UK Health Security Agency

Public health control and management of hepatitis A

2024 updated guidance

Contents

Document history

Date	Reason for change	Version number
1 November 2009	First published	0.1
15 June 2017	Updated pre-exposure immunisation recommendations	0.2
29 June 2017	Updated guidance on the public health management of hepatitis A infection based on review of epidemiology and and literature	0.3
6 July 2017	Updated to add temporary hepatitis A vaccination in adults recommendations	0.4
14 July 2017	Added hepatitis A vaccination in children temporary recommendations	0.5
19 July 2018	Updated the hepatitis A vaccine options in the adult and children's temporary vaccination recommendations	0.6
16 November 2018	Removed temporary recommendation documents	0.7
February 2024	Clarified anti-HAV IgG testing and HNIG issue, amended assessment of susceptibility and added oral fluid testing update; rebranded with UKHSA formatting; information sheets updated and moved to become stand alone documents	0.8

Executive summary

This guidance has been developed to aid the public health management of hepatitis A infection which aims to reduce the occurrence of secondary infections and to prevent and control outbreaks. The guidance has been developed based on a review of the current epidemiology of hepatitis A in England and Wales and a review of the literature on the efficacy of human normal immunoglobulin (HNIG) and hepatitis A vaccine for post-exposure prophylaxis. The 2024 guidance has minor updates to the 2017 guidance which replaced the 2009 guidance.

The main changes in 2017 compared to the 2009 guidance are:

- clarification of case definitions
- more inclusive criteria for defining a person as a close contact
- for post exposure prophylaxis of close contacts of cases, HNIG is now recommended (in addition to vaccine) for those aged 60 and over within 14 days of exposure
- for post exposure prophylaxis of close contacts of cases within 14 days of exposure, HNIG is now recommended (in addition to vaccine) for those who are HIV infected and with a CD4 count less than 200 cells/mm^3
- for post exposure prophylaxis of close contacts of cases within 14 days of exposure, HNIG is recommended (in addition to vaccine) for those with immunosuppression
- for post exposure prophylaxis where HNIG is indicated, if time permits, testing for IgG antibody to the hepatitis A virus (anti-HAV IgG) may be carried out to prevent unnecessary administration of a blood product
- for close contacts of cases, the time since exposure to the index has been amended using the date of onset of jaundice (in preference to symptoms) and clarified for single, intermittent and continuous exposures
- for close contacts who are food handlers and have not been immunised within 14 days of exposure and are at high risk of acquiring infection, reinforcement of hygiene is recommended and where possible the close contact should be advised to restrict activities to those which do not involve preparing and handling unwrapped ready-to-eat-food until 30 days post exposure unless demonstrated to be immune; exclusion from work is only considered if scrupulous hygiene cannot be achieved
- clarification of management of close contacts in nursery and pre-school settings
- a more comprehensive section on the management of outbreaks
- recommendations around the use of oral fluid testing for serological evidence of hepatitis A
- a revised national standard questionnaire which should be completed for all cases of hepatitis A, and includes a section on sexual history in view of outbreaks affecting predominantly GBMSM; the travel and migrant health section (TMHS) at Colindale will be collecting questionnaires for all cases known to be or suspected to be foreign travel-associated

The main substantive changes in 2024 guidance compared to 2017 guidance are:

- clearer criteria for feasibility of anti-HAV IgG testing prior to HNIG issue
- more detailed assessment of susceptibility of close contacts including definition of immune, primed and fully susceptible
- updated epidemiology and burden of disease

This guidance is split into 2 parts:

Part 1 describes the recommendations and rationale for management of cases, close contacts and outbreaks.

Part 2 gives the background for the guidance including the clinical features, epidemiology and laboratory testing of hepatitis A and the evidence for the recommendations.

Box 1. Summary of recommendations for the public health management of an index case and close contacts

Management of the index case:

- advise on good hygiene practices
- exclude from work, school or nursery until 7 days post onset of jaundice or in absence of jaundice, from the onset of compatible symptoms (such as fatigue, nausea or fever)
- identify possible source of infection
- undertake risk assessment, particularly if case occurs in a non-household setting
- complete national standard questionnaire

Management of non-immune close contacts identified within 14 days of exposure to index case:

- healthy close contacts aged less than 12 months: offer immunisation to those sharing a household with the infant contacts and persons who have been involved in nappy changing or assistance with toileting for the infant contact, to prevent tertiary infection;
- if the infant contact attends childcare, offer vaccine to the infant contact if 2 months or older (unlicensed) and reinforce hygiene in the childcare setting
- if immunisation is not possible, reinforce hygiene in the childcare setting to prevent tertiary transmission
- if there are concerns that high hygiene standards cannot be maintained in the childcare setting: exclude the infant contact for 30 days
- if exclusion is likely to have serious adverse consequences (for example, loss of employment): immunise children and staff in the childcare setting

- healthy close contacts aged one to 59 years: offer hepatitis A vaccine
- healthy close contacts aged 60 years or over: offer hepatitis A vaccine; in addition, if fully susceptible (see Box 8), offer HNIG
- close contacts with chronic liver disease, chronic hepatitis B or C infection, and immunosuppression, including HIV positive individuals with CD4 count less than 200 cells per cubic millimetre (mm^3): offer hepatitis A vaccine; in addition, if fully susceptible (see Box 8), offer HNIG
- close contact who is a food handler: offer hepatitis A vaccine

Management of non-immune close contacts identified more than 14 days post exposure:

- more than one close contact within the household and contacts seen within 8 weeks of exposure: offer hepatitis A vaccine to prevent tertiary infection
- close contact has chronic liver disease or chronic hepatitis B or C infection and is seen within 28 days of exposure: offer hepatitis A vaccine and HNIG to attenuate severity of disease
- close contact is a food handler: risk assessment of need for transfer to non-food-handling duties (see Figure 1)
- close contact attends childcare setting: reinforce hygiene in the childcare setting to prevent tertiary transmission. If there are concerns that high hygiene standards cannot be maintained in the childcare setting: exclude the infant contact for 30 days. If exclusion is likely to have serious adverse consequences (for example, loss of employment): immunise children and staff in the childcare setting

Management of non-immune contacts where the index case attends a high risk setting (beyond the household):

- index case is a food handler or staff in residential care setting: risk assessment for post-exposure prophylaxis of contacts within work setting
- index case is a child cared for in a pre-school childcare or reception setting: manage contacts working, or being cared for, in the same room as close contacts. If contacts seen more than 14 days post exposure and/or more than one case identified in the setting, consider widening immunisation in the early years setting and offering vaccine to close contacts of exposed contacts to prevent tertiary infection
- index case attends early years setting or primary school: if source of infection outside early years setting or school not identified, assume infection acquired within early years setting or school, unless oral fluid testing of household contacts suggests otherwise, and risk assess for the need to offer hepatitis A vaccine to classroom contacts, year or a wider population at risk in that setting

Part 1. Management and investigation of cases and close contacts

1.1 Risk assessment of cases

Information that should be collected on each case includes:

Caller details

- name, address, designation and contact number

Demographics

- name, date of birth, gender, ethnicity, birthplace, NHS number
- address including postcode, phone number
- contact details including phone number
- occupation, place of work/education
- GP name and contact details (address and phone number)

Clinical details

- symptoms and signs with onset and severity of symptoms including date of onset of jaundice, if present
- results of laboratory investigations (local and/or reference laboratory)
- other medical conditions
- medications
- alcohol or illicit drug use
- confirm serological findings are compatible with acute hepatitis A with the local microbiologist or virologist

Epidemiological details

- immunisation history (including dates)
- history of previous hepatitis A infection
- during the incubation period (8 week period prior to symptom onset) has the patient:
- had contact with a confirmed case?
- travelled abroad?
- had contact with someone who has been to a high-risk area?
- details of close contacts (including sexual contacts)
- food history if unlikely to be travel-related

Questionnaire

The national standard questionnaire for hepatitis A which should be completed with the above details. This questionnaire has been revised to include a section on sexual history which is to be completed if appropriate.

1.2 Key definitions

Box 2. Case definitions

Possible case is:

A person meeting the clinical case definition, that is, a person with an acute illness, discrete onset of symptoms and jaundice or elevated serum aminotransferase levels.

Probable case is:

A person that meets the clinical case definition (see above) and has an epidemiological link to a confirmed hepatitis A case.

or:

A person that meets the clinical case definition (see above) and has IgM antibody to the hepatitis A virus (anti-HAV IgM).

Confirmed case is:

A person that meets the clinical case definition (see above) and is confirmed through IgM and IgG antibodies to hepatitis A.

or:

A person with hepatitis A RNA (HAV RNA) detected regardless of clinical features.

or:

An asymptomatic person with no recent history of immunisation with anti-HAV IgM from oral fluid or serum and an epidemiological link to a confirmed hepatitis A case.

Box 3. Implications for public health action

Public health action should be taken for all confirmed and probable cases.

Attempts to confirm a probable case should always be made; however, for probable cases, post exposure immunisation should not be delayed among close contacts in the household setting. If public health action is likely to extend beyond the household setting, for example, immunisation in a school, then confirmation should be obtained before that intervention.

Individuals with an IgM result only (for example, probable cases or those persons who do not meet the case definitions) should be discussed with the local microbiologist or virologist to

request quantitative (measure of level of reactivity) IgG and IgM results, and to consider the laboratory findings in the broader clinical and epidemiological context (see Box 4 below for case scenarios).

The national standard questionnaire should be completed for all probable and confirmed cases.

All serum samples should be forwarded to UK Health Security Agency (UKHSA) Colindale, Virus Reference Department (VRD) as part of the national enhanced molecular surveillance of hepatitis A for confirmation and sequencing.

Box 4. Case definition example scenarios

Scenario 1

A 65 year old male presents at the GP feeling generally unwell but no discrete onset of symptoms and no jaundice.

Blood tests: elevated serum aminotransferase levels, and anti-HAV IgM reactive.

Risk factors: none.

Discussion with local microbiologist or virologist:

- anti-HAV IgM reactivity – low
- no anti-HAV IgG done

Action: request local IgG quantitative testing.

Discussion with local microbiologist or virologist:

- anti-HAV IgM reactivity – low
- anti-HAV IgG reactivity – high

Conclusion: patient has evidence of past hepatitis A infection and anti-HAV IgM reactivity unlikely to be associated with a recent infection.

Action: if there is still uncertainty from local microbiologist or virologist then sample can be referred to reference laboratory (VRD) for confirmation or exclusion. If, after discussion with the microbiologist or virologist, hepatitis A is thought to be unlikely, then it may be reasonable to wait for the reference laboratory result before commencing public health action.

Scenario 2

A 27 year old pregnant female presents at the GP with itching but with no jaundice.

Blood tests: elevated serum aminotransferase levels, anti-HAV IgG was not detected, and anti-HAV IgM reactive.

Risk factors: none.

Discussion with local microbiologist or virologist:

- patient may have obstetric cholestasis
- anti-HAV IgG – not detected
- anti-HAV IgM reactivity – low

Action: refer for confirmation and HAV RNA testing as anti-HAV IgM on its own is not diagnostic of hepatitis A infection. Given the alternative diagnosis (obstetric cholestasis) and the lack of anti-HAV IgG, it was considered reasonable to delay commencement of public health actions until the result is obtained from the reference labortatory. On reference testing HAV RNA is not detected.

Conclusion: patient has no evidence of hepatitis A infection at the time of sampling and anti-HAV IgM reactivity unlikely to be associated with a true recent infection, particularly in pregnancy.

Box 5. Infectious period for the index case

The infectious period is taken from 2 weeks before onset of first symptoms and until one week after the onset of jaundice or, if jaundice is not reported, one week after the onset of dark urine or pale stools. If there are no symptoms of jaundice, dark urine or pale stools, onset of other symptoms (such as fatigue, nausea, and fever) should be used. For asymptomatic cases the infectious period should be estimated using the timing of contact with the source if known (such as contact with an index case or consumption of contaminated food) and with consideration of the laboratory test results.

Box 6. Time since exposure

- in the case of continuous exposure (such as contacts in a shared household), the limit for administering prophylaxis should be timed from the onset of jaundice or onset of symptoms such as fatigue, nausea, fever in the absence of jaundice

- in the case of a single exposure in the infectious period, time since exposure should be calculated from day of the exposure
- in the case of intermittent exposure (such as contacts from school) time since exposure is defined as the last day of exposure to the index case in their infectious period

Where jaundice is not reported, the date of onset of dark urine or pale stools should be used. If there are no symptoms of jaundice, dark urine or pale stools, onset of other symptoms (such as fatigue, nausea, and fever) should be used.

Box 7. Close contact

Close contacts are individuals at high risk of being exposed to hepatitis A through close contact, equivalent to a household type exposure, with the index case during the infectious period. A risk assessment should be undertaken to identify close contacts, with particular consideration of those that have shared food and toilet facilities with the index case. There should be a low threshold for considering someone a close contact. Close contacts may include:

- a person living in the same household as the index case or regularly sharing food or toilet facilities with the index case during the infectious period, including extended family members and friends who frequently visit the household; this may also include those in shared accommodation (for example, some individuals in boarding schools) with shared kitchen and/or toilet facilities
- if the index case is a child in nappies or requiring assistance with toileting, any person who has been involved in nappy changing or assistance with toileting, including nursery school staff and childminders during the infectious period
- a person who has had sexual contact with the index case during the infectious period
- same room contacts in a pre-school childcare setting and reception class if the index case is a child, such as those working or being cared for in the same room as the index case during the infectious period
- in long-stay care facilities close contacts may include those sharing toilet facilities or food with the index case, and those who were assisted with activities of daily living (such as eating and toileting) by the index case during the infectious period
- individuals injecting drugs and sharing injecting paraphernalia with the index case

The risk of transmission in all settings should be assessed on a case by case basis by the local senior health protection lead.

Box 8. Immune, primed and susceptible close contacts

Close contacts who meet the following criteria are immune (that is, not susceptible) and do not need post-exposure vaccine or HNIG:

- reliable history or evidence of a complete course of hepatitis A vaccine in the past 10 years (for example, 2 monovalent doses or equivalent)

or:

- reliable history or evidence of one dose of monovalent vaccine (or equivalent) within the past 12 months

or:

- reliable history of hepatitis A infection or previous laboratory-confirmed hepatitis A (previous anti-HAV IgG positive, or HAV RNA positive)

Close contacts that have any other history of receiving a hepatitis A vaccine that does not fit the criteria above should be considered ‘susceptible but primed’ and require post-exposure vaccine but not HNIG (regardless of age or co-morbidities). For example:

- reliable history or evidence of one standard dose of hepatitis A vaccine at any point more than 12 months ago

or:

- reliable history or evidence of a complete course (for example, 2 monovalent doses) of hepatitis A vaccine more than 10 years ago

There is no upper limit to the amount of time a person can be in the ‘susceptible but primed’ state. For example, a single vaccine dose 20 years ago would still fulfil the criteria for being primed. While evidence suggests that a complete course of hepatitis A vaccination should give immunity beyond 25 years, a more precautionary approach is advisable for those close contacts who have had a definite exposure to hepatitis A.

Close contacts that meet the following criteria should be considered ‘fully susceptible’ and require post-exposure vaccine and should be considered for HNIG:

- no history or evidence of hepatitis A vaccine

and:

- no reliable history of hepatitis A infection or laboratory-confirmed hepatitis A (previous anti-HAV IgG positive, or HAV RNA positive)

HNIG is recommended to be given within 14 days from the last exposure. See Considerations for anti-HAV IgG testing for further information on testing prior to issue of HNIG.

Table 1 defines different risk groups who have an increased risk of spreading hepatitis A because of personal hygiene or occupation.

Table 1. People that pose an increased risk of spreading hepatitis A (source: Guidance on gastrointestinal infection)

Risk group	Description	Additional comments
A	Any person of doubtful personal hygiene or with unsatisfactory toilet, hand-washing or hand drying facilities at home, work or school	Risk assessment should consider, for example, hygiene facilities at the work or educational setting
B	All children aged 5 years old or under who attend school, pre-school, nursery or other similar childcare or child minding groups	Explore informal childcare arrangements
C	People whose work involves preparing or serving unwrapped food or drink to be served raw or not subjected to further heating	Consider informal food handlers, for example, someone who regularly helps to prepare buffets for a congregation
D	Clinical and social care staff who work with young children, the elderly, or other particularly vulnerable people, and whose activities increase the risk of transferring infection via the faeco-oral route. Such activities include helping with feeding or handling objects that could be transferred to the mouth	Someone may be an informal carer, for example, caring for a chronically sick relative or friends

1.3 Primary prevention

Hygiene

Hepatitis A virus is spread from person-to-person by the faecal-oral route. Good hygiene, principally thorough hand washing after toilet use and before food preparation, is the cornerstone of prevention. As faecal-oral transmission can occur during sex, particularly among gay, bisexual and other men who have sex with men (GBMSM), advice should be given about washing hands after sex (and also buttocks, groin and penis too), as well as using protection for fingering, rimming and fisting, changing condoms between anal and oral sex, and not sharing sex toys.

For travellers to countries of high and intermediate endemicity care should be taken to avoid exposure to hepatitis A through contaminated food and water. Advice is available through the National Travel Health Network and Centre (NaTHNaC) (1).

Active immunisation

There are 3 monovalent inactivated hepatitis A vaccines, 2 combined hepatitis A and hepatitis B vaccine and 2 combined hepatitis A and typhoid vaccines currently licensed for use in the UK (2). Numerous clinical trials have demonstrated that these vaccines are highly immunogenic and effective at preventing hepatitis A infection in up to 95% of recipients when a completed course (2 or 3 doses depending on the vaccine) are given prior to exposure (3).

The following groups are recommended to receive pre-exposure immunisation. Further details are available in chapter 17 of the Green Book:

1. People travelling to or going to reside in areas of high or intermediate prevalence. Those who visit friends or relatives in high or intermediate prevalence countries are particularly at risk of acquiring infection and often do not seek pre-travel health advice. GPs and practice nurses should be encouraged to consider the travel immunisation needs of this group opportunistically.
2. People with chronic liver disease.
3. People with haemophilia.
4. Gay, bisexual and other men who have sex with men.
5. People who inject drugs.
6. Individuals at occupational risk.

1.4 Management of the index case

Hygiene

Good hygiene practices are the cornerstone of the prevention of hepatitis A infection.

The index case and his or her family and other close contacts should receive verbal and written guidance on the importance of hand washing after using the toilet, changing nappies and before preparing food.

It is important that enhanced hygiene is practised by all family members as some may already have acquired hepatitis A infection and be excreting hepatitis A virus. Individuals whose personal hygiene is likely to be inadequate (for example, young children or people with learning disabilities) should be supervised to ensure that they wash their hands properly after defecation. If transmission during sex is the likely route, particularly between GBMSM, advice on how to prevent spread of hepatitis A during sex should also be given.

