. Hepatitis A outbreak associated with consumption of dates, England and Wales, January 2021 to April 2021. Euro Surveill. 2021;26(20):pii=2100432. https://doi.org/10.2807/1560-7917.ES.2021.26.20.2100432

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We report a national hepatitis A virus (HAV) outbreak linked to the consumption of Medjool dates. Twenty-nine cases of three genetically related sequences have been identified. Epidemiological investigations identified a suspected product (adjusted odds ratio: 47.36; 95% confidence interval: 1.79–1,256.07; p=0.021). Microbiological testing has confirmed the presence of HAV on dates recovered from two cases and the product has been recalled. Date consumption is currently likely to be increased in connection with Ramadan, with potential ongoing contamination risk.

An outbreak of genetically related hepatitis A virus (HAV) infections among people with no travel history was identified by the Public Health England (PHE) Virus Reference Department (VRD) in conjunction with local teams noting that the cases had eaten dates.

We describe investigations including case characteristics, phylogenetics, analytical studies, and control measures. We aim to flag the possible risk of hepatitis A

suspected or confirmed HAV case in the 60 days before onset. A probable case was a laboratory-confirmed HAV infection, with no or pending sequencing result, and with an epidemiological link to a confirmed HAV case with one of the three clustered sequences.

Outbreak description

Samples from all locally diagnosed HAV infections in England and Wales are routinely sent to the VRD for characterisation. The outbreak cases had HAV from three closely related Middle Eastern genotype IB sequences (≤ 2 bp different in a 505 bp segment) which clustered most closely with those found in travellers returning from Syria and Lebanon (Figure 1). The sequences have been submitted to the European Nucleotide Archive (ENA), accession numbers OD998295–OD998297.

By 18 May, there have been 31 cases (30 confirmed and one probable). Cases had a median age of 60 years (range: 6–93), were predominately white British (21/31) and were geographically dispersed in England and



RAPID RISK ASSESSMENT

Multi-country outbreak of hepatitis A in the EU/EEA

18 June 2025

Summary

Epidemiological situation

Between January and May 2025, Austria, Czechia, Hungary, and Slovakia reported a higher-than-expected number of hepatitis A virus (HAV) subgenotype IB cases. Two clusters involving two closely related HAV subgenotype IB strains were identified from sequence data from four countries (Austria, Germany, Hungary and Slovakia). This rise in HAV infections is primarily affecting adults experiencing homelessness, individuals who use or inject drugs, and those living in poor sanitary conditions. Additionally, cases have been reported among members of the Roma communities in both Czechia and Slovakia.

Risk assessment

People who have not previously been infected by, or vaccinated against hepatitis A are susceptible to HAV infection.

In the **European Union/European Economic Area (EU/EEA) countries currently experiencing outbreaks** (Austria, Czechia, Hungary, and Slovakia), the probability for sustained transmission and circulation of the virus within groups who are more likely to be exposed to HAV (i.e. people experiencing homelessness, people who use or inject drugs, and people living in poor sanitary conditions) is assessed as high. Within these groups, the risk of the disease is assessed as moderate for those below 40 years of age and high for adults 40 years of age or older, as the severity of the disease increases with age. For people with predisposing liver disease or older adults, the risk can be very high. The risk for the broader population in these countries is assessed as low to moderate.

In **non-affected EU/EEA countries**, as there currently are no reports of increases in HAV IB infections, and therefore considering the very low probability of infection, the risk for the broader population is assessed as very low to low. However, it is important to note that the probability of infection is higher among groups more likely to be exposed to HAV, and the impact of disease increases with age and predisposing conditions, thus the overall risk may vary across different population groups.

Recommendations

- Investigate HAV transmission routes in EU/EEA countries currently experiencing outbreaks (to spot possible



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FOODBORNE ILLNESS INVESTIGATIONS

