Public Health England

Public health control and management of hepatitis A

2017 Guidelines

About Public Health England

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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. This guidance updates the 2009 Guidance for the Prevention and Control of Hepatitis A Infection.

The main changes from the previous 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 <200 cells/ mm^3
- For post exposure prophylaxis of close contacts of cases within 14 days of exposure, HNIG is now 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 MSM. 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.*

This guidance is split into two sections: Part One describes the recommendations and rationale for management of cases, close contacts and outbreaks. Part Two gives the background for the guidance including the clinical features, epidemiology and laboratory testing of hepatitis A and the evidence for the recommendations.

See Box 1 for a summary of the recommendations.

Box 1. Summary of public health management of 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 close contacts identified within 14 days of exposure to index case

- Healthy close contacts aged <12 months: Offer immunisation to household contacts and persons who have been involved in nappy changing or assistance with toileting to prevent tertiary infection. If the infant contact attends childcare, offer vaccine to the infant contact if ≥2 months (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 (e.g. loss of employment): immunise children and staff in the childcare setting. Healthy close contacts aged 1-59 years: Offer hepatitis A vaccine
- Healthy close contacts aged 60 years or over: Offer hepatitis A vaccine + HNIG
- Close contacts with chronic liver disease, chronic hepatitis B or C infection, and immunosuppression, including HIV positive individuals with CD4 count <200 cells/mm^3: Offer hepatitis A vaccine + HNIG
- Close contact who is a food handler: Offer hepatitis A vaccine

Management of 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 + HNIG to attenuate severity of disease
- Close contact is a food handler: Risk assessment of need for transfer to non-food-handling duties (see Box 12)
- 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 (e.g. loss of employment): immunise children and staff in the childcare setting

Management of 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 in, 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/school not identified, assume infection acquired within early years setting / 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 One – 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 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 can be accessed from:
https://www.gov.uk/government/publications/hepatitis-a-case-questionnaire

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

Clinical case (Possible)
• A person with an acute illness, discrete onset of symptoms AND jaundice or elevated serum aminotransferase levels
Probable case
• A person that meets the **clinical case** definition 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
• A person that meets the clinical case definition AND is confirmed through **IgM** and **IgG** antibodies to hepatitis A • 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, e.g. immunisation in a school, then confirmation should be obtained before that intervention. Individuals with an IgM result only (e.g. 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 PHE Colindale, Virus Reference Department (VRD) as part of the national enhanced molecular surveillance of hepatitis A for confirmation and sequencing.

Box 4. Case 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/ virologist:
Anti-HAV IgM reactivity – LOW
No Anti-HAV IgG done
Action: Request local IgG quantitative testing
Discussion with local microbiologist/ 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/virologist then sample can be referred to reference laboratory (VRD) for confirmation/exclusion

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/ 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. 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 **two weeks before onset of first symptoms and until one week after the onset of jaundice**. Where jaundice is not reported a history of dark urine or pale stools should be enquired about. If there are no symptoms of jaundice, 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 a history of dark urine or pale stools should be enquired about. If there are no symptoms of jaundice, onset of other symptoms (such as fatigue, nausea, and fever) should be used

Box 7. Close contact

Individuals who are 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 (e.g. 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. Susceptible contact

Contact without previous laboratory confirmed hepatitis A and without a documented evidence of a completed course of hepatitis A vaccine in the past 10 years (or one dose of monovalent vaccine within the past 12 months).

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.

Box 9. Groups 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/educational setting
B	All children aged five 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	Consider informal food handlers, e.g. someone

	unwrapped food or drink to be served raw or not subjected to further heating	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, e.g. 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 men who have sex with men, (MSM) 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 three monovalent inactivated hepatitis A vaccines, two combined hepatitis A and hepatitis B vaccine and two 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 (two or three 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 Immunisation against Infectious Disease (2) (the “Green Book”) chapter 17:

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. Patients with chronic liver disease
3. Patients with haemophilia
4. 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 (see appendix 1) 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 (e.g. young children or those with severe 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 MSM, 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 (e.g. 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 from: https://www.gov.uk/government/publications/hepatitis-a-case-questionnaire A patient questionnaire should be completed for each confirmed or probable case. Questionnaires should be completed to aid local investigations and may be requested by the national centre 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 at tmhs@phe.gov.uk

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 (see appendix 1) Contacts whose personal hygiene is likely to be inadequate (e.g. 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 MSM, advice on how to avoid hepatitis A infection during sex should also be given.