Exclusion

The index case should be excluded from work, school or nursery until 7 days after onset of jaundice, or 7 days after symptom onset if there is no history of jaundice. This is irrespective of whether the index case is in a risk group or not.

Questionnaire

An assessment should be carried out to try to identify the possible source of infection (for example, history of foreign travel or history of contact with a known case of hepatitis A within the incubation period). If no obvious source of infection can be identified, and the index case attends a pre-school childcare setting or primary school, the infection may have been acquired from an asymptomatic infected child outside of the household, in a school or preschool setting; this has implications for public health action, which are covered in section 1.6.

The latest national standard questionnaire can be accessed in the government website, should be completed for each confirmed or probable case, and uploaded to HPZone/CIMS. Questionnaires aid local investigations and may be requested (or downloaded from HPZone/CIMS) by the national team if the case is linked to a regional, national or international outbreak. All questionnaires for travel-associated cases should be sent to the Travel and Migrant Health Section.

1.5 Management of close contacts

Hygiene

Providing advice on good hygiene, in particular careful hand washing after using the toilet is the cornerstone of preventing ongoing transmission within a household and contacts should receive verbal and written guidance. Contacts whose personal hygiene is likely to be inadequate (for example, young children, those with severe learning disabilities) should be supervised to ensure that they wash their hands properly after defecation. Those caring for non-toilet trained children should wash their hands immediately after nappy changing or toileting. If transmission during sex is the likely route, particularly between GBMSM, advice on how to avoid hepatitis A infection during sex should also be given.

Assessment of susceptibility and indications for post-exposure vaccine and HNIG

Use of HNIG

The mainstay of hepatitis A post-exposure prophylaxis is hepatitis A vaccine. Human normal immunoglobulin (HNIG) may provide short term immunity in the first 7 days post initiation of prophylaxis and is most effective soon after exposure. The total antibody level induced by active immunisation (vaccine) may be many orders of magnitude greater than can be provided by passive immunisation (HNIG). For this reason HNIG is not given more than 7 days after the first

dose of hepatitis A vaccine, or to an individual who is already primed by partial or previous immunisation (see Box 8).

For patients managed in the community, intramuscular (IM) HNIG is recommended. Subgam® can be issued from UKHSA stockholders on request. The current summary of product characteristics (SPC) covering these products do not mention intramuscular administration. Given the clinical imperative to treat these contacts urgently, it is reasonable to use available HNIG products intramuscularly so long as use via this route is acknowledged to be off-label. There are no specific contraindications to IM use listed. The functional biological activity of these produces is expected to be equivalent. In the absence of data from the manufacturers, users are asked to report back to UKHSA any concerns over tolerability with IM use.

Alternative HNIG products may be available in NHS Trusts (often labelled as SCIg) which can be used as an alternative to Subgam if HNIG is to be given in the hospital. Please see the hepatitis A immunoglobulin guidance for further details on alternative HNIG/SCIg products, dosage and administration.

Close contacts should be considered ‘immune’ (not susceptible) and do not require vaccine or HNIG if they have a:

- reliable history or evidence of a complete course of hepatitis A vaccine in the past 10 years (for example, 2 monovalent doses or equivalent)

or:

- reliable history or evidence of one dose of monovalent vaccine (or equivalent) within the past 12 months

or:

- reliable history of hepatitis A infection or previous laboratory-confirmed hepatitis A (previous anti-HAV IgG positive, or HAV RNA positive)

Close contacts that have any other history of receiving a hepatitis A vaccine that does not fit the criteria above should be considered ‘susceptible but primed’ and require vaccine but not HNIG (regardless of age or co-morbidities). For example:

- reliable history or evidence of one standard dose of hepatitis A vaccine at any point more than 12 months ago

or:

- reliable history or evidence of a complete course (for example, 2 monovalent doses) of hepatitis A vaccine more than 10 years ago

Close contacts that meet the following criteria should be considered ‘fully susceptible’ and require post-exposure vaccine and should be considered for HNIG:

- no history or evidence of hepatitis A vaccine

and:

- no reliable history of hepatitis A infection or laboratory-confirmed hepatitis A (previous anti-HAV IgG positive, or HAV RNA positive)

HNIG is recommended to be given within 14 days from the last exposure.

Considerations for anti-HAV IgG testing

Rapid anti-HAV IgG testing prior to administration of HNIG can be done, if feasible and immunity is suspected. Such testing can be used to avoid an unnecessary administration of a blood product which carries theoretical risks of transmission of unidentified infectious agents.

However, anti-HAV testing is not a pre-requisite for HNIG issue and anti-HAV IgG testing should not delay the administration of post-exposure vaccine.

The decision on whether to conduct anti-HAV IgG testing prior to HNIG issue requires consideration of several factors, including time since exposure, intensity of exposure, likelihood of pre-existing immunity and the time it will take to carry out an anti-HAV IgG test and get the result.

For example, it may be reasonable to consider anti-HAV testing in older persons born overseas in a hepatitis A endemic country as there is a higher likelihood of them being anti-HAV IgG positive compared to a UK born older person.

Conversely, testing may be less helpful and introduce delays where there has been continuous close contact from before the onset of jaundice (for example, household contacts). For these individuals, administration without testing may be warranted to achieve maximum potential benefit from HNIG.

Anti-HAV IgG testing will not be helpful in individuals who have had recent post-exposure vaccination, as IgG detected could be due to the immune response to vaccine rather than past natural infection. Anti-HAV IgG testing can therefore be considered prior to HNIG issue, provided results will be available within 3 days, and if:

- it is less than 10 days since last exposure
- it is less than 7 days since HAV vaccine

If an anti-HAV IgG result is negative or equivocal, HNIG can be given.

Public health actions for non-immune close contacts 14 days or less from exposure

Please also refer to Figure 2 for an algorithm for managing close contacts of cases of acute hepatitis A.

Below is a summary of the public health actions for susceptible (non-immune) contacts 14 days or less from exposure and a summary of the rationale. For full rationale see section 2.4.

Box 9. Public health actions for non-immune close contacts 14 days or less from exposure

Healthy infants less than 12 months

Recommendation

No post-exposure prophylaxis is required for healthy infant contacts aged less than 12 months not attending childcare if all those involved in nappy changing are immunised against hepatitis A and thus protected against tertiary infection.

Appropriate advice should be given on enhanced hygiene during infant care. If an infant contact attends childcare and is 2 months or older, he or she should be offered immunisation with monovalent hepatitis A vaccine in addition to reinforcing hygiene in the childcare setting. If the infant contact cannot be immunised, appropriate advice should be given on enhanced hygiene in the childcare setting.

If there are concerns that high hygiene standards cannot be maintained in the childcare setting, the infant contact should be excluded for 30 days to prevent tertiary infection. If exclusion is likely to have serious adverse consequences such as loss of employment for those caring for the infant contact, immunisation with monovalent hepatitis A vaccine can be offered to children aged 2 months or older and staff in the childcare setting. If an infant aged less than 12 months receives hepatitis A vaccine and requires long-term protection against hepatitis A, the dose given before the first birthday should be ignored and the full course of 2 doses should be given after the age of one year.

Rationale

Infants less than12 months of age very rarely develop symptomatic hepatitis A infection, and if they do it tends to be mild. However, infants who do not have maternal antibodies are at risk of developing subclinical infection and may go on to infect others. Immunogenicity studies provide evidence of a good immune response to vaccine in babies older than 2 months, suggesting that the evidence on post-exposure efficacy can be extrapolated to infants in this age group. In some countries infants aged less than 12 months are offered HNIG, this is not recommended in the UK due to the mild clinical illness in under 12 month olds.

Healthy persons aged 12 months to 59 years

Recommendation

A single dose of monovalent hepatitis A vaccine should be given to healthy close contacts aged one to 59 years. A risk assessment should be carried out to determine whether the patient is at continued risk of hepatitis A infection (for example, the patient fulfils the criteria for requiring immunisation as pre-exposure prophylaxis, see section 1.3 above). A second dose of vaccine is recommended 6 to 12 months after the first dose to ensure long term protection.

Rationale

There is good evidence for the use of vaccine post exposure in healthy persons aged 2 years and over when given within 14 days. There is good evidence from immunogenicity studies that hepatitis A vaccine produces an immune response in children from 12 months of age, and in the UK hepatitis A vaccine is licensed for children from 12 months. It is therefore reasonable to recommend post exposure immunisation to children from 12 months.

There is evidence from immunogenicity studies of a slower and lower response to vaccine with increasing age, particularly over the age of 60 years. The severity of hepatitis A increases with age, with an increased number of deaths in patients over the age of 60 years with hepatitis A listed on the death certificate seen in the UK. This combined evidence suggests that it is reasonable to extrapolate the findings on the efficacy of hepatitis A vaccine in post-exposure prophylaxis to patients up to the age of 59 years but not beyond this age.

Healthy persons aged 60 years and older

Recommendation

Contacts aged 60 years and over should be offered HNIG in addition to monovalent hepatitis A vaccine, if they are fully susceptible (see Box 8). A second dose of vaccine is recommended 6 to 12 months after the first dose to ensure long term protection.

Rationale

There is no direct evidence of the efficacy of vaccine in persons aged 60 years and over and there is evidence from immunogenicity studies of a lower and slower response to hepatitis A vaccine with increasing age, dropping particularly in those over the age of 60. The severity of hepatitis A infection increases with age, rising particularly after the age of 60 years.

Individuals under the age of 60 are likely to acquire immunity from post exposure immunisation, with little additional benefit from HNIG. The efficacy of HNIG in the secondary prevention of hepatitis A infection is established and was routine practice across all age groups. Therefore individuals over the age of 60 are likely to benefit from HNIG post exposure.

Persons with chronic liver disease, pre-existing chronic hepatitis B or C infection

Recommendation

Contacts with chronic liver disease, pre-existing chronic hepatitis B or C infection should be offered HNIG in addition to hepatitis A vaccine, if they are fully susceptible (see Box 8). The patient should be referred to their GP for a second dose of hepatitis A vaccine 6 to 12 months after the first dose to ensure long-term protection.

Rationale

People with chronic liver disease, including chronic hepatitis B or C infection are at risk of severe disease from hepatitis A infection. There is no direct evidence of the effectiveness of vaccine as post-exposure prophylaxis in this group. There is evidence from immunogenicity studies of a poorer response to pre-exposure vaccine. This group is therefore likely to benefit from the added protection conferred by HNIG if they do not have pre-existing immunity.

Persons with immunosuppression

Recommendation

Contacts with immunosuppression should be offered HNIG in addition to hepatitis A vaccine, if they are fully susceptible (see Box 8). The patient should be referred to their GP for a second dose of hepatitis A vaccine 6 to 12 months after the first dose as this may provide long-term protection, depending on the underlying cause of immunosuppression. Patients should be considered immunosuppressed if they are identified as ‘immunosuppressed' as listed in chapter 6 of the green book (4). If degree of immunosuppression is unclear discuss with patient’s clinician.

Rationale

There is a lack of published evidence of more severe disease from hepatitis A infection in those with immunosuppression. However epidemiological data suggest that some patients who die with or of hepatitis A have evidence of immunosuppression. In addition, there is evidence from immunogenicity studies of a poorer response to pre-exposure immunisation in those individuals.

Persons with HIV and a CD4 count of less than 200 cells/mm^3

Recommendation

Contacts that are severely immunocompromised due to HIV (CD4 count less than 200 cell/mm^3) should be offered hepatitis A vaccine, and if fully susceptible, they should also be offered HNIG. The patient should be referred to their GP for a second dose of hepatitis A vaccine 6 to 12 months after the first dose to ensure long-term protection.

Rationale

There is no published evidence of more severe disease from hepatitis A infection in those with HIV infection. There is no direct evidence of the effectiveness of post-exposure prophylaxis in this group. There is evidence from immunogenicity studies of a reduction in the rate, magnitude and longevity of immune responses to pre-exposure vaccine. However, there is evidence that the response improves with increasing CD4 cell counts and viral load suppression.

Pregnant or breastfeeding women

Recommendation

Pregnant and breastfeeding women should be managed the same as non-pregnant contacts.

Rationale

There is no evidence of risk from immunising pregnant women or those who are breast-feeding with inactivated viral vaccines.

Public health actions for non-immune close contacts more than 14 days post exposure

Please also refer to Figure 2 for an algorithm for managing close contacts of cases of acute hepatitis A.

Below is a summary of the public health actions for susceptible (non-immune) close contacts seen more than 14 days post exposure and a summary of the rationale. For full rationale see section 2.4.

Box 10. Public health actions for non-immune close contacts more than 14 days post exposure

Close contacts at risk of severe disease

Recommendation

Consideration should be given to offering HNIG to close contacts at risk of severe disease (that is, those with chronic liver disease or pre-existing chronic hepatitis B or C infection) up to 28 days post exposure, if they are fully susceptible (see Box 8). Two doses of hepatitis A vaccine given 6 months apart should also be offered to such high-risk contacts to provide long-term protection, irrespective of the time since exposure.

Rationale

There is no clear evidence of the efficacy of either vaccine or HNIG in preventing secondary infection when given more than 14 days after exposure. However, there are theoretical grounds for believing that HNIG may attenuate the severity of disease if given during the incubation period. This is of particular importance for unimmunised individuals with chronic liver disease who are at most risk of severe disease.

Close contacts who are food handlers and have not received vaccine within 14 days of exposure

Recommendation

If it has not been possible to offer vaccine within 14 days of exposure to a food handler who is or has been a close contact of a person with hepatitis A, a risk assessment of the likelihood of developing secondary infection and the risk of onward transmission should be undertaken by the Health Protection Team in conjunction with Environmental Health colleagues (see Figure 1). This includes assessment of susceptibility of acquiring HAV (see Box 8), and review of work duties, which may require a visit to the workplace.

If the close contact is non-immune to HAV and at high risk of acquiring infection (for example, index case is a child less than 5 years old or index case regularly cooked for the contact or

index case had poor personal hygiene or diarrhoea or contact had sex with index case), then reinforcement of hygiene should be recommended.

The workplace management must satisfy themselves that hand washing facilities are adequate and that there is scrupulous attention to hygiene.

Where possible, the close contact should be advised to restrict activities to those that do not include preparing and handling unwrapped ready-to-eat food (that is, will not be further cooked) until 30 days post exposure (see Figure 1) unless demonstrated to be immune.

Exclusion from work should only be considered if scrupulous hygiene cannot be achieved.

Rationale

There is a considerable risk of the close contact who is a food handler developing hepatitis A infection via secondary transmission (if not vaccinated within 14 days). Their occupation as a food handler could facilitate tertiary transmission into the wider community. Transfer to duties that do not involve direct contact with ready-to-eat food for 30 days is a proportionate response to allow for the average incubation period of hepatitis A of 28 to 30 days, noting that peak excretion of virus occurs before onset of jaundice. There is no clear evidence of the efficacy of either vaccine or HNIG in preventing secondary infection when given more than 14 days after exposure.

All other household close contacts

Recommendation

In households with more than one close contact, hepatitis A vaccine should be offered to all contacts seen within 8 weeks of onset of jaundice in the index case to prevent tertiary cases within the household.

If a close contact who attends nursery or other pre-school childcare setting or reception class does not receive vaccine within 14 days of exposure, enhanced hygiene measures should be implemented at the pre-school setting to reduce the risk of asymptomatic transmission of infection.

If there are concerns that high hygiene standards cannot be maintained in the childcare setting, the young contact attending the nursery/pre-school setting should be excluded for 30 days to prevent tertiary infection. If exclusion is likely to have serious adverse consequences such as loss of employment for those caring for the young contact who is excluded from a nursery/pre-school setting, immunisation with monovalent hepatitis A vaccine can be offered to children aged 2 months or older and to staff in the childcare setting.

Rationale

There is no clear evidence of the efficacy of either vaccine or HNIG in preventing secondary infection when given more than 14 days after exposure. However there is evidence that vaccine can prevent tertiary infections. Due to the continuous exposure and intensity of contact in households, tertiary cases are more likely to occur in households compared to other close contacts.

Figure 1. Risk assessment for close contacts who are food handlers

This is a graphical version of Close contacts who are food handlers and have not received vaccine within 14 days of exposure, above.