UKHSA probes rise in hepatitis A cases

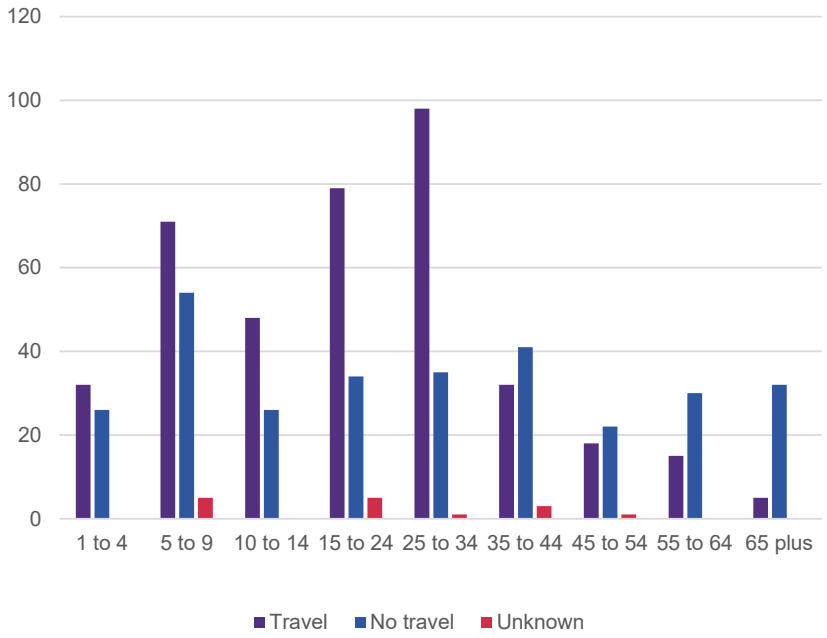
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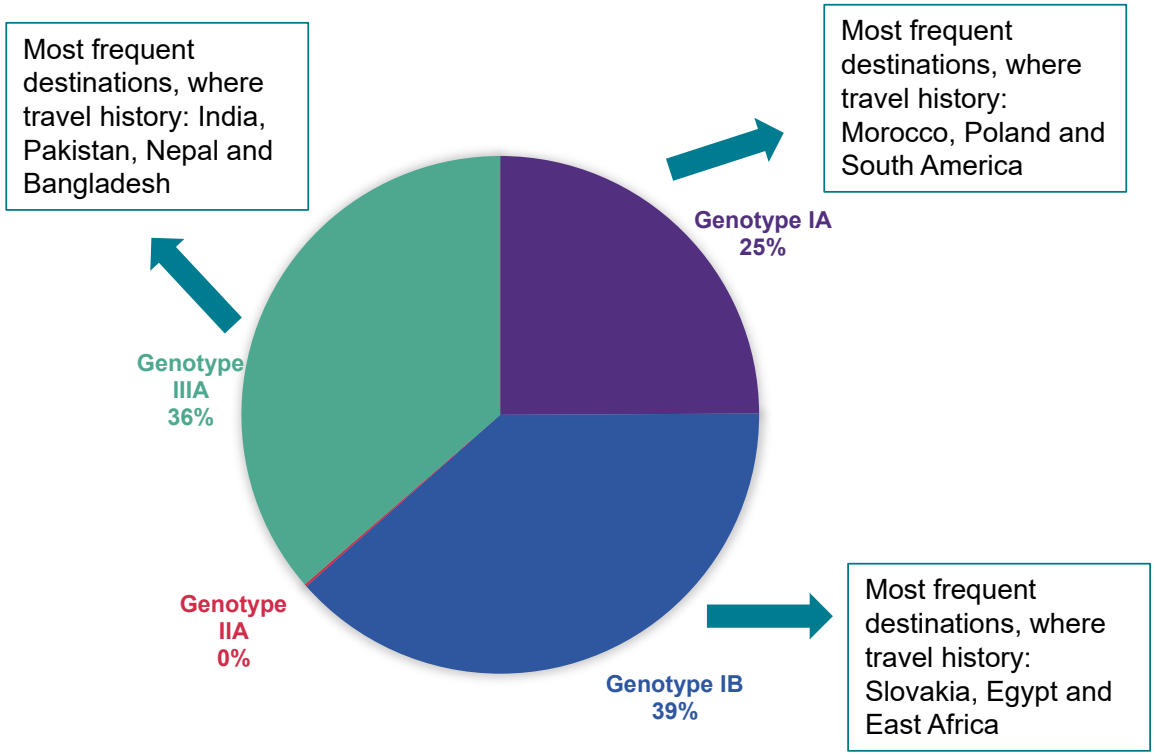
The hepatitis A virus.