Assessment of susceptibility

Close contacts that have documented evidence of a completed course of hepatitis A vaccine in the past 10 years (or one dose of monovalent vaccine within the past 12 months) should be considered immune. Those who have had laboratory-confirmed hepatitis A (previous anti-HAV IgG positive, or HAV RNA positive) are also considered immune.

Prior to administration of HNIG, if testing is feasible then it should be undertaken to avoid an unnecessary administration of a blood product which carries *theoretical* risks of transmission of unidentified infectious agents. Anti-HAV IgG testing should not delay the administration of post-exposure vaccine.

Public Health actions for susceptible contacts ≤14 days from exposure

Please refer to box 13 for an algorithm for managing close contacts of cases of acute hepatitis A. Assessment and prophylaxis for close contacts should occur as soon as possible within 14 days of exposure.

Below is a summary of the public health actions for susceptible contacts ≤14 days from exposure and a summary of the rationale. For full rationale see section 2.4.

Box 10. Public Health actions for susceptible contacts ≤14 days from exposure

Healthy infants < 12 months	**Recommendation** No post-exposure prophylaxis is required for healthy infant contacts aged <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, he/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 and staff in the childcare setting. If an infant aged <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 <12 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 > 2 months, suggesting that the evidence on post-exposure efficacy can be extrapolated to infants in this age group. In some countries infants aged <12 months are offered HNIG, this is not recommended in the UK due to the mild clinical illness in <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 1-59 years. A risk assessment should be carried out to determine whether the patient is at continued risk of hepatitis A infection (e.g. the patient fulfils the criteria for requiring immunisation as pre-exposure prophylaxis, see section 1.3 above). A second dose of vaccine is recommended 6-12 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	**Recommendation** Contacts aged 60 years and over should be offered HNIG in addition to monovalent hepatitis A vaccine. A second dose of vaccine is recommended 6-12 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 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. The patient should be referred to their GP for a second dose of hepatitis A vaccine 6-12 months after the first dose to ensure long-term protection.
	Rationale Patients 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 other immunosuppression	**Recommendation** Contacts with immunosuppression should be offered HNIG in addition to hepatitis A vaccine. The patient should be referred to their GP for a second dose of hepatitis A vaccine 6-12 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 patients 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/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 <200 cells/mm^3)	**Recommendation** Contacts that are profoundly immunocompromised due to HIV (CD4 count <200 cell/mm^3) should be offered HNIG in addition to hepatitis A vaccine, unless known to be immune. The patient should be referred to their GP for a second dose of hepatitis A vaccine 6-12 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 susceptible close contacts seen >14 days post exposure

Please refer to box 13 for an algorithm for managing close contacts of cases of acute hepatitis A.

Below is a summary of the public health actions for susceptible close contacts seen >14 days post exposure and a summary of the rationale. For full rationale see section 2.4.