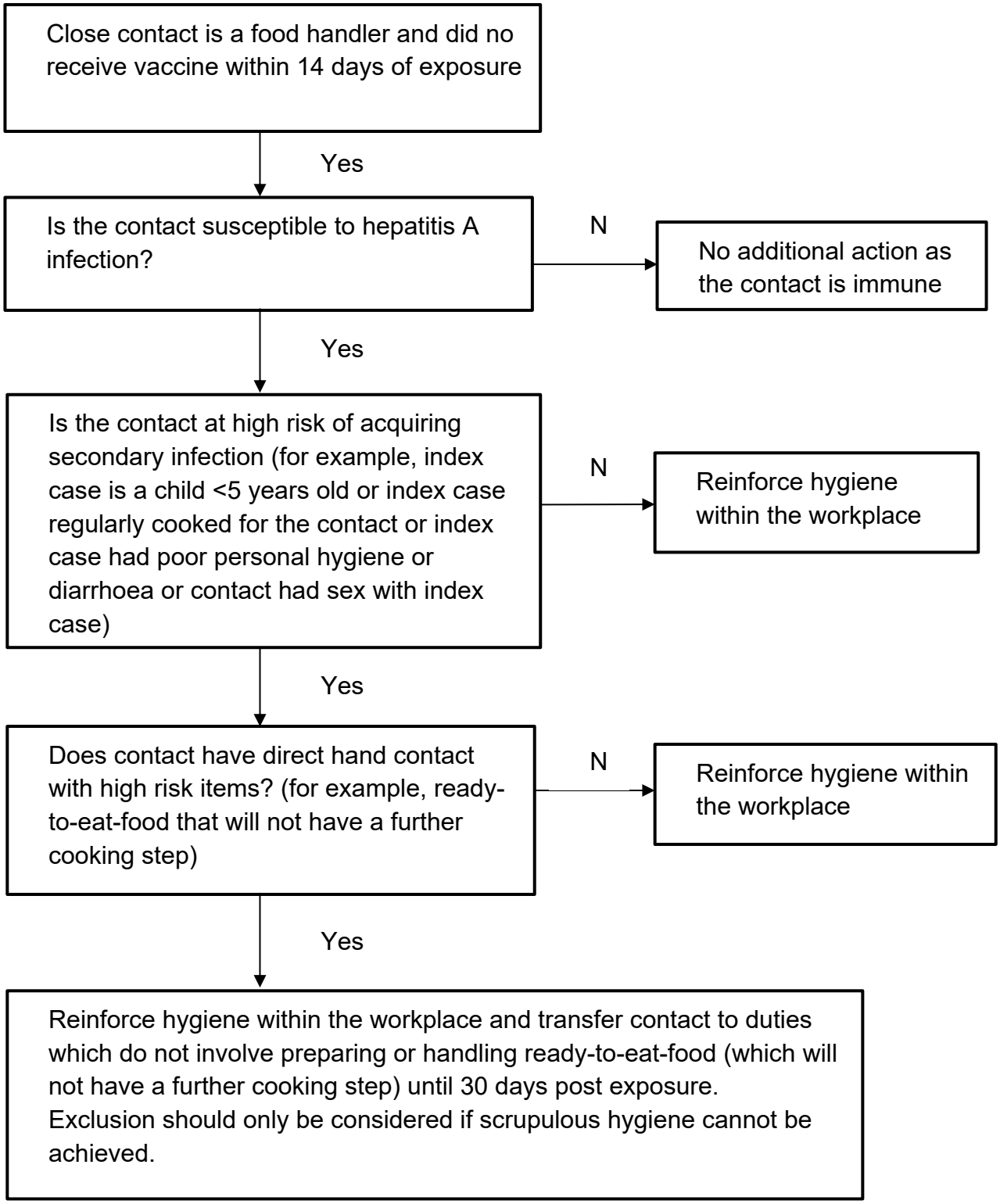
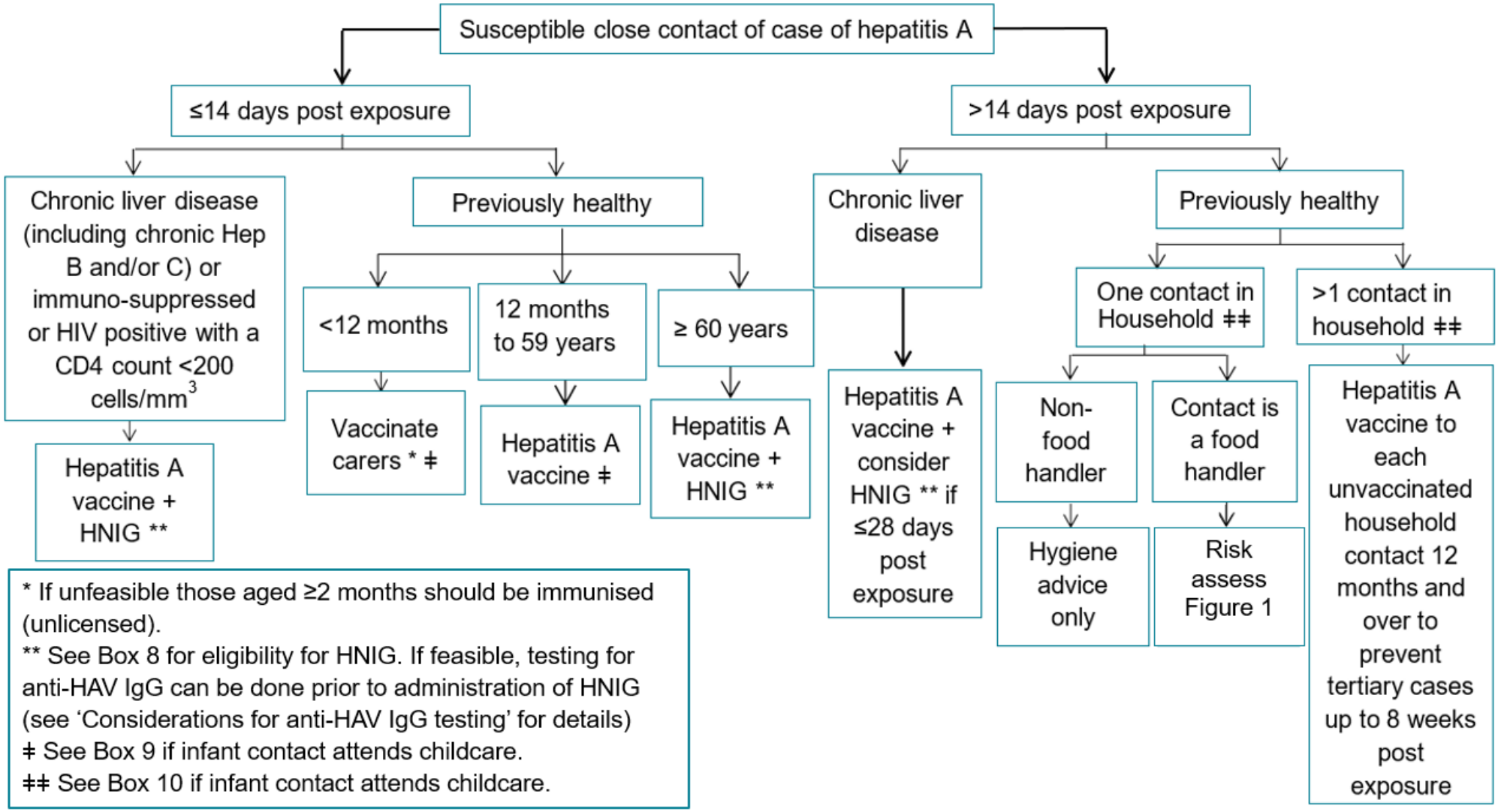


Figure 2. Algorithm for management of susceptible close contacts

This is a graphic version of boxes 9 and 10.



1.6 Management of contacts where index case attends a high risk setting

In this section, the management of contacts is considered where the index case works in a job and/or attends a setting (beyond the household) where the nature of their role or duties, or the interactions with others may be equivalent to close contacts in a household setting.

Box 11. Management of contacts where index case attends a high-risk setting

Index case is a food handler in a workplace

Food handler including those working in the health and social care setting

Recommendation

If the index case is a food handler (see Table 1) the health protection team in conjunction with Environmental Health colleagues should carry out an assessment of the risk that transmission of infection may have occurred within the workplace. As part of the risk assessment, it is often helpful to visit the establishment and interview the supervisors in addition to the index case to understand their duties. Individuals (including staff and patients) who have had potential repeated faeco-oral exposure to the index case (for example, eating food prepared by the index case or assisted with feeding and toileting) and are identified within 14 days of the last exposure, should be offered vaccine, with or without HNIG as appropriate (see Box 8).

Rationale

Outbreaks of hepatitis A have occurred as a result of infected food handlers contaminating food. There is evidence of the effectiveness of post exposure immunisation within 14 days of exposure.

Index case attends pre-school or primary school settings

Pre-school childcare and reception classes (early years)

Recommendation

In early years childcare settings such as a nursery or child minder (for example, those working, or being cared for, in the same room as the index case) a restricted group of individuals whose risk of acquiring infection is equivalent to the risk in a household setting should be identified and managed as close contacts if the index case is identified within 14 days. When this is not possible, immunisation of a larger group (whole classroom or beyond) can be considered on a case-by-case basis.

As asymptomatic infection is common in pre-school children, if vaccine cannot be administered to close contacts within 14 days of exposure to the index case consider i) extending immunisation to all children in that setting; and ii) immunising household contacts to prevent tertiary transmission. In addition, it is important to consider the source of infection, for example, recent travel, as is recommended for a case in primary school (see section below).

Oral fluid testing of household contacts may be carried out (on discussion with Colindale VRD) to identify household transmission, and therefore indicate a likely external source to the early years setting. Pre-reception children may attend multiple childcare settings. When this is the case, all childcare settings should be considered as a potential source.

If no source of infection can be identified outside the early years setting (for example, history of travel, known contact with hepatitis A outside the school, household member with oral fluid confirming recent hepatitis A infection), the case may have acquired the infection through asymptomatic transmission within the early years setting. In these circumstances offering hepatitis A vaccine to all children and adults within a defined group at risk in the early years setting may prevent continuing transmission. A risk assessment is required to determine if a small group can be defined to minimise unnecessary immunisation (see section on primary school settings below).

If more than one case occurs in this setting, wider immunisation should also be considered as it could be considered a cluster.

Rationale

Asymptomatic hepatitis A infection is common in pre-school and reception class children. As there is poor hygiene among pre-school children, secondary and tertiary transmissions are likely to occur with a considerable risk of onward transmission to household contacts of exposed children. Contacts of an index case in a pre-school childcare setting and reception class should therefore be considered equivalent to household type contacts and may be protected by post-exposure immunisation within 14 days of exposure. However, in practice when nursery or school groups are large the risk may not be equivalent to household settings for all contacts. Immunising larger groups increases the likelihood of immunising individuals unnecessarily and decreases the cost-benefit of the intervention. Hence efforts should be made to identify a restricted group of contacts in these settings.

If more than 14 days has elapsed, some exposed children may be incubating the virus so immunisation of other children in that setting and household contacts of the exposed children could interrupt onward transmission in to the community.

A single case of hepatitis A in an early years setting with no external source indicates that the case may have acquired infection within this setting. This means there are at least 2 cases (index case and unidentified asymptomatic case) in the early years setting, that is, a cluster.

While efforts should be made to improve hygiene standards, this is difficult to enforce and maintain among young children, and immunisation is therefore likely to be necessary to interrupt transmission.

Oral fluid testing in nursery settings has demonstrated recent infection in children in the same group as the index case.

Primary school setting excluding reception classes

Recommendation

When a single case of hepatitis A occurs in a primary school, either in a child or an adult member of staff, an assessment should be carried out to try to identify the source of infection. In the absence of a clear source of infection for example, recent travel, oral fluid testing of household contacts may be carried out to identify household transmission, and therefore indicate a likely external source to the school. Before undertaking oral fluid swabbing, it should be discussed with Colindale VRD.

If no source of infection can be identified outside the school setting (for example, history of travel, known contact with hepatitis A outside the school such as household member with oral fluid confirming recent hepatitis A infection), the case may have acquired the infection through asymptomatic transmission within the school. In these circumstances offering hepatitis A vaccine to all children and adults within a defined group at risk in the school may prevent continuing transmission. A risk assessment is required to determine whether a small group at risk can be defined (for example, close friends of the index case within the school) or whether wider immunisation in the same class, year, multiple years or whole school may be appropriate. Factors to consider include the degree of mixing between classes and years at play and meal times, whether different years share hand washing and toilet facilities.

Rationale

Asymptomatic acute hepatitis A infection is more common in infants and young children. A single case of hepatitis A in a school with no external source indicates that the case may have acquired infection within the school. This means there are at least 2 cases (index case and unidentified asymptomatic case) in the school (a cluster). Hygiene is poorer among younger children which facilitates onward transmission in this setting.

While efforts should be made to improve hygiene standards, this is difficult to enforce and maintain among primary school children. Oral fluid testing in primary school settings has demonstrated recent infection in children in a different class or year from the index case.

Hepatitis A vaccine has been used successfully to interrupt tertiary transmission and control outbreaks, including in primary schools. The effectiveness of immunisation depends on how

well the at-risk group is defined, the vaccine uptake achieved, and the time elapsed since exposure to existing cases.

Index case attends other school or higher education or other workplace

Secondary school and higher education and other workplace including hospitals

Recommendation

Hepatitis A post-exposure prophylaxis is not usually indicated when a single case has occurred in a secondary school, college / university, other work place or hospital. When a case occurs in a secondary school setting, the school should be given recommendations about the importance of appropriate hygiene measures and parents of children in the same class should be informed of the risk of possible exposure. However special consideration may be given where a single case has occurred within a non-residential special educational needs school; further action may be based on a local risk assessment. In hospital settings it is assumed that discussions with the Infection Control Team (ICT) would occur in the event that a healthcare worker is infected.

Rationale

Even if no external source is identified, a single case likely acquired infection outside these settings. Secondary attack rates are lower in these settings as hygiene standards are generally better than in pre-school and primary school settings (however the exception may be in some special educational needs schools) and contact is generally not equivalent to household type exposures. Reinforcing hygiene measures alone should be effective in preventing onward transmission. Asymptomatic infection is less likely in older children and adults so cases are more likely to be detected.

Box 12. Example scenario: index case is a carer in a residential home setting (care home, nursing home or residential setting for people with learning disability)

Post-exposure prophylaxis against HAV is not usually indicated when a single case has occurred in a hospital, secondary school, college/ university or work place, as transmission of HAV is generally limited to household-type close contacts. However, in closed settings such as residential care or nursing homes housing elderly or otherwise vulnerable residents who may require intensive assistance with activities of daily living, for example, toileting and eating, there may be a risk of onward transmission and risk of severe disease among vulnerable residents. In these settings it can often be difficult to implement stringent infection control precautions, as one would expect in a hospital setting. Although reports of transmission from carer to vulnerable residents are rare, these have necessitated wider immunisation of staff and residents within the home, to prevent continuing transmission and poor outcomes among vulnerable residents.

On receiving notification of a single case in a carer in this setting, a careful assessment of the risk of onward transmission and identifying close contacts within the home, is essential to preventing secondary transmission. Experience of the management of an unusual transmission incident from a carer to a vulnerable resident in a residential care home in the East of England highlights nuances in the risk assessment in this setting. The index case was a care worker who had recently travelled to a high-endemicity country, and the second case was a resident looked after by the index case at the nursing home where the index case worked demonstrating that infected care workers can potentially spread the disease to elderly patients and other groups at risk of severe complications from HAV infection.

Factors to consider in the risk assessment if index case was working as a carer during the infectious period

Assessment of risk to vulnerable contacts:

1. What are the carer's duties? A detailed understanding of the nature of their duties will be essential – assistance with feeding, toileting, food handling.

2. Did they look after only one resident or others as well? (Gives an idea for the scale of the potential problem)

3. If a food handler, did they prepare or serve food in the infectious period? If so, how often?

4. Did they have diarrhoea at any point whilst at work? If yes, and helping with feeding or personal care, have a low threshold for considering this as a close contact and offer post exposure prophylaxis to that contact.

5. Did they at any point have direct hand contact with food? If yes, offer post exposure prophylaxis to relevant contacts.

6. Did they consistently use personal protective equipment (PPE), gloves and so on while feeding? Inconsistent use of gloves while assisting in toileting has been identified as a risk factor in an outbreak among adults in a developmental disability home. General understanding of infection control and hygiene practices will also guide the risk assessment.

Assessment of transmission risk to colleagues in the work place:

1. Did the index case share accommodation or food with other members of staff? If yes, consider these individuals as household contacts and offer post exposure prophylaxis to relevant individuals.

2. At work, did they regularly share toilet facilities with other members of staff? If yes, consider factors such as access to handwashing, toilet cleaning regimen, whether the index case had diarrhoea, in deciding whether relevant members of staff would be considered as close contacts and offered post exposure prophylaxis.

3. Consider a visit to the home to get a better understanding of infection control practices.

1.7 Management of local outbreaks

The previous sections of the guidance covers management of a single case of hepatitis A and their contacts. When epidemiological and/or microbiological associations suggesting wider spread have been established, an outbreak should be considered.

Examples of outbreaks include:

- 2 or more cases in different years in the same primary school who are not close contacts outside school
- 2 or more cases in a nursing or residential home
- a cluster of cases with an identical strain in a community with a defined geographical or social network
- 2 or more cases in different households in the same social network
- a cluster of cases associated with a single food item, single event or single location (including a single location overseas such as a holiday resort or hotel)

Multi-agency response

Management of local outbreaks of hepatitis A, for example, in a school, hospital, residential care, prison or community requires a multi-agency response. An outbreak control team (OCT) or incident management team (IMT), should be convened by the local health protection team.

In the event of an outbreak associated with overseas travel, the UKHSA National Hepatitis Team and the UKHSA Travel and Migrant Health section should be informed.

For details of membership and actions of an outbreak control team, please refer to the Communicable disease outbreak management: operational guidance.

For hepatitis A outbreaks, the following persons should also be considered for inclusion in an outbreak control team:

- commissioners and/or providers (Integrated Care Board representative, NHS England)
- depending upon the setting, representatives as appropriate from the implicated institutions, for example, a school nursing service,
- UKHSA National Infection Service –Virus Reference Department clinical scientist or consultant virologist
- UKHSA National Infection Service – Blood Safety, Hepatitis, STI and HIV Division (or Immunisation and Vaccine Preventable Diseases Division) clinical scientist or consultant epidemiologist
- UKHSA Travel and Migrant Health Section senior scientist or consultant epidemiologist (for national outbreaks associated with overseas travel only)

Expert advice on outbreak investigation and management is available from the Blood Safety, Hepatitis, STI and HIV Division, and expert advice on laboratory investigation is available from the Virus Reference Department (VRD), both at UKHSA National Infection Service, Colindale (020 8200 4400).

Before the OCT/IMT is convened, as much information as possible should be obtained to inform the risk assessment. Laboratory samples from all cases should have been referred to the reference laboratory and additional tests (for example, oral fluid testing, sequencing) should have been discussed with VRD, Colindale.

For detailed information please refer to Appendix 6 of the Communicable disease outbreak management: operational guidance.

Considerations of the IMT/OCT

In suspected hepatitis A outbreaks the OCT / IMT should pay particular attention to:

Initial response

- confirming validity of information on which outbreak is based – requires laboratory confirmation of initial cases
- relevant clinical and demographic features of cases: onset and nature of symptoms and signs
- outbreak and case definitions noting that the outbreak definitions may change as the incident evolves. The characteristics of person, place and time can inform a working case definition that can be refined by the laboratory results
- identification of population at risk
- agree early and active case finding
- if there are close contacts identified who would be subject to follow up in the UK but have travelled overseas, contact the UK International Health Regulations National Focal Point for advice

Epidemiology

- descriptive: person (age, sex, ethnicity, country of birth, occupation, contacts), place (residence, setting of outbreak, travel), time (onset of symptoms and jaundice, key events); food questionnaire findings of note
- hypothesis generating: source of infection and routes of transmission
- consider analytical studies to test hypothesis

Microbiology

- review RNA, oral fluid and serum serology results
- timing of samples in relation to onset of symptoms
- review sequencing and phylogeny to confirm or refute epidemiological findings, indicate geographical or food origin, and link to other known outbreaks

- consider further clinical and environmental samples for testing for example, oral fluid in household contacts

Risk assessment

- likelihood of continuing public health risk to guide decision-making and implement immediate control measures

Operational issues

- consider implementation of wider immunisation in schools, community or residential care settings, including funding, staffing, patient group direction (PGD), cold chain, venue options and suitability (GP surgery, mobile vaccine bus or sentinel schools)
- consider vaccine procurement options (Colindale IVPDD team can alert manufacturers and connect OCT/IMT with vaccine supply teams)

Communications

- agree a communication strategy
- agree lead organisation for media responsibility if multiple agencies involved

Control measures

- review actions already taken and consider future interventions: post exposure prophylaxis, local authority environmental health assessment, reinforcing hygiene, communications, wider immunisation, exclusions from work

De-escalation

- agree definition of end of the outbreak, for example, no linked cases over 2 incubation periods)
- produce an outbreak report and lessons learnt

Outbreak interventions

Recommendation for vaccine and/or HNIG prophylaxis for outbreaks

Monovalent hepatitis A vaccine is the preferred prophylaxis for use in an outbreak setting. Those immunised should be informed that they should receive a second dose of vaccine 6 to 12 months after the first dose to ensure long term protection. However, this second dose is not necessary as part of outbreak control.