Published: June 11, 2025, 12:04 am
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HAV genotypes and travel association in England, 2024

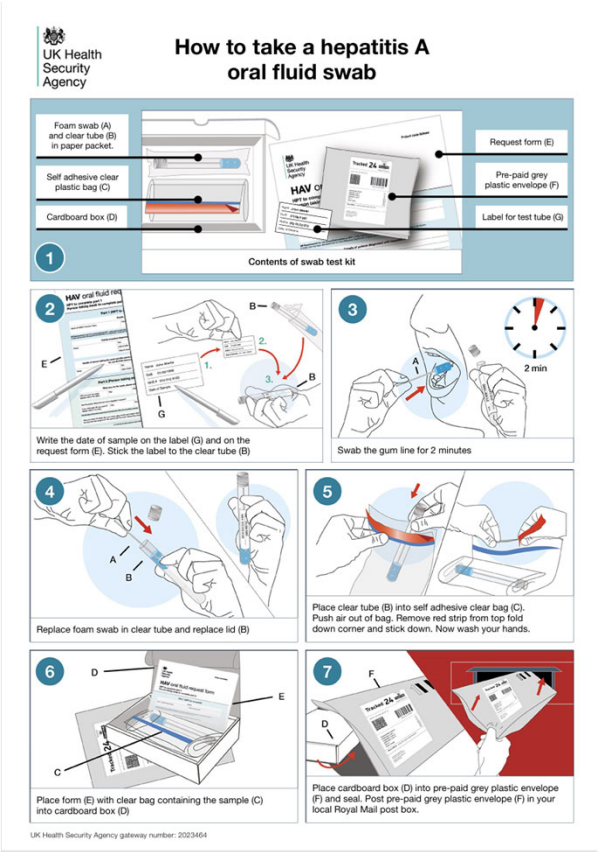


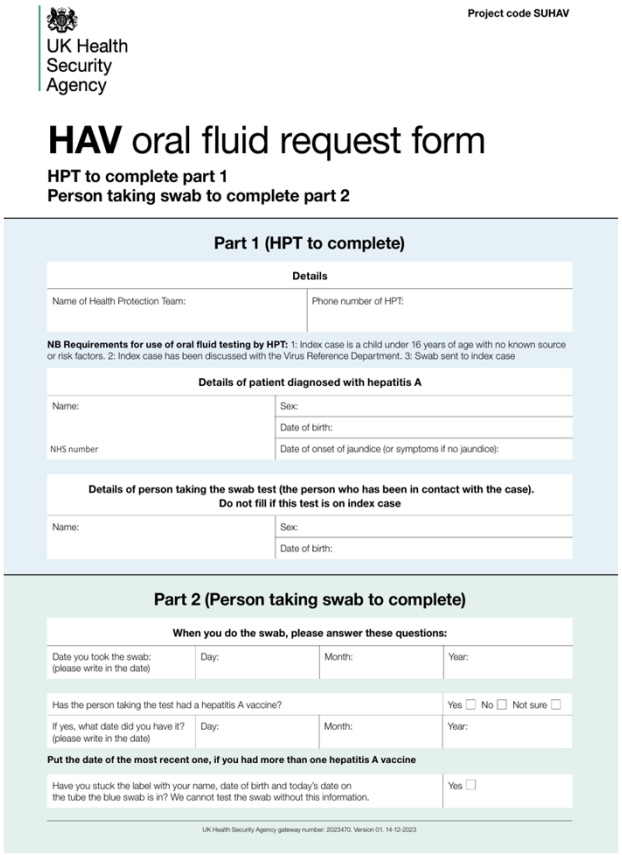


Laboratory reports of hepatitis A infections in England and Wales 2024 v1.0

HAV oral fluid for IgM and IgG testing

- Reference lab in-house assay based on modification of a commercial test
- Collection is crevicular fluid and not saliva
- Easy, non-invasive self-swabbing at home
- Tests for IgM and IgG separately for more informative interpretation of the serology markers
- Antibody is stable on the swab and can be safely sent via routine postal service
- Role in (i) serosurveys and (ii) understanding transmission to inform wider public health actions
- Challenges
  - Inadequate samples invalidate results
  - Cannot do PCR for RNA





[Hepatitis A infection: prevention and control guidance - GOV.UK]

HAV oral fluid testing (OFT) in understanding transmission dynamics

- Helps characterise clusters
  - define the direction and extent of secondary transmission in the household
  - inform further and more targeted prevention and control measures
- Use in public health guidance:
  - Index case is a child (under 16 years) and the source is unknown (no history of travel)
  - If household contacts of index case are OFT negative, then this indicates child may have acquired infection in school
  - Likely transmission or cluster in school warrants assessment for school vaccination