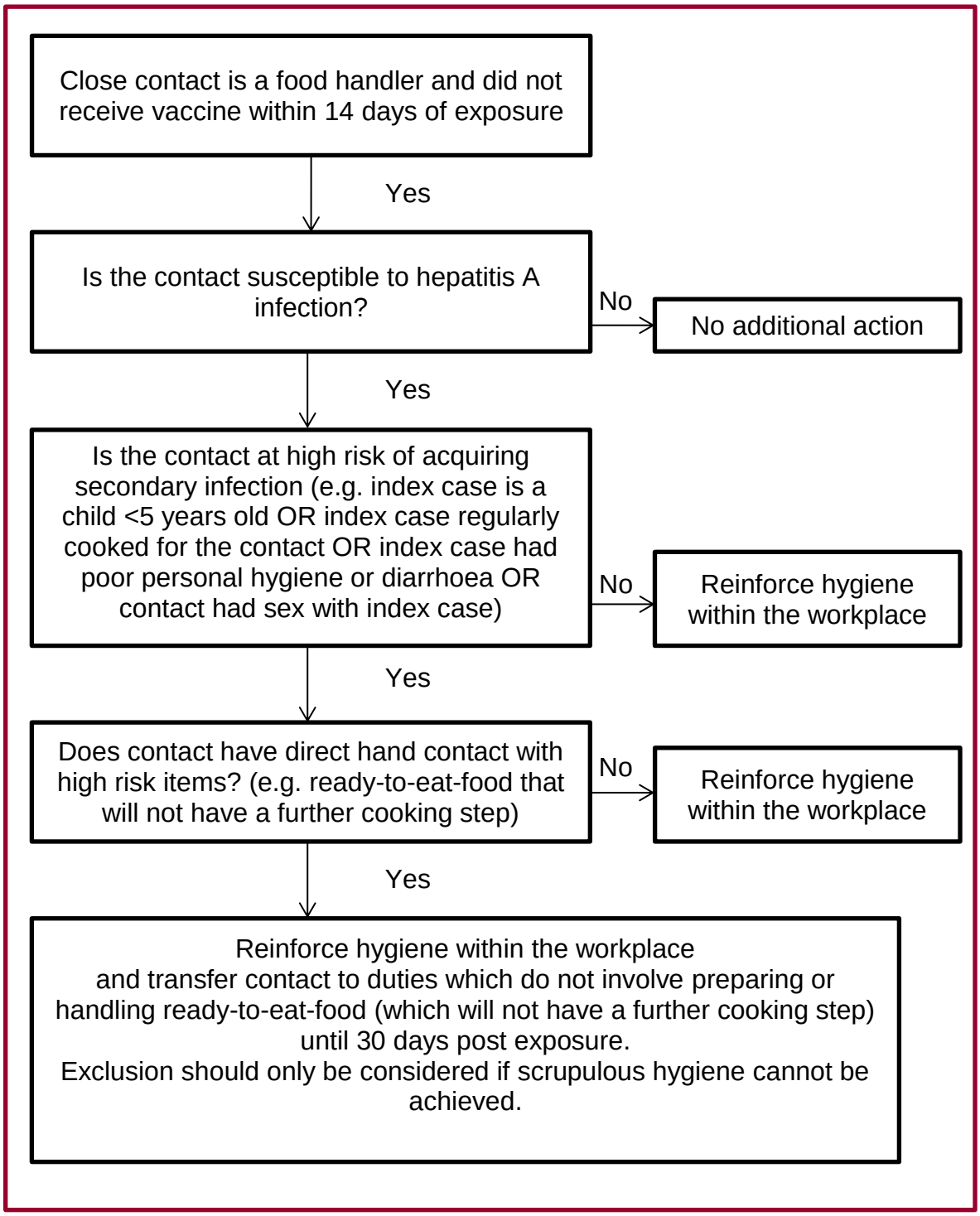
Box 11. Public Health actions for susceptible close contacts seen >14 days post exposure

with chronic liver disease, pre-existing chronic hepatitis B or	**Recommendation** Consideration should be given to offering HNIG to close contacts at risk of severe disease (i.e. those with chronic liver disease or pre-existing chronic hepatitis B or C infection) up to 28 days post exposure. 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.