HNIG should be offered in addition to vaccine for those who are at particular risk of severe disease as described in section 1.5 and if they fulfil the criteria for a close contact after a detailed risk assessment has been conducted (it is therefore given as post-exposure prophylaxis). However, if immunisation is being offered to that individual as part of an attempt to interrupt wider transmission in the population, vaccine only should be offered.

Summary of evidence base around vaccine use in outbreaks

Prior to the introduction of hepatitis A vaccine, HNIG was used to control outbreaks. Once the vaccine was introduced a combination of the 2 was used successfully in well-defined communities and in general population outbreaks in low endemicity areas. Evidence suggests that vaccine is effective in preventing disease both pre and post exposure. Vaccine has the potential to reduce clinical cases and limit the sub-clinical infections that play an important role in maintaining outbreaks. Widespread vaccine prophylaxis may have limited success in preventing secondary cases if exposure occurred more than 14 days before prophylaxis is given. However, vaccine is particularly useful at preventing tertiary infection and thus interrupting ongoing transmission.

The effectiveness of mass immunisation depends on how well the at-risk population is defined, the susceptibility of the population, the endemicity of the area, the coverage achieved with the intervention and the time elapsed since exposure to existing cases. There is some evidence that wider immunisation targeting groups who are likely to be susceptible and be able to spread infection most efficiently (for example, children) may be effective in closed communities or settings (for example, schools) and small, open communities (for example, small towns or villages). However, there is a lack of evidence on impact of immunisation in outbreaks in large open communities even if high coverage is achieved. An alternative strategy to mass immunisation includes immunisation of household and other close contacts.

Environmental cleaning

Excellent hygiene practice and environmental cleaning can interrupt transmission. Environmental cleaning should include: Increasing regular cleaning of surfaces, equipment and toys using normal detergent, particularly frequently touched surfaces – taps, door handles, stair rails, light switches, computer keyboards, at least twice daily is recommended in an outbreak. In nurseries and early years settings suspend use of communal soft toys or equipment, water, soft dough and sand play. Efficient hand washing is essential to prevent spread and should be closely monitored, particularly with younger children.

Intervention options in specific outbreak settings

To inform consideration of intervention options in outbreak settings, a review of outbreaks reported to Health Protection Teams between 2011 and 2015 was undertaken. The findings are summarised in section 2.4.

Outbreaks in closed settings

Educational institutions

Two or more cases of probable/ confirmed hepatitis A in students or staff at a school or nursery indicate an outbreak, unless there is epidemiological and microbiological evidence suggesting they are unlinked. In outbreaks in educational settings, the risk assessment should consider whether:

- a human source in school is most likely

- a population at risk can be defined (same class, same year, multiple years or whole school)
- improved hygiene will be sufficient to interrupt transmission
- there is evidence of spread in the wider community which may require a broader approach

In primary schools and pre-school childcare (early years) settings, as hand hygiene is poor and environmental cleaning difficult to enforce, and secondary transmission quite common, wider immunisation is recommended. In secondary schools, immunisation is not routinely recommended but may be considered if hygiene practices are not thought to be sufficient to interrupt transmission.

To facilitate containment of transmission at an earlier stage after identification of an index case and to avoid unnecessary testing and immunisation in schools when an external source has not been identified, VRD can test oral fluid from household contacts of a confirmed acute hepatitis A case where the index case is a child (under 16 years at school) or is a member of teaching staff at the school (see section on Oral fluid testing).

It is important to define a group at risk in which to intervene that makes sense epidemiologically and locally. For example, immunising only the classes or years of the cases may not be appropriate if they have siblings in different classes or years and/or if there is a lot of mixing between years at meal and play times and/or different years or classes share hand washing and toilet facilities. This is supported by oral fluid testing in primary school and nursery outbreaks settings where recent infection in children in a different class or year from the index case has been demonstrated.

Care homes

While the potential of outbreaks associated with infected food handlers or food items are well reported (5), care homes have also been implicated in outbreaks. Nursing or residential care homes housing elderly or other vulnerable residents pose challenges in implementing stringent infection control arrangements and hygiene practices. Staff at these facilities often have multiple roles such as preparing food and assisting residents with their toileting. There is a risk of onward transmission and risk of poor clinical outcomes in a more vulnerable group.

Reports of transmission from carer to vulnerable residents are rare but have been documented. A report of an outbreak in a developmental disability home for adults in the USA highlights the risk posed to unvaccinated vulnerable residents and the significant public health resources required to manage such outbreaks (6). These demonstrate that infected care workers can potentially spread the disease to elderly patients and other groups at risk of severe complications from HAV infection.

If 2 or more linked cases occur in a care home setting, given the limited potential for hygiene alone in preventing ongoing transmission within these settings and the complex staff and resident mixing patterns, wider immunisation (beyond post exposure prophylaxis to close contacts) to staff and residents within the home to prevent tertiary transmission should be considered. This would be in addition to environmental cleaning.

A careful risk assessment should be conducted to inform whether immunisation can be offered to a defined sub-group of staff and patients (for example, same unit or floor) or to all residents and staff identified within the home.

The risk assessment should consider:

- whether the cases in members of staff or residents or both?
- whether a food source or a human source is more likely?
- where are the cases located? (for example, same floor, same unit, linked by common staff members)
- do the genotyping and sequencing results indicate linked cases?
- can a population at risk be defined among residents and staff?
- how much time has elapsed from the onset of symptoms in the cases?
- what are the logistical implications (for example, size of home) of a decision to offer vaccine and /or HNIG to all staff and residents?
- a visit to the home to inform the risk assessment – to understand lay out, staff movements, staff duties, infection control arrangements and hygiene practices.

Outbreaks in community settings

In a community outbreak associated with person to person spread in addition to reinforcing hygiene messages, immunisation options are wider mass population immunisation or immunisation of household and close contacts.

The risk assessment should consider the following factors that may influence the vaccine strategy:

- the likely transmission networks, for example, household and social networks, adults versus children, to identify whether a population at risk can be sensibly and practically defined
- the size of the community – whether a small, discrete geographical area such as a village or small town versus large sprawling conurbation
- infectious disease dynamic parameters: proportion of population that are susceptible and expected vaccine uptake. While these are rarely known for a defined population, as the basic reproduction number is likely to be less than 2 for hepatitis A in an average population in England, achieving vaccine uptake of 50% or more may be effective in slowing an outbreak (see section on evidence of vaccine use in management of outbreaks)

How community-wide immunisation campaign is implemented will vary according to local intelligence, population acceptance of immunisation, human and financial resource and availability of an appropriate immunisation site or venue.

For example, if the outbreak covered a particular area and was thought to be predominantly spread by school-aged children, immunisation could be done in schools in that catchment area. Targeting schools to immunise children may achieve higher vaccine uptake in a ‘captive’ group

and who have poorer hygiene and are likely the focus of spread, thus creating a ‘buffer’ of immune children to interrupt ongoing community transmission.

Venues for immunisation include schools as described above, GP vaccine surgeries, mobile vaccine bus, places of worship, community centres. Excellent community communications and social mobilisation are needed for adequate vaccine coverage to interrupt transmission in the wider community.

Part 2. Background and rationale

2.1. Hepatitis A: the disease

The hepatitis A virus (HAV) is a non-enveloped positive stranded RNA picornavirus which is transmitted by the faecal-oral route. In developed countries person-to-person spread is the most common method of transmission (7), while in countries with poor sanitation faeces-contaminated food and water are frequent sources of infection (8). Hepatitis A infection can also be spread during sexual intercourse and through injecting drug use (8), and there have been a number of recent outbreaks among gay, bisexual and other men who have sex with men (GBMSM) (9, 10) and persons who inject drugs (PWID) (11) in the UK.

The average incubation period of hepatitis A virus is around 28 days (range 15 to 50 days) (8). The course of hepatitis A infection is extremely variable. In children under 5 years of age 80 to 95% of infections are asymptomatic while in adults 70 to 95% of infections result in clinical illness (12). Severity of symptoms increases with age (8). Clinical features include a high temperature, flu-like symptoms, nausea and vomiting, abdominal pain, diarrhoea or constipation, pale stools, dark urine, itchy skin and jaundice (yellowing of the skin and the whites of the eyes). Fulminant hepatitis occurs rarely (less than 1% overall but has been reported in the UK (13)), but rates are higher with increasing age and in those with underlying chronic liver disease, including those with chronic hepatitis B or C infection (12). Infection during pregnancy is associated with maternal complications (14 to 16). Hepatitis A does not appear to be worse in HIV-infected patients when compared to HIV uninfected persons (17), which may reflect the fact that the hepatitis damage in hepatitis A is thought to be the result of host immune mechanisms (18). Infection is followed by lifelong immunity.

Hepatitis A virus is excreted in the bile and shed in the stools of infected persons. Peak excretion occurs during the 2 weeks before onset of jaundice; the concentration of virus in the stools drops after jaundice appears (19) but may persist for more than 40 days (20). Children may excrete the virus for longer than adults, although a chronic persistent state does not exist.

Transmission of hepatitis A infection within households is very common. Recent studies have found secondary attack rates in susceptible household contacts of 12% in Italy (21), 19% in Greece (22), 25% in Kazakhstan (23), and 34% in Brazil (24).

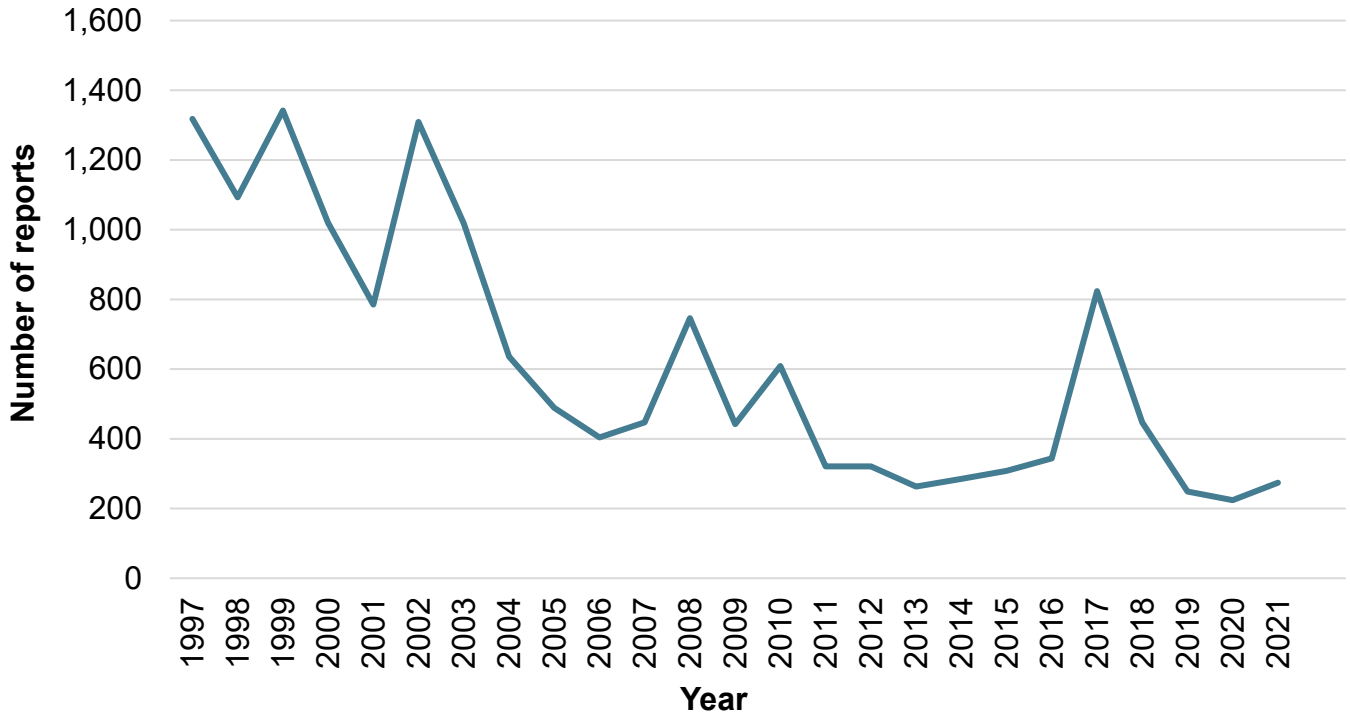
Children under the age of 6 years are particularly effective transmitters of hepatitis A infection (23, 25) and during outbreaks asymptomatic children have been identified as the source of secondary spread (26). Hand hygiene is important in preventing spread (27, 28). Transmission from children is common, with secondary attack rates of between 2.6% and 27.6% reported in nurseries or day care centres (29 to 34) and secondary attack rates of between 2.9% and 50% reported in primary schools (35 to 37) in Europe and the US.

Foodborne outbreaks can occur due to the contamination of food at the point of service or due to contamination during growing, harvesting, processing or distribution. Foodborne outbreaks may be under-reported (38) and recent national and international foodborne outbreaks have been found to be associated with various foods including sundried tomatoes (39 to 43), frozen berries (44 to 48), mussels (49) and frozen pomegranate arils (50). A review of published food borne outbreaks in the USA found that infected food handlers who handled uncooked food, or food after it had been cooked, during the infectious period were the most common source of published foodborne outbreaks (5). A single hepatitis A infected food handler has the potential to transmit hepatitis A to large numbers of people, although reported outbreaks are rare. Such outbreaks often involve secondary cases among other food handlers who ate food contaminated by the index case (5).

2.2 Epidemiology of hepatitis A in England and Wales

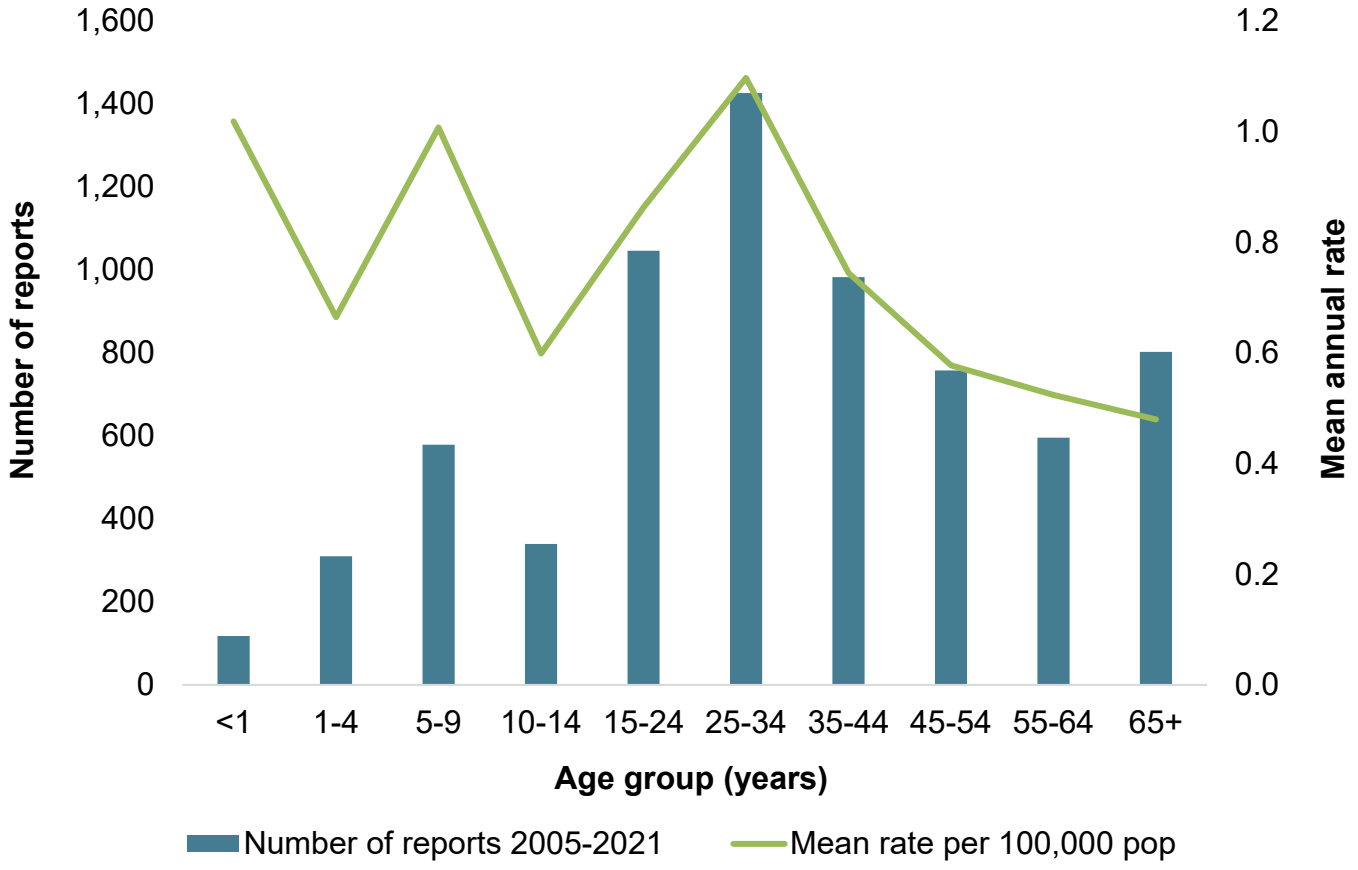
As in other developed countries, the number of hepatitis A infections in England and Wales has fallen dramatically over the past 15 years (51). The number of laboratory reports of hepatitis A in England and Wales has fallen from 1,318 in 1997 to 274 in 2021, with a resurgence in 2016 to 2017 assoicated with a national outbreak mainly among gay, bisexual and other men who have sex with men (GBMSM). The impact of the COVID-19 pandemic including personal and social distancing, travel restrictions, health service disruption and reduced access, and reduced reporting by laboratories likely contributed to a lower number of laboratory reports in 2020 with some evidence of recovery in 2021 (see Figure 3).