Epidemiology and Infection

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Original Paper

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Oral fluid testing facilitates understanding of hepatitis A virus household transmission

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Abstract

The public health response to sporadic hepatitis A virus (HAV) infection, hepatitis A, can be complex especially when the index case is a child and no obvious source is identified. Identifying an infection source may avoid mass immunisation within schools when transmission is found to have occurred within the household. Screening of asymptomatic contacts via venepuncture can be challenging and unacceptable, as a result non-invasive methods may facilitate public health intervention. Enzyme-linked immunoassays were developed to detect HAV immunoglobulin M (IgM) and immunoglobulin G (IgG) in oral fluid (ORF). A validation panel of ORF samples from 30 confirmed acute HAV infections were all reactive for HAV IgM and IgG when tested. A panel of 40 ORF samples from persons known to have been uninfected were all unreactive. Two hundred and eighty household contacts of 72 index cases were screened by ORF to identify HAV transmission within the family and factors associated with household transmission. Almost half of households (35/72) revealed evidence of recent infection, which was significantly associated with the presence of children ⩽11 years of age (odds ratio 9.84, 95% confidence interval: 2.74–35.37). These HAV IgM and IgG immunoassays are easy to perform, rapid and sensitive and have been integrated into national guidance on the management of hepatitis A cases.

Introduction

Hepatitis A virus (HAV) is a picornavirus causing faecal-orally transmitted acute liver disease, hepatitis A. The UK has a low annual incidence of infection [1]. In the absence of sustained endemic transmission and in the presence of high levels of hygiene and sanitation, the UK does not have universal hepatitis A childhood immunisation. Public Health England (PHE) recommends selective immunisation for to those who are at increased risk of infection including travellers to endemic areas, those at occupational risk, persons who inject drugs and men who have sex with men [2]. Susceptibility to HAV infection varies in the population; it is highest in those under 30 years of age, with >80% of such individuals being seronegative for antibody to HAV [3]. Seroprevalence increases with age and by the age of 60 more than three quarters of the population are seropositive from previous infection or immunisation [3]. There is potential for localised outbreaks in England and Wales, especially if primary schools are involved as young children are frequently implicated in spread due to variable levels of personal hygiene and high levels of susceptibility [4].

In England and Wales 290 confirmed cases were reported in 2016 [1]; of these 53.8% had a travel history. Where the source of the infection remained unknown these sporadic cases may have been person-to-person transmissions from sub-clinical undiagnosed infections in individuals from higher risk populations including those with undeclared recent travel to endemic countries, or direct infections from contaminated food. Asymptomatic infection in young children is often implicated in the spread of infection during extended outbreaks [4] and transmission of infection within affected households is relatively common [5]. When the index

[Hepatitis A infection: prevention and control guidance - GOV.UK]

Haywood B, Tedder RS, Beebeejaun K, et al. Oral fluid testing facilitates understanding of hepatitis A virus household transmission. *Epidemiology and Infection*. 2019;147:e105. doi:10.1017/S095026881900027X

Use of seroprevalence surveys

- Estimate HAV seroprevalence and susceptibility rates across different age groups and risk groups in England
  - Inform vaccination strategies and screening / testing recommendations / policy
- Monitor immunity in MSM population for whom there is a targeted vaccination programme
  - infer if adequate vaccination occurring BUT cannot differentiate between vaccine and infection
  - identify inequalities in uptake
- Supports incident management and more efficient administration of HNIG as post exposure prophylaxis (PEP)
  - e.g. indicating testing prior to HNIG issue for elderly household close contacts especially if born in endemic countries as high seropositivity in elderly

Summary

- Testing and diagnostics key to surveillance and control of HAV – informs public health actions and guidance
- Key opportunities:
  - Mandatory clinical reporting of positive results to public health for action
  - Local and national reference labs- established network
  - Molecular surveillance for (free) confirmation and typing – rapid identification of clusters
  - Development of non-invasive, remote sampling methods: oral fluid
    - improve case ascertainment, community access and focused public health interventions
  - Potential use with other surveillance modalities: waste-water surveillance
- Challenges:
  - Interpretation of serology results as false positives can occur
  - Serology cannot differentiate between past infection vs. vaccination
  - PCR not possible on oral fluid