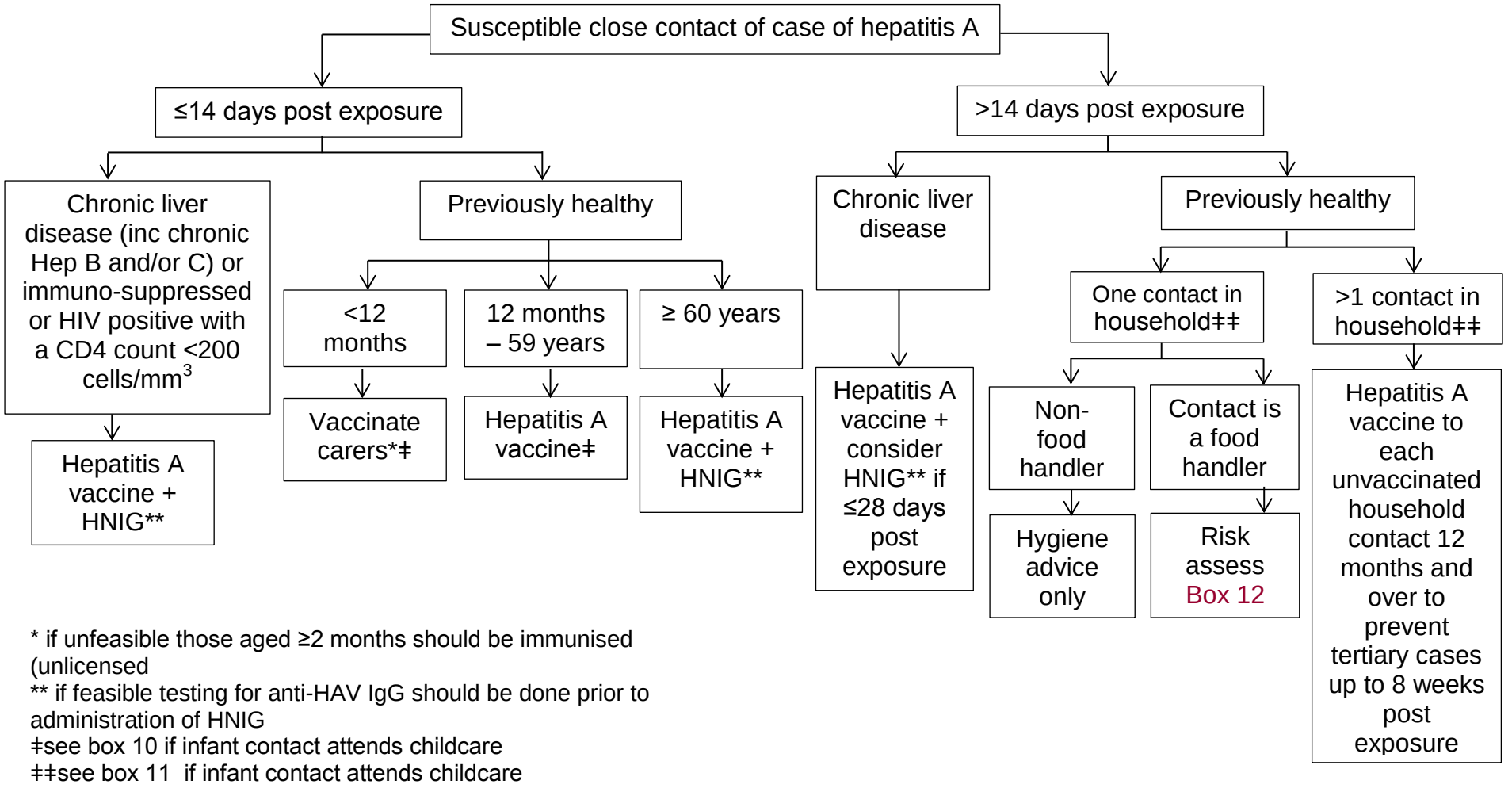
	Rationale There is no clear evidence of the efficacy of either vaccine or HNIG in preventing secondary infection when given >14 days after exposure. However, there are theoretical grounds for believing that HNIG may attenuate the severity of disease if given during the incubation period. This is of particular 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/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 Box 12). 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 susceptible to HAV and at high risk of acquiring infection (e.g. index case is a child <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 (i.e. will not be further cooked) until 30 days post exposure (see box 12) 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 28-30 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 >14 days after exposure.

All other household close contact	**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 infant school does not receive vaccine within 14 days of exposure, enhanced hygiene measures should be implemented at nursery or infant school 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 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 and 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 >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.

Box 12. Risk assessment for close contacts who are food handlers



Box 13. Algorithm for Management of Susceptible Close Contacts



* if unfeasible those aged ≥2 months should be immunised (unlicensed
** if feasible testing for anti-HAV IgG should be done prior to administration of HNIG
‡see box 10 if infant contact attends childcare
‡‡see box 11 if infant contact attends childcare

1.6 Management of contacts where the index case attends a high risk setting (beyond the household)

Box 14. Management of contacts where the index case attends a high risk setting (beyond the household)

Work setting: Food handler including those working in the Health and Social Care setting	**Recommendation** If the index case is a food handler (see definition) 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 (e.g. 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.
	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.

Pre-School childcare and reception class (early years)	**Recommendation** In early years childcare settings such as a nursery or child minder (e.g. 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 to 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, e.g. 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 (e.g. 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/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 two cases (index case and unidentified asymptomatic case) in the early years setting, i.e. 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	**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 e.g. 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 (e.g. 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 (e.g. close friends of the index case within the school) or whether wider

	immunisation in the same class / year / multiple years / 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 two cases (index case and unidentified asymptomatic case) in the school i.e. 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.
Other school or workplace settings	**Recommendation** Hepatitis A post-exposure prophylaxis is not usually indicated when a single case has occurred in a secondary school, 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 15. Example Scenario

Index case is a carer in a residential home setting (care home/nursing home/learning disability)

Post-exposure prophylaxis against HAV is not usually indicated when a single case has occurred in a hospital, secondary school or work place, as transmission of HAV is generally limited to household-type close contacts. However, in closed settings such as residential care / nursing homes housing elderly or otherwise vulnerable residents who may require intensive assistance with activities of daily living e.g. 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 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 etc. 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 –

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

1. 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.