Figure 3. Annual laboratory reports of hepatitis A for England and Wales 1997 to 2021 in England and Wales



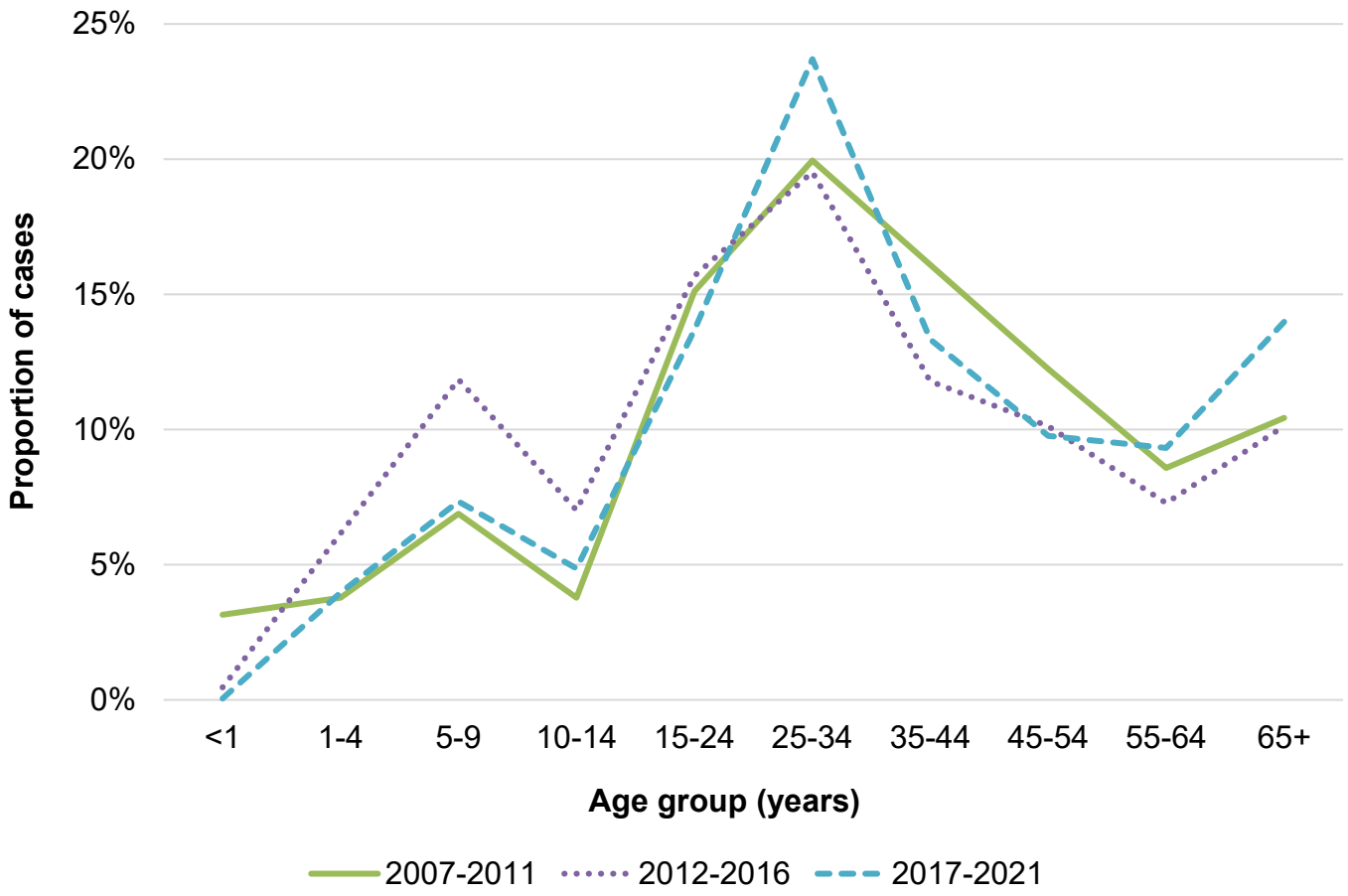
While acknowledging caveats around differential case ascertainment because of asymptomatic infection, and differing testing, diagnosis and reporting practices, the rate of laboratory confirmed cases of hepatitis A shows an age-related trend with the highest rates in young adults, a very small number of reported cases in children under one year, a rise in early childhood (5 to 9 years old) and the majority of cases in adults (see Figure 4). There has been a mild increase in the proportion of cases reported in over 65 year olds over the last 5 years. They accounted for 10% of cases in 2007 to 2016 and 14% of cases from 2017 to 2021 (see Figure 5).

Figure 4. Number of reports and mean annual rate of laboratory reports of hepatitis A per 100,000 population[1] by age group for 2005 to 2021 in England and Wales



[1] ONS mid-year population estimate.

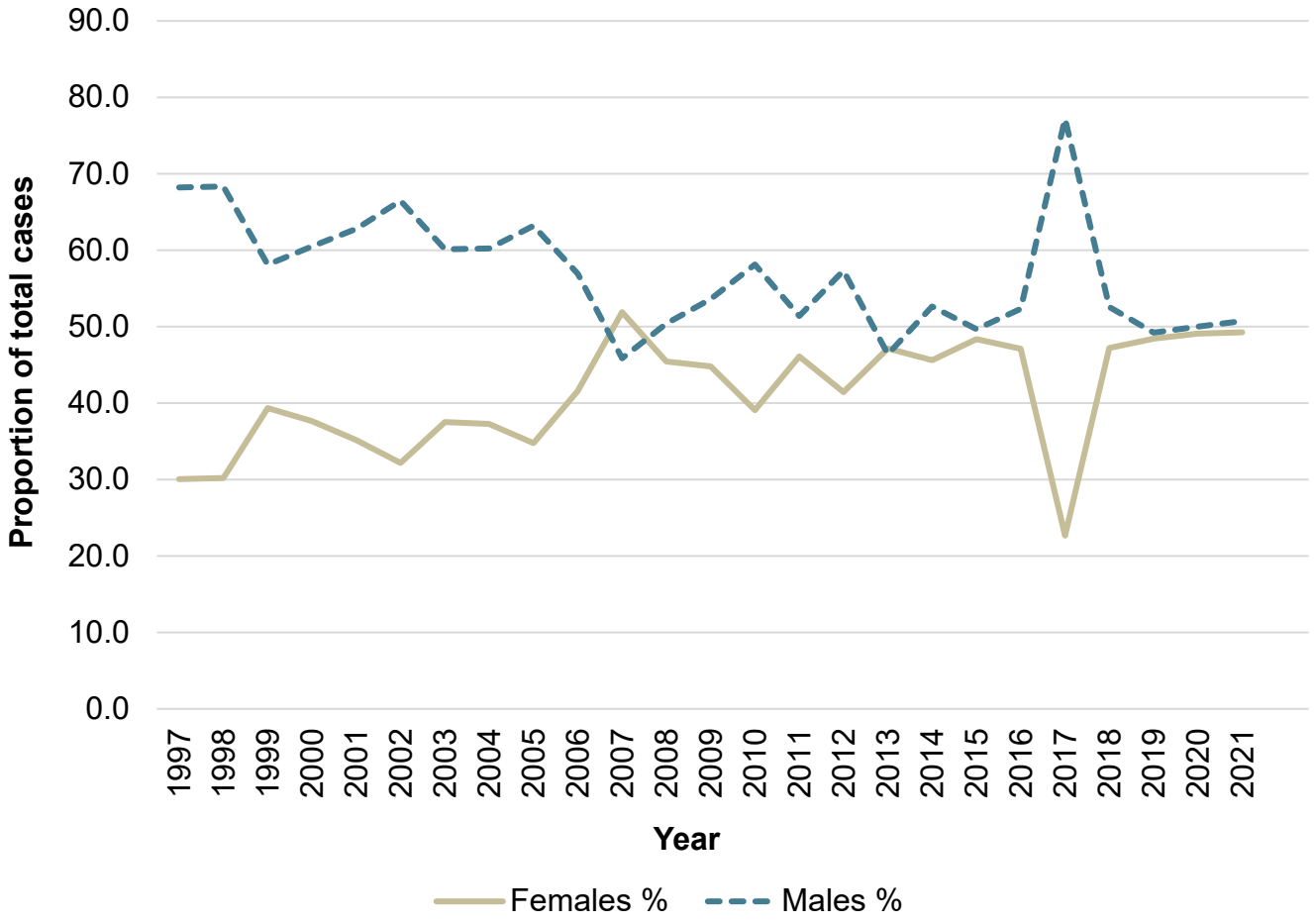
Figure 5. Proportion of annual laboratory reports of hepatitis A by age group for 1998 to 2014 in England and Wales



The low rates of laboratory reports in children under 5 is likely to reflect the fact that infection is commonly asymptomatic or mild in this age group and that they have a lower likelihood of exposure. The increase of reports in children between 5 and 9 years old is possibly linked to pre-school settings attendance and consequent increased exposure compared to earlier years. The high rates of laboratory reports in young adults will be influenced by a number of outbreaks in GBMSM and PWIDs in 2000 to 2005 and the large outbreak mainly in GBMSM in 2016 to 2017, but may also be contributed to by travel to endemic countries (9 to 11). The decline in rates of laboratory reports from early adulthood is likely to reflect the increase in seroprevalence (and thus decline in susceptibility) with age due to immunisation or infection.

The proportion of male cases decreased from 68% in 1997 to 51% in 2021 (see Figure 6).

Figure 6. Proportion of annual laboratory reports of hepatitis A by gender 1997 to 2021 in England and Wales

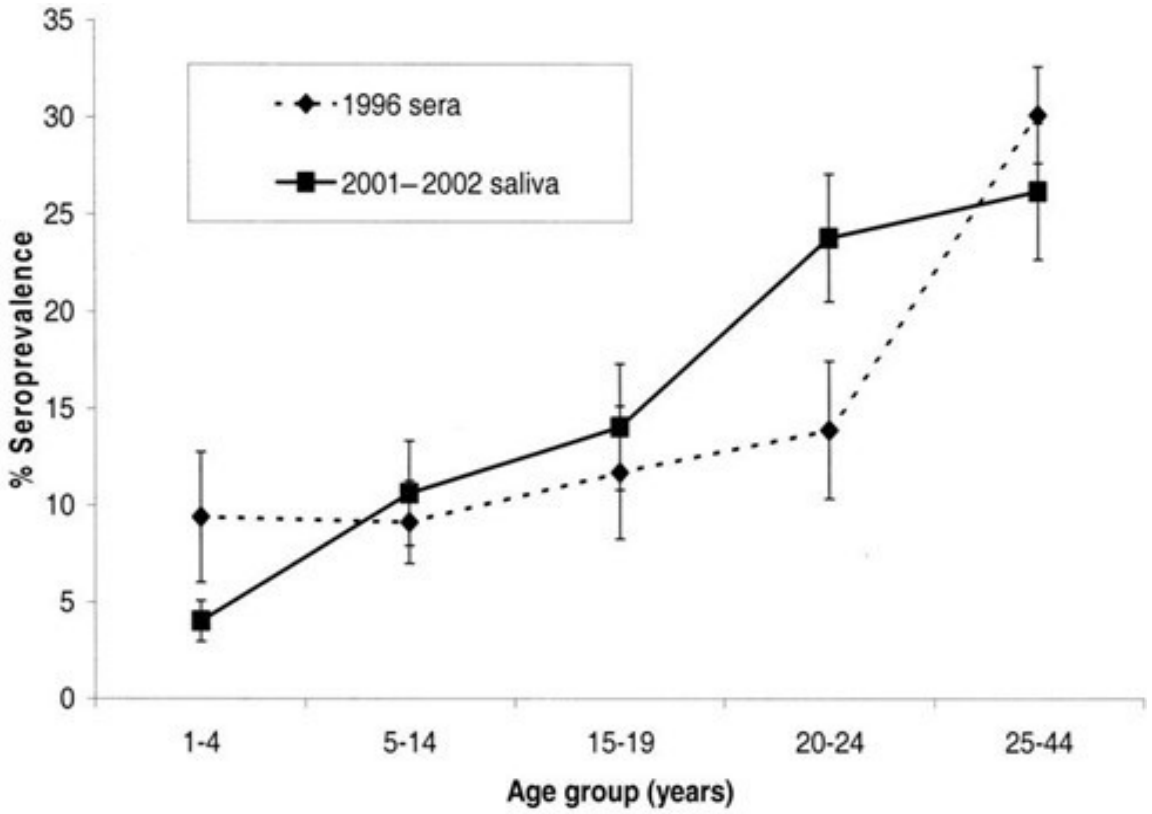


The figure presents the proportion of annual laboratory reports where sex was known. On average, only a small percentage of cases did not have sex information reported (2% annually). The increase in case numbers in 2017, and the larger proportion of HAV reports in males compared to females, coincides with the national HAV outbreak predominantly among GBMSM.

Routine data from statutory notifications and laboratory reports contains very little information on risk factors for disease acquisition. However, a study on routine laboratory reports between 1992 and 2004 found that rates of infection were more than double in persons with names indicating a South Asian ethnic origin (52). The study also found that travel was an important risk factor with 85% of those of South Asian origin acquiring their infection abroad. Unfortunately, the completeness of systematically reporting of travel history is low so describing trends is challenging. A project aiming to improve the collation of travel history for cases of hepatitis A using multiple sources, estimated that in 2013 and 2014, 46% (N=120) and 69% (n=170) of cases respectively had a reported travel history. Of these, a total of 214 cases in 2013 to 2014 had reported recent travel abroad before their hepatitis A infection. The most commonly reported countries of travel reported were: Pakistan (57), India (25), Egypt (19), Morocco (11), Romania (8), Somalia (5), Philippines (5), Afghanistan (5), Hungary (4) and Greece (4). Where information was available (N=102), visiting friends and relative was the most common reason for travel (n=66, 65%) (53).

A study of residual sera from 4188 individuals in England and Wales in 1996 demonstrated a rise in seroprevalence from 8.6% in those aged 1 to 9 years to 73.5% in those aged over 60 years (54). A later study, in 2001 to 2002, of approximately 5,500 oral fluid samples on persons aged less than 45 years from across England and Wales also showed an increase in seroprevalence with age, from 10% in those aged less than 1 year to 26% in those aged 25 to 44 years (55). Seroprevalence was higher amongst those of non-white ethnicity (44.1% in South Asians, 41.2% in Blacks and 33.8% in those of mixed race) and natural HAV infection (seropositivity in non-vaccinees) was independently associated with South Asian and mixed ethnic groups on logistical regression analysis.A smaller study based on oral-fluid testing of 257 children aged 7 to 12 years in an ethnically diverse region of northwest England found a similar raised seroprevalence in Indian (54.1%) ethnic groups and in children born outside the UK (54.1%) (56).

Figure 7. Comparison of hepatitis A virus seroprevalence estimates in England and Wales from 2001 to 2002 oral fluid survey with a 1996 population-based seroprevalence survey by Morris-Cunnington and others (55)



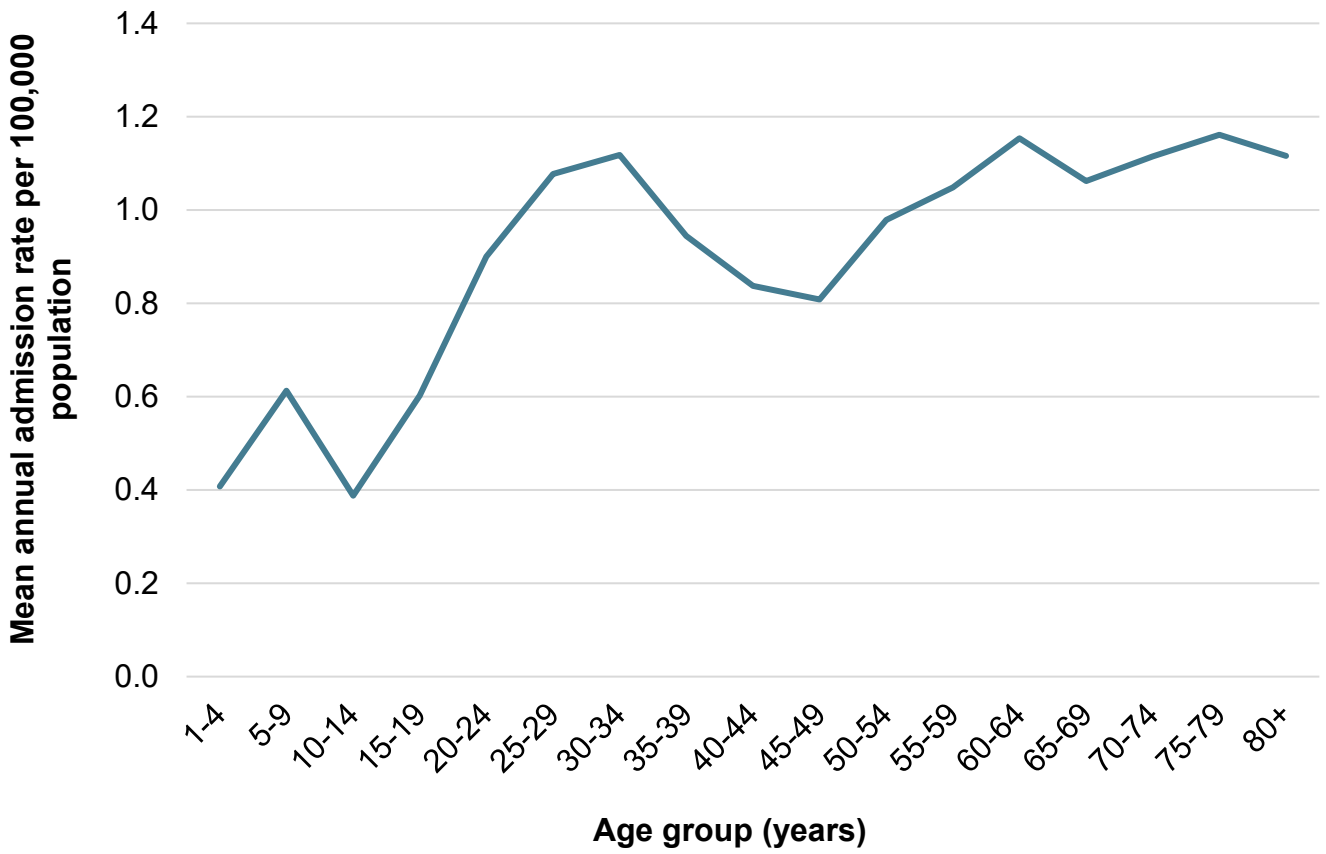
Source: Morris-Cunnington MC, Edmunds WJ, Miller E, Brown DWG. ‘A population-based seroprevalence study of hepatitis A virus using oral fluid in England and Wales’. American Journal of Epidemiology 2004: volume 159, pages 786 to 794, by permision of Oxford University Press.

Whilst acknowledging general under-reporting of viral hepatitis in hospital admission and deaths data, it can give an indication of severe morbidity and mortality from acute hepatitis A infection. From 2005 to 2021 inclusive, Hospital Episode Statistics (HES) data recorded 9,540 individuals

admitted with a diagnosis of hepatitis A infection in England. This includes 2,743 individuals who were admitted on more than one occasion with a diagnosis of hepatitis A infection (so may include coding errors as well as true re-admissions for hepatitis A), making a total of 15,500 episodes, ranging from 393 to 1,010 admissions per year, where the highest admission episodes coincided with the large outbreak in GBMSM in 2017.

The mean annual admission rate was higher in people aged 30 to 34 and in people aged 60 and above (see Figure 8). Length of hospital stay can be used as a proxy for severity of disease. Where multiple records of a patient's length of hospital stay were reported, the episode reporting the highest number of days was used to calculate the average duration of admission: mean = 5 days, median = 2 days. The proportion of individuals who have an episode of hepatitis A greater than 2 days increases with age; with over 60% of over 75 year olds being admitted for over 2 days (see Figure 9). Episode has been used rather than total spell in hospital as it is specific for the duration of admission due to hepatitis A infection.

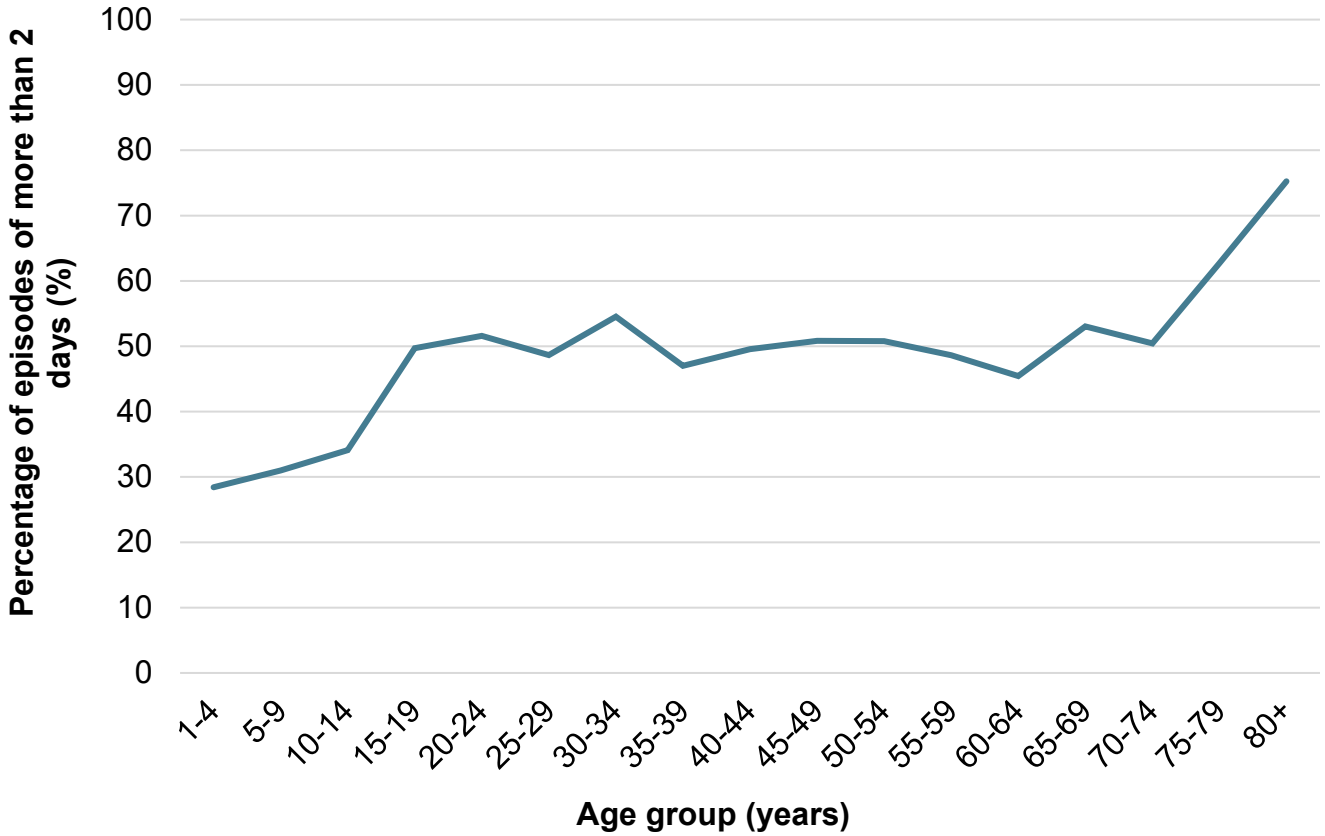
Figure 8. Mean annual admission rate for hepatitis A per 100,000 population by age group 2005 to 2014 in England[2]



[2] Admitted patient care HES figures are available from 1989 to 1990 onwards. Changes to the figures over time need to be interpreted in the context of improvements in data quality and coverage (particularly in earlier years), improvements in coverage of independent sector activity (particularly from 2006-07) and changes in NHS practice. For example, apparent reductions in activity may be due to a number of procedures which may now be undertaken in outpatient settings and so no longer include in admitted patient HES data. Conversely, apparent increases in activity may be due to improved recording of diagnosis or procedure information.Note that Hospital Episode Statistics (HES) include activity ending in the year in question and run from April to March, for example, 2012 to 2013 includes activity ending between 1 April 2012 and 31 March 2013.

Data source: Hospital Episode Statistics (HES) Health and Social Care Information Centre.
Data source: Office for National Statistics: Mid-2011 population estimates, England; estimated resident population by single year of age and sex; based on the results of the 2011 census.

Figure 9. Percentage of all hepatitis A-related hospital admissions which are for more than 2 days duration by age group 2005 to 2021 in England[2]



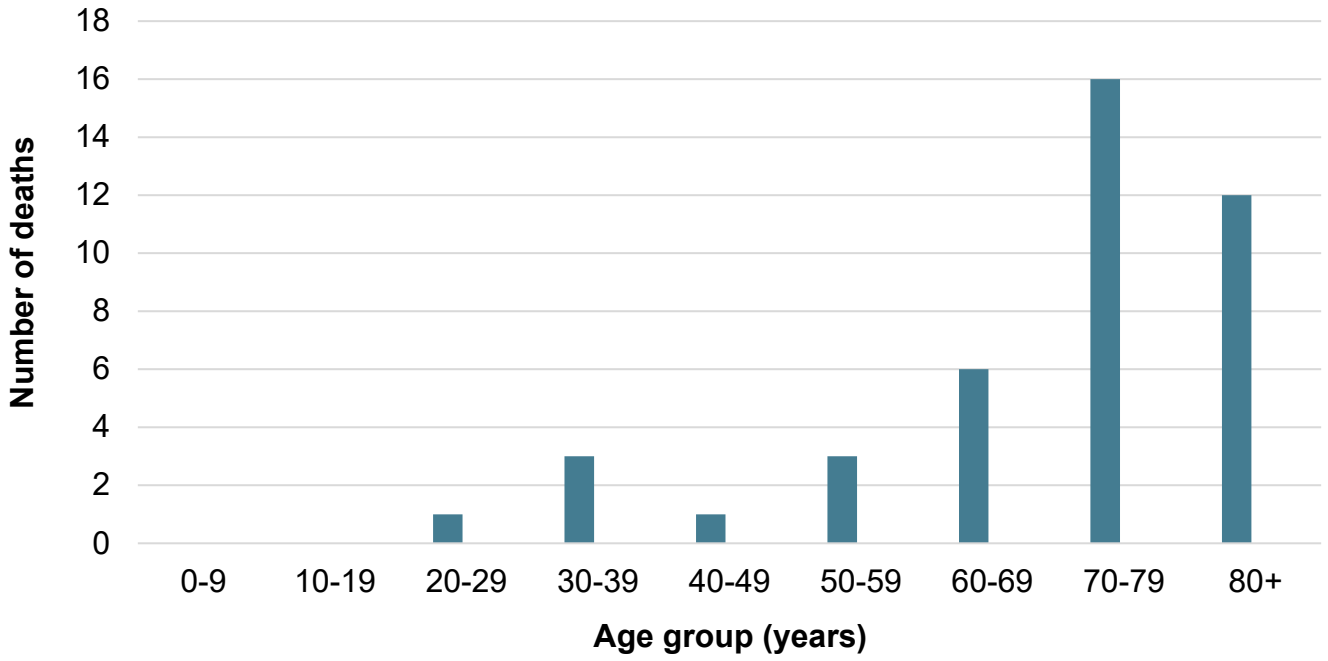
Data source: Hospital Episode Statistics (HES), Health and Social Care Information Centre

A further indication of severe morbidity can be derived from liver transplant data. In the 10 years from 2005 to 2014 inclusive, the UK Transplant Registry recorded one liver transplant performed on a patient with hepatitis A recorded as their primary liver disease at registration, and one patient with hepatitis A recorded at time of transplant. Both of these patients were over 40 years of age.

Hepatitis A is a very rare cause of death in England and Wales. In the years from 2005 to 2021 there were 42 deaths where hepatitis A was written as an underlying cause of death from ONS (see Figure 10). In addition, of the 9,540 individuals recorded in in HES, 263 were noted to have died during their admission (although the death may be unrelated to their hepatitis A infection[3]).

[3] Hospital Episode Statistics data cannot be used to determine the cause of death of a patient while in hospital. Deaths recorded on the Hospital Episode Statistics database may be analysed by the main diagnosis for which the patient was being treated during their stay in hospital, which may not necessarily be the underlying cause of death. For example, a patient admitted for a hernia operation (with a primary diagnosis of hernia) may die from an unrelated a heart attack. The Office for National Statistics collects information on the cause of death, wherever it occurs, based on the death certificate and should be the source of data for analyses on cause of death.

Figure 10. Number of deaths in England and Wales between 2005 to 2021 where hepatitis A was written on the death certificate as an underlying cause of death



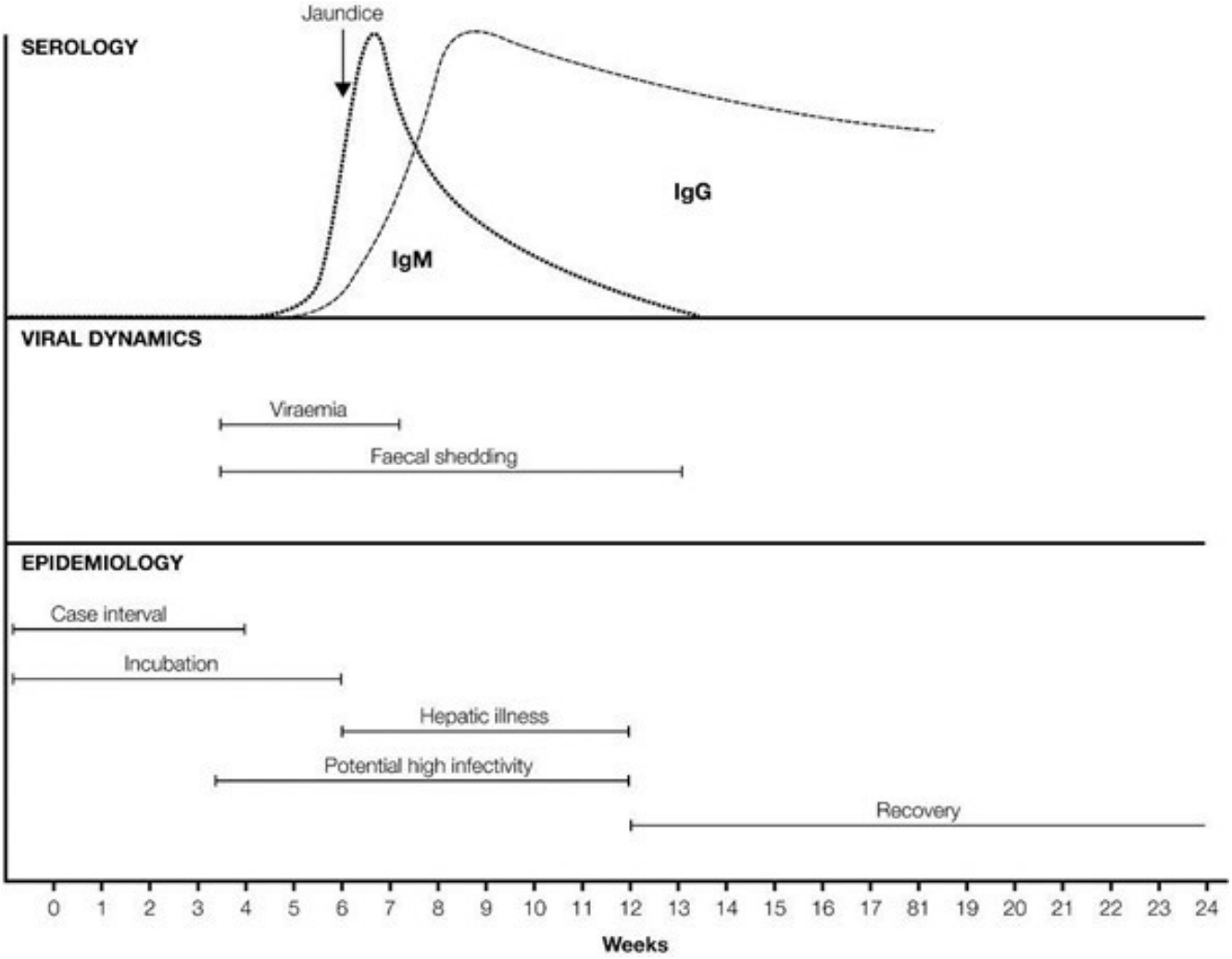
Data source: Office for National Statistics.

Information on co-mordities in people who died was available for 38 deaths in which hepatitis A was likely to have been a cause in England and Wales in the 10 years from 2005 to 2014. Among these deaths 22% (n=8) occurred in patients with chronic liver disease and an additional 5% (n=2) were noted to have had a liver transplant (although it was unclear if this was as a result of or prior to the hepatitis A infection). Also 16% (n=6) of deaths occurred in individuals who had a comorbidity which is likely to have caused immunosuppression by the condition itself or medication to treat the condition (such as cancer). However, 58% (n=22) of deaths occurred in those with chronic conditions (such as kidney disease, chronic obstructive pulmonary disease, diabetes, cardiac disease, hepatitis C) where immunosuppression was unlikely but unknown. In total only 37% (n=14) of deaths occurred in individuals without another comorbidity recorded on the death certificate.

2.3 Laboratory testing for hepatitis A

Timely laboratory testing is essential in recognising cases of hepatitis A infection and enabling initiation of preventive measures for contacts of cases. See Figure 11 for a diagram of the antibody response of hepatitis A. Ideally laboratory testing for diagnosing hepatitis A should include hepatitis A RNA; in the absence of routine RNA testing, anti-HAV IgM and anti-HAV IgG should be conducted to strengthen the diagnostic accuracy. Hepatitis A IgM and IgG antibody should be available within 48 to 72 hours of receipt of a sample in the laboratory. Many laboratories use a hepatitis A total antibody assay instead of a pure IgG assay to check immune status. Tests other than antibody tests are not widely available for example, HAV RNA PCR on blood and faeces.

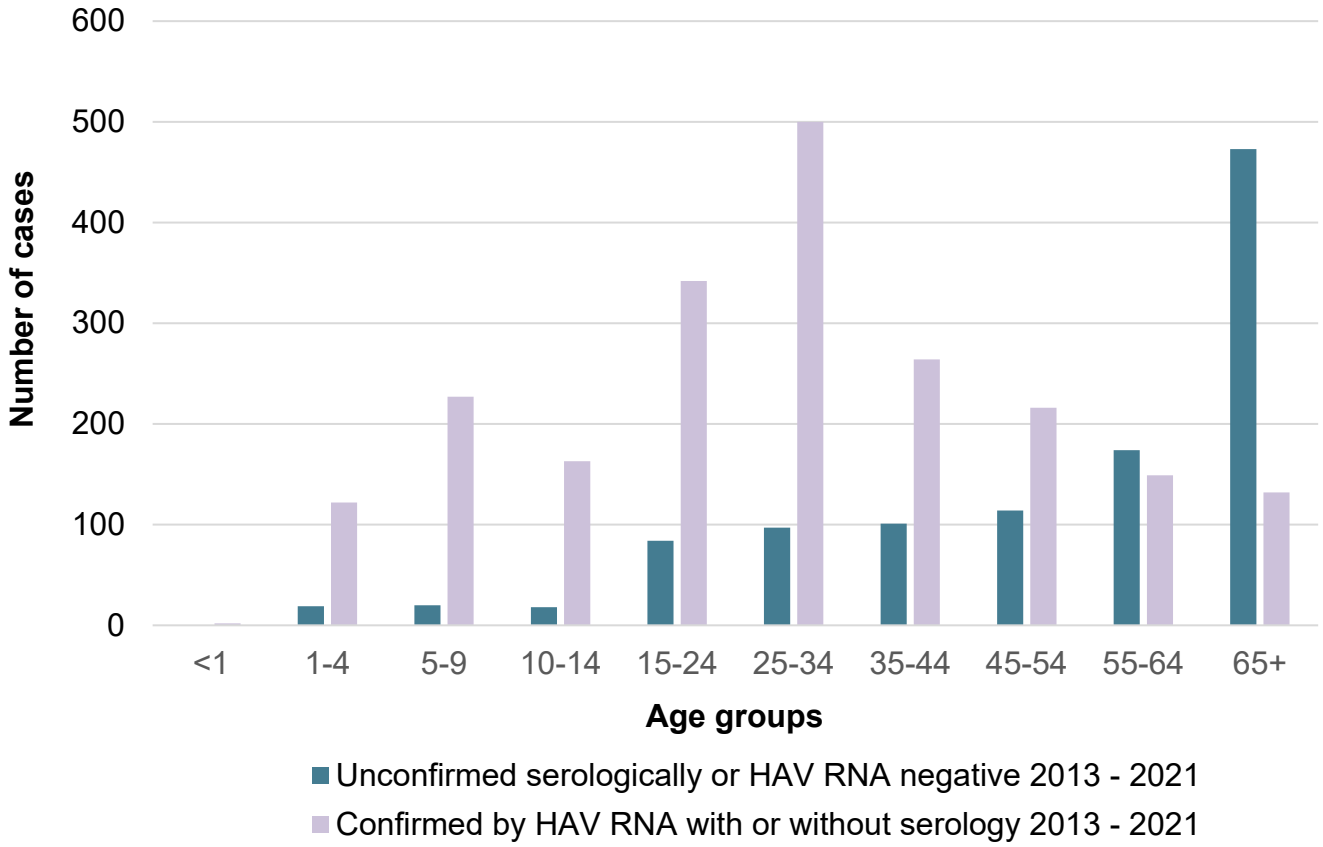
Figure 11. Immunological response to hepatitis A infection



Diagnosis of acute hepatitis A

Hepatitis A IgM testing is generally carried out by enzyme immunoassay (EIA) methods, often by automated analysers on serum or plasma (57). Appropriate samples for testing are clotted blood, or in some centres EDTA-anti-coagulated blood. A reactive anti-HAV IgM EIA is compatible with recent hepatitis A infection. However, reactive anti-HAV IgM results should be interpreted with care, as false positive results are common, particularly where there is weak reactivity or in those without clinical symptoms of acute viral hepatitis (58). In the provisional analysis of 2021 data from enhanced molecular surveillance of HAV, 48.4% of serum samples (156 of 322) reported as anti-HAV IgM positive on the Second Generation Surveillance System (SGSS) and sent to the viral reference laboratory (VRD) were not confirmed as acute HAV infections (59). Data collated from samples referred to VRD for confirmation and enhanced surveillance shows that as age increases so does the likelihood of false positivity (Figure 12).