2. 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:

- Two or more cases in different years in the same primary school who are not close contacts outside school

- Two 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
- Two or more cases in different households in the same social network
- A cluster of cases associated with a single food item / single event /single location (including a single location overseas such as a holiday resort or hotel)

Management of local outbreaks of hepatitis A e.g. in a school, hospital, residential care, prison or community requires a multi-agency response. An Outbreak Control Team (OCT), should be convened by the local Health Protection Team.

In the event of an outbreak associated with overseas travel, the PHE National Infection Service, Colindale and the PHE 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 that can be found here;

https://www.gov.uk/government/publications/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 (i.e. Clinical Commissioning Group representative, NHS England)
- Depending upon the setting, representatives as appropriate from the implicated institutions e.g. a school nursing service,
- PHE National Infection Service –Virus Reference Department senior scientist / consultant virologist
- PHE National Infection Service –Immunisation, Hepatitis and Blood Safety Department senior scientist / consultant epidemiologist
- PHE Travel and Migrant Health Section senior scientist/consultant epidemiologist (for national outbreaks associated with overseas travel only)

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

Before the OCT 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 (e.g. 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;

https://www.gov.uk/government/publications/communicable-disease-outbreak-management-operational-guidance

In suspected hepatitis A outbreaks the OCT 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 (ihrnfp@phe.gov.uk or 020 8327 6412)

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/refute epidemiological findings, indicate geographical/food origin, and link to other known outbreaks
- Consider further clinical and environmental samples for testing e.g. 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/ residential care settings, including funding, staffing, patient group direction (PGD), cold chain, venue options and suitability (GP surgery/ mobile vaccine bus/sentinel schools)
- Consider vaccine procurement options (Colindale IHBSD team can alert manufacturers and connect OCT 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

Final Phase

- Agree definition of end of the outbreak, e.g. no linked cases over two incubation periods)
- Produce an outbreak report and lessons learnt

Use of vaccine and/or HNIG prophylaxis for outbreaks

Recommendation

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

Prior to the introduction of hepatitis A vaccine, HNIG was used to control outbreaks, whilst once the vaccine was introduced a combination of the two 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 on-going 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 (e.g. children) may be effective in closed communities or settings (e.g. schools) and small, open communities (e.g. 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 & early years settings suspend use of communal soft toys/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.

Closed settings such as educational institutions

Two or more cases of probable/ confirmed hepatitis A in students or staff at a school or nursery in the absence of epidemiological and microbiological evidence that suggest they are unlinked indicate an outbreak. 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, 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 2.3, 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/years of the cases may not be appropriate if they have siblings in different classes/years and/or if there is a lot of mixing between years at meal and play times and/or different years/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.

Closed setting: 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 two 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 (e.g. same unit/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? (i.e. same floor, same unit, linked by common staff members etc.)
- 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 (e.g. 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.

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 e.g. 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 <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 2.4)

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 Two - Background and Rationale

2.1 Clinical Features of Hepatitis A

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 men who have sex with men (MSM) (9, 10) and persons who inject drugs (PWID) (11) in the UK.

The average incubation period of hepatitis A is around 28 days (range 15–50 days) (8). The course of hepatitis A infection is extremely variable. In children under 5 years of age 80-95% of infections are asymptomatic while in adults 70-95% of infections result in clinical illness (12). Severity of symptoms increases with age (8). Fulminant hepatitis occurs rarely (<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 (14-16). 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 two 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 (29-34) and