Figure 12. False positivity of anti-HAV IgM positive serum samples referred to VRD for confirmatory testing 2013 to 2021 from England and Wales



Data source: UKHSA enhanced surveillance of hepatitis A

Testing of anti-HAV IgG at the same time as IgM is desirable as it can help interpretation. IgM reactivity in the absence of detectable anti-HAV IgG should raise doubts over the specificity of the IgM reactivity. A high IgG reactivity together with a moderate level of IgM indicates HAV infection in the recent past rather than current acute infection.

Interpretation of laboratory results requires clinical details, principally the date of onset of jaundice, also including liver function tests, together with information on the age of the patient (false IgM results are more easily recognised in the elderly, a group likely to have had hepatitis A in childhood) and risk factors for hepatitis A (for example, contact with a case, foreign travel, MSM) (60).

Negative IgM results should be interpreted in the light of the anti-HAV IgG result and the onset date of illness – a negative result less than 5 days after the onset of illness may not exclude hepatitis A and a repeat sample should be obtained as IgM results may be negative if tested in the early stages of infection (61).

Positive serology results consistent with acute hepatitis A should be promptly notified by the testing laboratory to the local HPT. Results of doubtful significance should be reported by laboratories with suitable interpretive comments.

Molecular characterisation

Genotyping, sequencing and phylogenetic analysis is performed by VRD and can confirm epidemiological links and identify clusters, as well as indicate the likely geographical origin of the strain of non-travel related cases and whether it has been associated with travel or food associated outbreaks (43, 48, 49, 62). It is clear that significant numbers of non-travel related cases occur each year which may indicate that contaminated food stuff may be a more common than is thought. Typing of hepatitis A virus is an invaluable tool and has increased our understanding of the molecular epidemiology of the virus and is only possible by the continued submission of samples from both travel associated and non-travel associated cases.

Testing for immunity for hepatitis A

The presence of detectable anti-HAV IgG suggests immunity to hepatitis A from previous natural infection or from hepatitis A immunisation.

Oral fluid testing

Prospective collection of oral fluid or serum/plasma on close contacts of cases at the same time of provision of post exposure prophylaxis may help to characterise clusters, define the direction and extent of secondary transmission in the household, inform further and more targeted prevention and control measures, including immunisation, and improve the overall surveillance of hepatitis A infection.

To facilitate containment of transmission at an earlier stage after identification of an index case and to avoid unnecessary testing and immunisation in schools when an external source has not been identified, VRD can test oral fluid from household contacts of a confirmed acute hepatitis case where the index case is a child (under 16 years) or a member of teaching staff at a school, where the likely source is unknown (for example, no travel history of index case during incubation period).

The oral fluid collecting kits for measles mumps and rubella (MMR) testing can be used for taking oral fluid specimens from close contacts for testing for hepatitis A, with MMR documentation replaced with a hepatitis A letter, request form and pictorial instructions.

Ideally the oral fluid test should be taken before or at the same time of immunisation; where this is not possible this should be taken as soon as possible after immunisation and preferably by the next working day after immunisation. It is critical that date of immunisation and date of sample are recorded to aid interpretation of results. As part of the national enhanced surveillance of hepatitis A and to help interpret the oral fluid test results, the serum sample from the index case should also be forwarded to VRD.

VRD should be contacted prior to the oral fluids being taken to provide information on the index case and to discuss the household; in addition to the household contacts an oral fluid sample should be taken from the index case. Results will be reported back to the Health Protection

Team (HPT) who may then forward the result to the patient's GP. If the oral fluid testing is unclear a blood sample may be requested to confirm the results. Oral fluid testing beyond the household contacts of an under 16 year old index case must be discussed with VRD.

2.4 Evidence base for recommendations

Human normal immunoglobulin

The current human normal immunoglobulin (HNIG) (Subgam) issued by Public Health England (PHE) and NHS laboratories is prepared by Bio Products Laboratory (BPL) from pooled plasma from non-UK blood donors. Non-UK pooled plasma has been used since March 1999 due to a theoretical risk of the transmission of vCJD. All immunoglobulins are prepared from HIV, hepatitis B and hepatitis C negative donors (63). The WHO second international standard for anti-hepatitis A immunoglobulin is 49 International Units per ampoule (IU/ampoule) when reconstituted in 0.5.ml (98 International Units per milliliter (IU/ml)) (64). This figure is based on a level of antibody associated with protection in clinical studies, although none of these studies have investigated the minimum protective level. In 2008, the batches of Subgam available in the UK only contained 60.3 to 86.8IU/ml (65).

Although these lower levels of antibody may be associated with protection, current UKHSA hepatitis A HNIG guidelines (63) recommend administering a larger volume to achieve a prophylactic effect (500mg to those under 10 years old and 1,000mg to 10 year olds and over). Please consult the most up-to-date version of the Immunoglobulin: when to use for current recommended dosage.

Efficacy of HNIG up to 14 days post-exposure

The minimum level of anti-hepatitis A antibodies in immunoglobulin required to prevent secondary infection is unknown. The original studies on the effectiveness of post-exposure administration of immunoglobulin to prevent secondary cases of hepatitis A were carried out in the 1940s and 1950s, when natural infection was common and levels of antibody in the adult population were likely to be high. At this time it was not possible to test the anti-HAV levels in the immunoglobulin used. These early efficacy studies were mainly carried out in outbreak settings, when the date of exposure to an index case was unknown. The estimated efficacies from these studies varied from 47% to 91%, with HNIG generally being more effective at preventing icteric illness than non-icteric hepatitis (see Table 2). A number of factors that could not be assessed at the time these studies were conducted may have been responsible for such wide variations in measured efficacies, such as production factors affecting levels of antibody in immunoglobulin and pre-existing immunity in the treated population.

The wide variation in the reported effectiveness of HNIG in post-exposure prophylaxis, coupled with a fall in the seroprevalence of hepatitis A in the donor population and the wide range of anti-HAV titres measured in different immunoglobulin lots (66, 67) has led some to doubt the adequacy of protective anti-HAV levels in HNIG that has anti-HAV titres below the WHO standard (68, 69). However, a recent randomised controlled trial of immunoglobulin versus

vaccine in the prevention of secondary cases of hepatitis A used immunoglobulin of known potency and dosage (18.83 IU/ml, 0.02ml/kg) - (C.Victor, personal communication) and its results can be used to estimate the effectiveness at this potency and dosage level. In this study 17 of 620 (2.7%) of susceptible household contacts given HNIG within 14 days of exposure developed hepatitis A compared to a secondary attack rate of 25.3% in a previous study amongst an untreated population of similar age structure in the same setting (23) giving an estimated efficacy of the HNIG used in this study of 84%. This data suggests that although current batches of Subgam contain anti-HAV antibody concentrations below the WHO standard, they are still likely to be effective at preventing the majority of secondary cases when administered within 14 days of exposure.

Table 2. Efficacy of HNIG for post-exposure prophylaxis against hepatitis A

Setting	Type of study	Protective efficacy or effectiveness
Outbreak, children's summer camp, USA, 1944 (70)	Non-placebo controlled study of HNIG versus no treatment	Against jaundice 87% Against clinical hepatitis 69%
Outbreak, children's home, USA, 1945 (71)	Randomised non-placebo controlled study of HNIG versus no treatment	Against jaundice 91% Against clinical hepatitis 76%
School outbreak, school contacts and their household contacts of preschool age, USA, 1947 (72)	Retrospective cohort, HNIG versus no treatment	93%
Outbreak, Institution for learning disabilities, USA, 1952 (73)	Randomised non-placebo controlled study, HNIG 0.05 ml/lb versus no treatment	Against jaundice 86% No efficacy against non-icteric hepatitis
	Randomised non-placebo controlled trial, HNIG 0.01 ml/lb versus no treatment	Against jaundice 80% No efficacy against non-icteric hepatitis
Household contacts aged 2 to 9 years within 14 days of exposure Israel, 1964 (74)	Randomised placebo-controlled trial of 2 different lots of HNIG (1953 to 1954 versus 1961)	46.9% (1953 to 1954 IG) 87.5% (1961 IG)
Outbreaks, schools, psychiatric hospitals, children's homes, England, 1966 to 1968 (75)	Randomised non-placebo controlled trial	65.3%
Outbreak, household contacts in rural community, USA, 1970 (76)	Retrospective cohort	87%

Setting	Type of study	Protective efficacy or effectiveness
Outbreak, household contacts seen either within 2 weeks or greater than 2 weeks since exposure, USA, 1983 to 1984 (77)	Observational study	95.7 % when administered <2 weeks post-exposure (statistically significant) 62% when administered >2 weeks post exposure(not statistically significant)
Outbreak, isolated Mormon community, USA, 1988 (78)	Retrospective cohort	80%
Ten outbreaks, school setting, Slovakia 1993 to 1995 (79)	Retrospective cohort	51 secondary cases developed in 3,837 contacts given HNIG
Household contacts of cases 2002 to 2005, Kazakhstan (80)	Randomised double-blind active-control noninferiority trial	84% see Table 3 for more details
Household contacts of notified cases in Amsterdam 2004 to 2012 (81)	Retrospective cohort	0 cases identified in 113 contacts given HNIG (classified susceptible due to total anti-HAV negative and without symptoms)
Household contacts of notified cases in Sydney 2008 to 2010 (82)	Retrospective cohort	0 cases identified in 24 contacts given HNIG (classified susceptible due to lack of previous immunisation or infection)

A study of immunogenicity comparing HNIG and hepatitis A vaccine in healthy adults under 50 years concluded that vaccine led to a rapid rise in anti-HAV and antibody levels after the first injection reached levels similar to or higher than levels for HNIG recipients by 4 weeks (83).

Efficacy of HNIG more than 14 days post exposure

There is little data on the effectiveness of using HNIG more than 14 days after exposure, and the studies that exist present conflicting results.

In 1944 the first controlled study to evaluate the effectiveness of HNIG in an outbreak setting found that cases of clinical hepatitis continued to occur in the HNIG-immunised group up to 10 days post-administration, but that these cases were predominantly non-icteric or of short duration (70). Another study of HNIG administered in an outbreak setting, carried out in 1952, found a similar predominance of non-icteric disease in those treated with HNIG in the 2 weeks post administration (73). This has been taken as evidence that the administration of HNIG late in the incubation period results in attenuation rather than prevention of the disease, and the study from 1944 is widely cited to support this claim (84). These studies were not designed to study the effect of giving HNIG late in the incubation period, the numbers of patients developing disease in both the treated and non-treated groups shortly after HNIG administration were small, and no statistical analysis was done of the differences between the groups. A more recent study reported a reduction in the secondary attack rate in patients given HNIG more than 2 weeks after exposure, although the reduction was not statistically significant. No evidence was presented on the severity of the disease in the treated and untreated groups and the exact time after exposure was not reported (77).

A number of other studies in outbreak settings also reported that cases of hepatitis A continue to occur up to 2 weeks post administration of HNIG and do not present evidence that these cases were of reduced severity (67, 68, 85). In addition, a placebo-controlled study in 1974 found no reduction in the frequency of icteric disease in patients given immunoglobulin in the last 15 days of the incubation period (86) and a case report of a group of 83 soldiers who were given HNIG 2 to 3 weeks after a suspected point source exposure reported a 21.4% attack rate in the treated group, with no modification in signs or symptoms of disease compared with an unspecified number of patients who did not receive immunoglobulin (87).

In summary, there is no evidence to suggest that HNIG given late in the incubation period (past 14 days exposure) prevents disease, and conflicting reports on whether it attenuates the severity of the disease that occurs. However, as administration of HNIG results in a rapid rise in anti-HAV levels there are theoretical grounds for assuming that it could ameliorate the severity of clinical disease when given up to 28 days post exposure, which may be of particular importance for those at particular risk of severe disease.

Effectiveness of HNIG at preventing onward transmission

Although the timely administration of HNIG prevents a substantial proportion of clinical cases of secondary hepatitis A infection, its effectiveness at preventing sub-clinical infection and thus interrupting onward transmission is less clear. A study of 8 chimpanzees given pre or post-exposure HNIG and challenged with virulent hepatitis A found that all became infected with the challenge virus and 5 of 6 shed detectable HAV in their stools between 2 and 6 weeks post challenge (88). Studies from the 1950s (89) found nearly identical incidences of biochemically-diagnosed hepatitis in children treated with HNIG and untreated controls, and more recently a serological study of 186 susceptible household contacts who received prophylactic HNIG found that 64 (34%) had acquired a secondary infection, but only 12 (6%) developed clinical disease (90). However, the recent randomised controlled trial of HNIG versus vaccine conducted in

Kazakhstan found similar levels of sub-clinical infection in those receiving vaccine and HNIG which suggests that both may be equally effective at preventing onward transmission (80).

Hepatitis A vaccine

Three hepatitis A monovalent vaccines are available in adult and paediatric formulations (Havrix®, Vaqta®, and Avaxim®). They are prepared from different strains of the hepatitis A virus; all are grown on human diploid cells (MRC5). These vaccines can be used interchangeably (91).

Immunogenicity studies using monovalent inactivated hepatitis A vaccine have shown that the vast majority of vaccinees develop seroprotective levels of neutralising antibody by 14 days post immunisation (92 to 95). However, the contribution of IgM to protection within 2 weeks of immunisation is unclear (96). The one study which measured antibody levels earlier than this found that all 8 healthy volunteers tested had seroprotective antibody levels (>15 mIU/ml) within 12 to 15 days post immunisation (97).

The combined vaccine containing purified hepatitis A virus and purified recombinant hepatitis B surface antigen (Twinrix) may provide a slower immune response and so is not recommended for post-exposure prophylaxis, however Ambirix can be used as post-exposure prophylaxis in under 16 year olds (2).

Mathematical models based on up to 12 years of follow-up data predict that antibodies will persist for at least 25 years (98). Hepatitis A vaccine induces immunological memory so it will provide protection far beyond the duration of anti-HAV antibodies (99). It is therefore not considered necessary to provide a booster dose after full primary immunisation (100). An anamnestic response has been shown to be triggered by a second dose of vaccine even when it is given several years after the first dose (99).

Efficacy of hepatitis A vaccine for post exposure prophylaxis

Early indications of the effectiveness of post-exposure hepatitis A vaccine came from a randomised controlled trial of vaccine use during a community outbreak which found that no additional cases of hepatitis A occurred in vaccine recipients more than 18 days after immunisation (101).

More recently, direct evidence from randomised trials has accumulated of the efficacy of hepatitis A vaccine as post exposure prophylaxis.

A limited randomised controlled trial of vaccine versus no treatment given within 8 days of symptom onset in the index case to household contacts aged 1 to 40 years showed an efficacy of vaccine in preventing infection of 82% (95% CI 20-96%), with an efficacy of 100% (9 of 207 versus 0 of 197) in preventing clinical hepatitis A (21).

Table 3 summarises published efficacy data for post exposure hepatitis A vaccine.

Table 3. Efficacy of vaccine for post-exposure prophylaxis against hepatitis A

Setting	Type of study	Protective efficacy or effectiveness
Outbreak in a Jewish community, USA, vaccine given to children age 2 to 16 years 1991 (101)	Double-blind, placebo-controlled trial	100%
Household contacts of sporadic cases in Naples, 1997 (21)	Randomised controlled trial of vaccine versus no treatment	82%
Ten outbreaks, school setting, Slovakia 1993 to 1995 (79)	Retrospective cohort	16 secondary cases developed in 2,171 vaccinated contacts
Household contacts of cases 2002 to 2005, Kazakhstan (80)	Randomised double-blind active-control noninferiority trial	79%
Household contacts of notified cases in Amsterdam 2004 to 2012 (81)	Retrospective cohort	8 secondary cases developed in 167 vaccinated contacts (classified susceptible due to total anti-HAV negative and without symptoms)
Household contacts of notified cases in Sydney 2008 to 2010 (82)	Retrospective cohort	95.6%

During 10 outbreaks of hepatitis A in Slovakia direct contacts of confirmed hepatitis A were randomly assigned to receive a dose of hepatitis A vaccine or HNIG (79). Although no data is provided on the timing of administration of HNIG and hepatitis A vaccine after contact with the index case, the patients given HNIG received their intervention earlier, as patients in the immunisation group were not immunised until their hepatitis A serostatus had been determined. There were significantly fewer secondary cases amongst vaccine recipients (16, 0.7%) than amongst HNIG recipients (51, 1.3%) in the 45 days after the intervention. This was not a controlled study, and there were a number of biases, (only seronegative patients received hepatitis A vaccine, whereas no serological testing was undertaken on the HNIG group and there was a delay in administering hepatitis A vaccine relative to HNIG).

However, these biases were likely to have overestimated, rather than underestimated the efficacy of HNIG relative to hepatitis A vaccine.

In 2007 a non-inferiority randomised controlled trial was conducted in Almaty, Kazakhstan to specifically address the relative efficacy of vaccine versus immunoglobulin in preventing laboratory-confirmed symptomatic hepatitis A infection when given within 14 days of exposure (day of onset of first symptoms in the index case) (80). The potency of HNIG used was 18.83 IU/ml of anti-HAV at a dose of 0.02ml/kg. This was substantially lower than the dose of anti-HAV currently used in the UK. The study enrolled 1,090 susceptible contacts aged 2 to 40 years (83% household contacts and 17% day-care contacts). This study was a non-inferiority study powered to detect a vaccine efficacy 20% lower than the efficacy of HNIG. The study did not contain a placebo arm, and so it was not possible to directly measure the efficacy of HNIG and vaccine in preventing secondary cases. However, the efficacy of HNIG and vaccine can be estimated based on the secondary attack rates found in untreated household contacts from a study carried out in the Almaty population prior to the trial (see Table 4). As can be seen, the estimated efficacy of HNIG in this study is 5% higher than that of vaccine at 14 days post exposure, although this was not statistically significant and the pre-specified criterion for non-inferiority was met. The study did not find any evidence of reduced efficacy of vaccine given in the second week post exposure compared to the first week post exposure, although the number treated in the first week was low and the study was not powered to answer this question.

Table 4. Secondary attack rates and estimated efficacy of hepatitis A vaccine vs. HNIG when given within 14 days of exposure, Almaty, Kazakhstan, 2002 to 2005 (80)

	Secondary attack rate when administered 1 to 7 days post exposure (95% CIs)	Estimated efficacy 1 to 7 days post exposure (95% CIs)	Secondary attack rate when administered 8 to 14 days post exposure (95% CIs)	Estimated efficacy 8 to 14 days post exposure (95% CIs)	Overall estimated efficacy 1 to 14 days post exposure (95% CIs)
Hepatitis A vaccine	4 out of 79= 5.1% (1.4%, 12.5%)	76% (51 to 100%)	21 our of 489= 4.3% (2.7%, 6.5%)	80% (68 to 91%)	79% (68% to 90%)
Immunoglobulin	2 out of 68= 2.9% (0.4%, 10.2%)	86% (66 to 100%)	15 our of 454= 3.3% (1.9%, 5.4%)	84% (74 to 94%)	84% (75% to 94%)

Efficacy of hepatitis A vaccine in older adults

Direct evidence of the efficacy of hepatitis A vaccine in preventing secondary cases of hepatitis A in older adults is lacking. The majority of efficacy trials of hepatitis A vaccine as post-exposure prophylaxis were both conducted in healthy populations under the age of 40, particularly children (21, 79, 80, 101) however, published observational studies of vaccine as post exposure for older adults have been reassuring (81, 82).