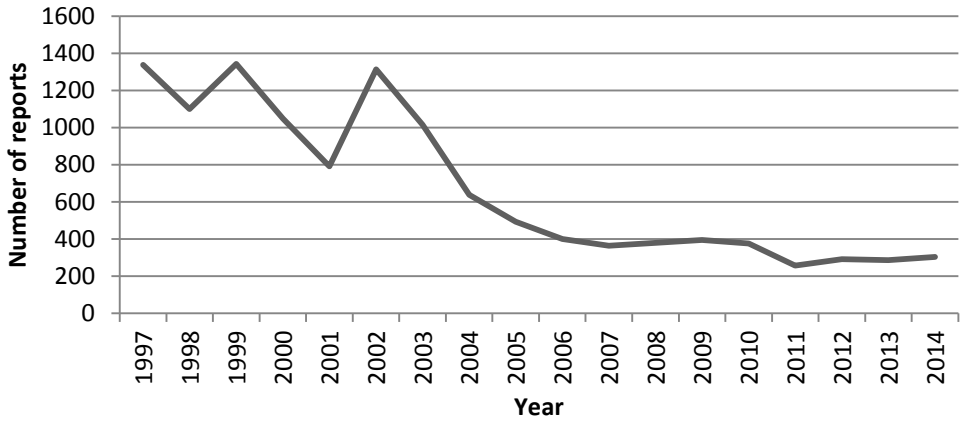
secondary attack rates of between 2.9% and 50% reported in primary schools (35-37) in Europe and the US.

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 (39-43), frozen berries (44-48), 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 1,337 in 1997 to 303 in 2014 (See Figure 1).

Figure 1. Annual laboratory reports of hepatitis A for England and Wales 1997-2014 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 (see Figure 2), with no reported cases in children under one year in the last 5 years and a rise in early childhood. There has been an increase in the proportion of cases

reported in over 65 year olds over the last 15 years. They accounted for 7% of cases in 2000-2004 and 18% of cases from 2010-2014 (see Figure 3). 2.3

Figure 2. Number of reports and mean annual rate of laboratory reports of hepatitis A per 100,000 population[1] by age group for 2005-2014 in England and Wales

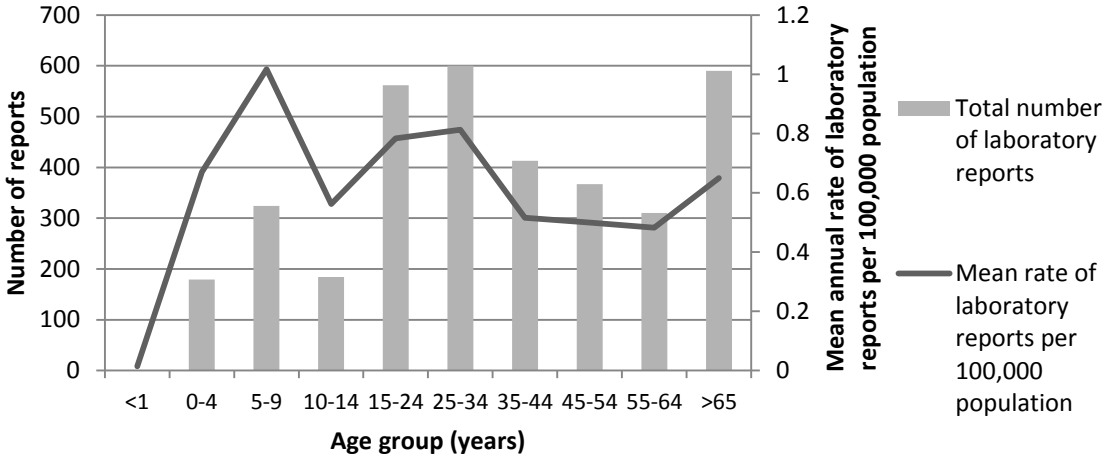
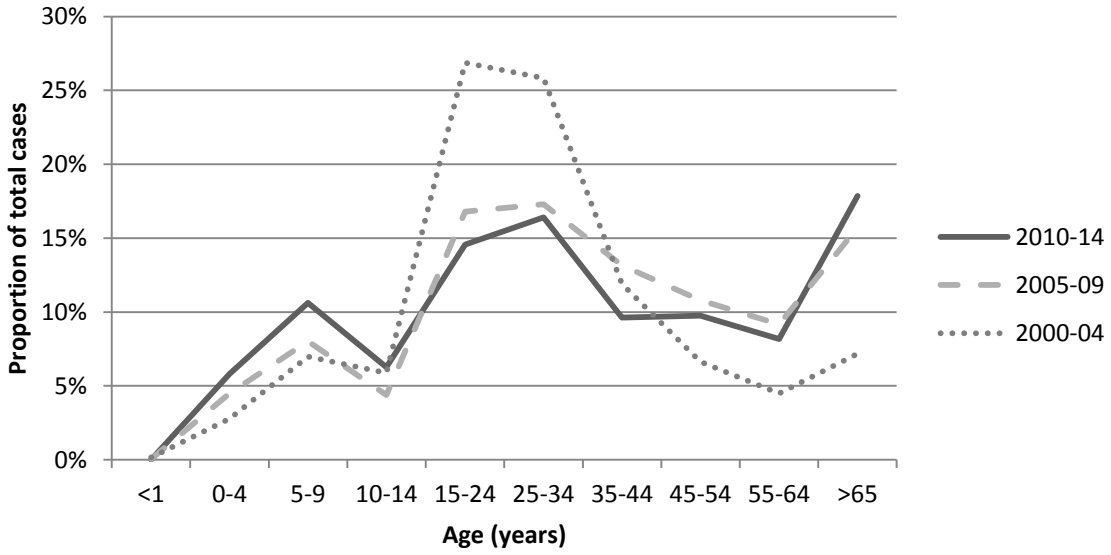


Figure 3. Proportion of annual laboratory reports of hepatitis A by age group for 2000-2014 in England and Wales

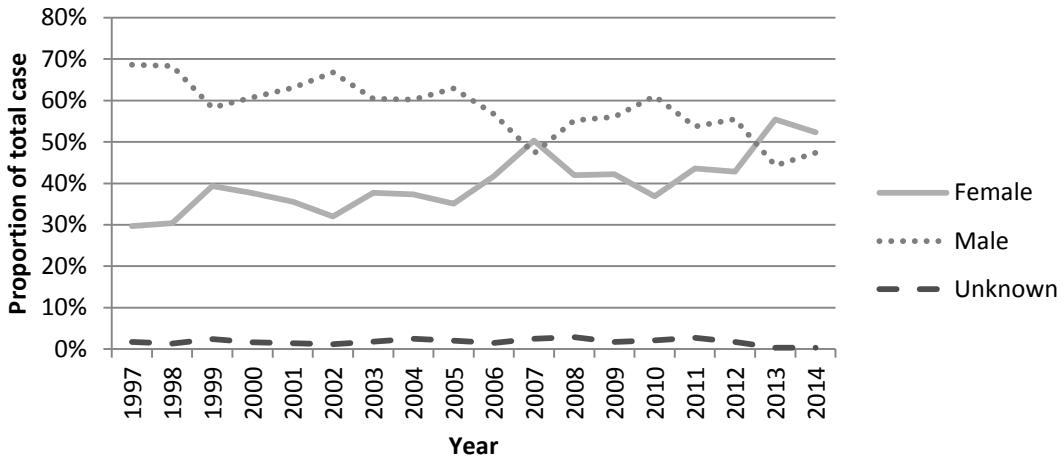


The low rates of laboratory reports in children under five is likely to reflect the fact that infection is commonly asymptomatic or mild in this age group and that they have a lower likelihood of exposure. The high rates of laboratory reports in young adults will be influenced by a number of outbreaks in MSM and PWIDs in 2000-2005, but

[1] ONS mid-year population estimate used to calculate

may be contributed to by travel to endemic countries (9-11). 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 69% in 1997 to 47% in 2014 (see Figure 4).

Figure 4. Proportion of annual laboratory reports of hepatitis A by gender 1997-2014 in England and Wales