A study from the Netherlands reports the impact of post exposure interventions following local protocol; which is to test for susceptibility before administering treatment and in susceptible individuals to offer immunoglobulin if at risk of severe infection, or hepatitis A vaccine if healthy and at low risk (aged less than 30, or, 30 to 50 years and vaccinated less than 8 days post-exposure). Results showed that of the 192 susceptible contacts during the study period, 167 (87%) were vaccinated (mean 6.7 days post-exposure), 24 (13%) were given immunoglobulin (mean 9.7 days post-exposure) and one refused post exposure prophylaxis.

At follow-up testing, 8 out of 112 (7%) had a laboratory confirmed infection of whom 7 were symptomatic. Secondary infections were identified in 8 of the original 192 contacts identified (4%). All secondary infections occurred in immunised contacts, and half were older than 40 years of age. In healthy contacts immunised per-protocol, less than 8 days post-exposure, relative risk of secondary infection in those older than 40 years was 12.0 (95% CI 1.3-106.7). This is based on secondary infection in 3 out of 10 contacts aged over 40 years who received vaccine per-protocol and 4 out of 90 contacts under 40 years who received vaccine per-protocol (81).

In contrast a study from Australia which analysed roughly one year before and one year after the introduction of new guidance to recommend vaccine rather than HNIG for all contacts has shown that of the 318 'susceptible contacts' of hepatitis A cases (with no history of disease or immunisation) there were 10 (3%) secondary cases, 9 in 58 contacts who were not given vaccine or HNIG, 1 case in 144 given vaccine, 0 cases in the 113 given HNIG and 0 cases in the 3 given HNIG and vaccine. The attack rate of hepatitis in contacts receiving post exposure prophylaxis was 1 out of 260 (0.38%). The secondary cases were all aged less than 25 years, and the case in the immunised contact was an adolescent co-traveller to an endemic country, who developed symptoms at day 21 after vaccine and 35 days after symptom onset of their younger sibling. This study identified a higher uptake of post exposure prophylaxis after the change to vaccine from HNIG with 76% to 89% after introduction of the new guidelines (82).

Immunogenicity studies have shown that older persons have a lower and slower immune response to hepatitis A vaccine. Two studies compared immunogenic response to vaccine in under 40 year olds and 40 year olds and older. Both studies found reduced seroconversion rates 15 days post immunisation in the 40 year olds and older group; seroconversion rates (≥10 mIU/ml of anti-HAV) of 77% in persons aged 40 to 62 years compared to 97% in persons aged 20 to 39 years in one study (102), and seroconversion rates (≥20mIU/ml) of 23% in patients aged 40 to 65 years compared to 60% in those aged 18 to 39 in the other (103). Recently published meta-analysis of data 70 individuals in published studies (98, 102) and 10 in unpublished studies (and the same number of matched controls from the same studies) has shown that at 15 days after the first vaccine dose 79.7% (95% CI 68,8-88.2) of 40 year olds and older (mean age 47.0) compared with 92.3 (84.0-97.1) of 20 to 30 (mean age 24.2) were seropositive. At one month seropositivity was 97.5% (91.2-99.7) and 97.4% (91.0-99.7) in the 40 and older and 20 to 30 year olds respectively (104).

Recently published data of rates by 10 year age bands from a previously published randomised controlled trial (105) found that seroconversion rates after vaccine at 15 and 30 days, were 74% (n=125) and 90% (n=128) of 40 to 49 year olds after one HAV vaccine, 54% (n=37) and 81% (n=42) of 50 to 59 year olds, and 30% (n=10) and 50% (n=10) of 60 year olds and older seroconverted (106).

Another study to look at immunogenicity rates across 10 year age bands found an overall tendency to slightly lower geometric mean titres with age (107). All those aged 60 years and younger had seroprotective levels of anti-HAV (≥10 mIU/ml) one month post immunisation

compared to 93% in those aged over 60 years. As the lower limit of anti-HAV required to prevent hepatitis A has not been established, it is not possible to estimate whether the antibody levels achieved in the older age groups in these studies were too low to achieve seroprotection. The fact that the non-inferiority RCT of vaccine versus HNIG carried out in Kazakhstan used immunoglobulin of low potency (18.83 IU/ml, 0.02ml/kg) - (C.Victor, personal communication) and still achieved an estimated efficacy of 86% implies that the minimum seroprotective levels of anti-HAV are lower than had previously been thought (80).

While post exposure vaccine efficacy data is lacking in older adults, immunogenicity studies indicate a reduction of seroprotection with age, particularly for those aged 60 years and over. As a result of the evidence of immunogenicity of hepatitis A vaccine in healthy younger adults and relatively low potency of immunoglobulin in the UK (65) the marginal benefit of HNIG is unlikely to justify its use in those under the age of 60 years.

Efficacy of hepatitis A vaccine in children less than 2 years old

In the UK, hepatitis A vaccine is not licensed for children under the age of 12 months.

There is no direct evidence of the efficacy of hepatitis A vaccine in preventing secondary cases of hepatitis A in children younger than 2 years old.

Several immunogenicity studies have evaluated the use of hepatitis A vaccine in children under 12 months (108 to 111). These studies generally show that hepatitis A vaccine induces seroprotective levels of anti-HAV in the majority of infants, although the percentage of infants achieving seroprotective levels after a single dose varies between studies. In a study where the first dose of a 3 dose schedule was given at 2 months of age, 97% of infants who had no evidence of maternal antibodies had seroprotective anti-HAV levels (≥33 mIU/ml) one month later (109). In a study in which the first dose was given at 4 months of age 85.4% achieved anti-HAV levels ≥10mIU/ml one month later (110). A study in which the first dose was either given at 6, 12 or 15 months of age found seroprotective levels (≥33mIU/ml) one month after immunisation in 54%, 60% and 73% of infants respectively (108).

Hepatitis A vaccine was generally well tolerated in the infants studied. A number of minor adverse events such as injection site pain, unusual crying and fussiness were reported, but there were no serious vaccine related adverse events.

Efficacy of hepatitis A vaccine in patients with chronic liver disease

There is no direct evidence of the efficacy of hepatitis A vaccine in preventing secondary cases of hepatitis A in patients with underlying chronic liver disease. An immunogenicity study of hepatitis A vaccine in patients with chronic liver disease demonstrated a lower seroconversion rate one month post immunisation in susceptible persons with chronic hepatitis B (83.7% seroconversion rate), chronic hepatitis C (73.7%) and chronic liver disease of non-viral aetiology (83.1%), compared with a 93% seroconversion rate in healthy persons. There was no data available on seroconversion rates 15 days post immunisation (112).

Efficacy of hepatitis A vaccine in HIV individuals

There is no direct evidence of the efficacy of post exposure prophylaxis in immunosuppressed patients. Patients with HIV have been studied more extensively than other patient groups with immunosuppression for pre-exposure efficacy.

Response rates to the hepatitis A vaccine are generally reduced in HIV-infected persons compared to HIV-negative persons, and correlate with the CD4 cell count at the time of immunisation (113). Rates are 50 to 95% overall, but range from 9% at CD4 counts <200 cells/mm^3 to 95 to 100% at CD4 counts >300 to 500 cells/mm^3. Highly active antiretroviral therapy (HAART) is associated with improved anti-HAV levels (114). More recent studies support the findings that patients with HIV have a lower response rate but that increasing CD4 count is correlated with improved response (115 to 120). The duration of protection in HIV-infected people is unknown, but may be shorter than in HIV-negative persons. There is no data on the efficacy of post exposure prophylaxis in HIV-infected people. Given the lack of direct data and the evidence of a lower and slower immune response to vaccine in this group, the British HIV Association (BHIVA) recommend HIV-infected people should be offered vaccine as post exposure prophylaxis, and if the CD4 count is <200 cells/mm^3 they should also receive HNIG (121).

Efficacy of hepatitis A vaccine in other immunosuppressed patients

A literature review of 11 studies (totalling 921 patients) which measured pre-exposure vaccine efficacy in immunocompromised individuals reported an overall serological response rate of 37% at least one month after one vaccine, and 82% after 2 vaccines (122). The review included patients who were immunocompromised as a result of immunosuppressive medications, stem cell transplants and HIV. In a study of children on immunosuppressive treatment, for Juvenile Idiopathic Arthritis, the response rate was 48% at 4 weeks after one vaccine (123).

Efficacy of hepatitis A vaccine and management in pregnancy and during breast-feeding

There is no evidence of risk from immunising pregnant women or those who are breast-feeding with inactivated viral vaccines (124). Evidence about infection while breastfeeding comes from 3 women with acute hepatitis A which identified antibodies in breastmilk, and HAV RNA was detected in 2 specimens, however none of the 3 infants acquired clinical hepatitis A infection, therefore mothers should not be encouraged to discontinue breastfeeding (125).

Efficacy of hepatitis A vaccine when used more than 14 days post-exposure

There are no studies examining the efficacy of hepatitis A vaccine used more than 14 days post exposure. There is weak anecdotal evidence that hepatitis A vaccine given after 14 days post exposure may attenuate clinical illness. In one study 3 army recruits were coincidentally given hepatitis A vaccine more than 2 weeks after an unrecognised exposure to hepatitis A. Although the vaccine did not prevent infection, the immunised recruits required significantly fewer days hospitalisation and had significantly lower average maximal liver enzyme levels than 3 non-immunised colleagues (126).

Simultaneous administration of hepatitis A vaccine and HNIG

Several immunogenicity studies in healthy volunteers have shown that the simultaneous administration of vaccine plus immunoglobulin leads to protective levels of antibody production (127 to 130). However, the simultaneous administration of vaccine and immunoglobulin resulted in lower anti-HAV titres, on average, than the administration of vaccine alone, indicating that there is some interference of HNIG with the immune response. These studies have led some to conclude that protective antibody levels may persist for a shorter time when HNIG and vaccine are given simultaneously, which could necessitate the administration of a further booster dose to ensure long-lasting immunity (127, 128). However, subsequent to these studies, evidence has accumulated that underlying immune memory provides protection following hepatitis A vaccine even after loss of detectable antibody, and a WHO Consensus Group has recommended that this immunological memory may be relied upon to protect against symptomatic infection (100). As the studies of the simultaneous administration of vaccine and HNIG demonstrated good anamnestic responses to subsequent doses of vaccine, immunological memory should be sufficient to prevent clinical disease in patients who receive HNIG simultaneously with the first dose of vaccine.

Severity of disease

Severity of disease in older patients

It is well established that severity of disease increases with increasing age (12). Three large studies (with 256 to 770 patients) have identified increasing age as being associated with increasing severity of disease (131 to 133). However, several small studies (each with less than 100 patients) have not found age to be statistically significantly associated with disease severity (134 to 138). The epidemiology presented in section 2.2 shows increasing numbers of deaths with hepatitis A recorded on the death certificate with increasing age.

Severity of disease in patients with chronic liver disease

Several studies have shown that patients with chronic liver disease are at increased risk of developing severe disease when infected with hepatitis A (139 to 141). This is supported by the epidemiology presented in section 2.2 which has found a high proportion of chronic liver disease in patients who died with hepatitis A recorded on their death certificate.

Severity of disease in HIV-positive patients

There is very limited data about severity of hepatitis A in HIV-positive patients, however one study of 256 patients with acute hepatitis A reported no association was identified between underlying disease (including HIV) and the occurrence of serious complications (131).

Severity of disease in patients with co-morbidities (including immunosuppression)

There is very limited data about the severity of hepatitis A in patients with immunosuppression. Three large studies of severity of disease (with 256 to 770 patients) included patients with a range of comorbidities including diabetes, HIV, and alcohol dependence. These studies did not consistently report a significant association with severity of disease and the comorbidities

included (131 to 133). One study of 256 patients from the US found an association with age and death from hepatitis A, but did not find an association with underlying disease (including diabetes, liver disease and HIV) and occurrence of a serious complication (131). In a study of 713 patients severity of disease of hepatitis A was found to be associated with hepatitis B antigen positivity (p=0.050) and significant alcohol intake history (p=0.007), whereas anti hepatitis C positivity (p=1.000) and diabetes mellitus (p=0.115) had no significant difference (132). In a study of 770 patients with HAV multivariate analysis identified age as an independent factor for the severity of hepatitis A, whereas 16 patients with comorbidity (including diabetes, HBV, alcoholic liver disease, fatty liver disease) all recovered without complications (133).

The epidemiology presented in section 2.2 identified a substantial proportion of people with comorbidities and likely immunosuppression in patients who died with hepatitis A recorded on their death certificate.

Evidence of vaccine use in management of outbreaks

In addition to households, outbreaks have been documented in a range of settings where close contact occurs including MSM communities (9, 10, 142, 143), PWID (11), nurseries or day care centres (144 to 146), primary schools (35 to 37), residential homes for people with learning disabilities (6, 147) and care homes (148). A review of 268 hepatitis A outbreaks identified that the only variables associated with shorter outbreak duration were early administration of HNIG or vaccine and a school setting (149). In the UK there was a recent large incidence response in association with a food handler with acute hepatitis A which used immunisation and no secondary cases were identified (150). An outbreak report from a school in 2010 found vaccine to be an effective control measure (151).

In a 2003 literature review of Italian hepatitis A outbreaks and the role of hepatitis A vaccine, 3 scenarios were identified as most likely to occur in Italy: outbreaks in small closed communities (nursery or a primary school), outbreaks in communities of limited dimensions (small towns or villages) and open community settings in which epidemics occur at regular intervals (person-to-person transmission). While acknowledging that most of the evidence was from weak observational studies, the authors reported a rapid decline in outbreak cases after immunisation was introduced as a control measure in open and closed communities, but noted that it was not possible to quantify the contribution of vaccine versus natural history of the disease.

They did, however, recommend in closed community outbreaks, immunisation of primary school or nursery classmates in addition to close contacts. For small open community outbreaks they recommended immunisation of more susceptible age groups such as children and adolescents. For large open community epidemics, in endemic areas, they did not find evidence that mass immunisation would be effective in controlling outbreaks, recommending instead immunisation of close family contacts of acute cases and other non-immunisation control measures (152). It is important to note that Italy differs from the UK in that it has endemic areas for hepatitis A.

The level of vaccine coverage needed to interrupt transmission in outbreaks will vary according to the susceptibility of the population and the estimated basic reproduction rate (R0) which varies according to country, for example, 1.1 to 1.5 in USA (153) and 2.2 in Italy pre-vaccine introduction (154). In England R0 is more likely to be similar to the US. Therefore even taking the upper estimate for R0 of 1.6, a modest immunisation coverage of 40% in a susceptible population is likely to make the effective reproductive number, Re less than 1 and bring an outbreak to a close.

A descriptive analysis of hepatitis A outbreaks reported to PHE in 2011-2015 (unpublished) was undertaken to understand the characteristics of English clusters in terms of size, setting and if wider immunisation was offered. Information on 19 outbreaks was collected. The main characteristics of these outbreaks are reported in Table 5. Notification of the case to the HPT was delayed if there was no jaundice.

The majority of outbreaks were associated with a primary school aged child and the outbreak setting was mainly a mix of households and nurseries or schools. Oral fluid testing was used in 3 outbreaks to understand the transmission dynamics (Table 5). Mass immunisation was carried out in 16 of the 19 outbreaks (see Table 6), mainly in educational (nursery or school) settings and by school or practice nurses. High vaccine uptake (median 80%) was achieved with funding predominantly provided by clinical commissioning groups (CCGs) (Table 6).

Table 5. Summary of hepatitis A clusters and incidents characteristics, in England, 2011 to 2015 (n=19)

Characteristic	Categorical or numeric value
Median delay onset of symptoms to HPT notification (n=15 clusters)	15 days, range: 8 to 51
Median delay onset of jaundice to notification to the HPT (n=17 clusters)	7 days (range: 2 to 17)
Median age of index cases (N=16 clusters)	9.5 years (range: 2 to 52)
Genotype (n= 10 clusters)	1A: 30% 1B: 70%
Oral fluid testing used	3 clusters
Median number of household contacts	5 (range: 1 to 46)
HNIG offered	6 clusters , 53 contacts (all contacts over 50 years old)
Median number of linked cases by outbreak (n=17 clusters , total 63 cases)	2 (range: 1 to 17)
Median age of all secondary cases (n=5 clusters, 39 cases)	9.5 years (range: 0 to 58)

Characteristic	Categorical or numeric value
Sex of secondary cases: (n=4 clusters, 19 cases)	12 (63%) : female
Cluster settings	Combined (household and school or nursery): 3 Household: 4 School or nursery: 7 Other: 2 (1 choir trip and 1 care home)

Table 6. Summary of hepatitis A wider immunisation in response to outbreaks in England, 2011 to 2015 (16 clusters)

Characteristic	Categorical or numeric value
Cluster setting (n=16)	Primary schools: 10 Nursery: 4 Care home: 1 Choir: 1
Extent of immunisation in educational settings (school or nursery) (n=10 clusters)	Same class or room: 1 Same year: 1 Whole structure: 6 All groups sharing toilet or specific area with index case: 2
Total number of people immunised	2,508
Median number of immunisations per cluster	90 (range: 27 to 1,000)
Median immunisation uptake	80% (range 49 to 100%)
Immunisations (n=10 clusters)	School or nursery nurses: 5 Practice nurses: 5
Funding of wider immunisation (n=8 clusters)	CCG: 6 NHS England: 1 Registered GPs:1

Source: Isidro Carrion on behalf of 2017 HAV guidance working group.

Hepatitis A Guidance Working Group

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Abbreviations

Abbreviation	Definition
anti-HAV IgM	hepatitis A virus antibodies IgM
anti HAV IgG	hepatitis A virus antibodies IgG
BHIVA	British HIV Association
BPL	Bio Products Laboratory
CD4	Cluster of Differentiation 4
CI	confidence interval
GP	general practitioner
HAV	hepatitis A virus
HNIG	human normal immunoglobulin
HPT	health protection team
ICT	incident control team
IVPDD	Immunisation and Vaccine Preventable Diseases Division
MMR	measles, mumps, rubella
GBMSM	gay, bisexual and other men who have sex with men
OCT	outbreak control team
PGD	Patient Group Direction
PHE	Public Health England
PWID	people who inject drugs
RNA	ribonucleic acid
UK	United Kingdom
UKHSA	UK Health Security Agency
US	United States
vCJD	variant Creutzfeldt–Jakob Disease
VRD	Virus Reference Department
WHO	World Health Organization

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