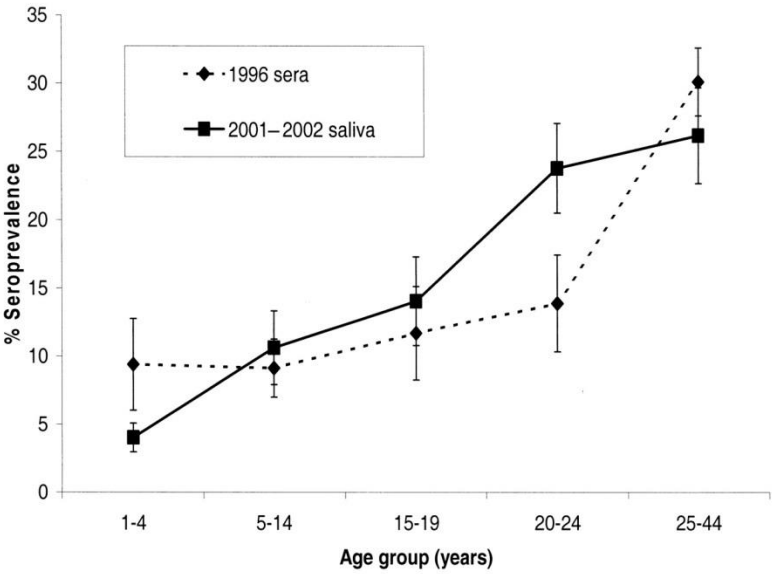


Routine data from statutory notifications and laboratory reports contain very little information on risk factors for disease acquisition. However, a study on routine laboratory reports between 1992 and 2004 found that rates of infection were more than double in persons with names indicating a South Asian 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 reporting of travel history has fallen in the past 10 years, from 24% in 1997 to 16% in 2014, so it is not possible to establish whether there are any trends in travel-associated disease. Preliminary results from an ongoing project, aiming to improve the collation of travel history for cases of hepatitis A using multiple sources, has determined 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 2013-2014 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 1-9 years to 73.5% in those aged over 60 years (54). A more recent study, in 2001-2002, of approximately 5,500 oral fluid samples on persons aged less than 45 years

from across England and Wales showed a similar trend with age, from 10% in those aged <1 years to 26% in those aged 25-44 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 7-12 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 5. Comparison of hepatitis A virus seroprevalence estimates in England and Wales from 2001-2002 oral fluid survey with a 1996 population-based seroprevalence survey by Morris-Cunnington et al (55).

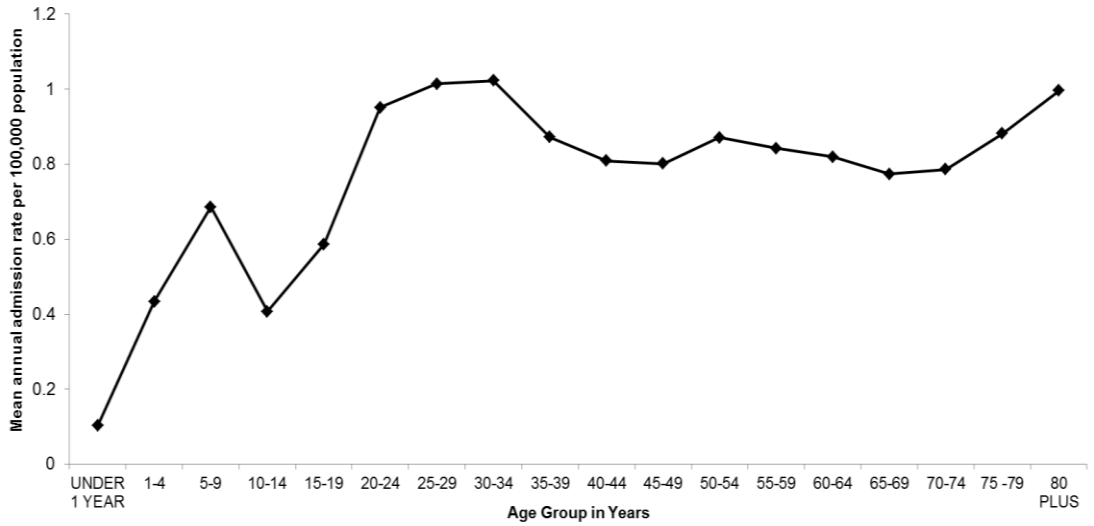


Source: Morris-Cunnington MC, Edmunds WJ, Miller E, Brown DWG. A population-based seroprevalence study of hepatitis A virus using oral fluid in England and Wales. American Journal of Epidemiology, 2004; 159: 786-794, by permision of Oxford univeristy Press.

Whilst acknowledging general under-reporting of viral hepatitis in hospital admission and deaths data, they can give an indication of morbidity and mortality from acute hepatitis A infection. From 2005-2014 inclusive, Hospital Episode Statistics (HES) data recorded 4035 individuals admitted with a diagnosis of hepatitis A infection in England. This includes 333 individuals who were admitted on more than one occasion with a diagnosis of hepatitis A infection, making a total of 4463 episodes (range 364-493 per year) recorded so may reflect coding errors or a complication of hepatitis A. Mean annual admission rate peaks in the 30-34 year age group and again in the over 80 age group (See Figure 6).

The duration of hospital episode can be used as a proxy for severity of disease. The mean duration of admission is 5 days. The proportion of individuals who have an episode of hepatitis A greater than 2 days increases with age; with over 60% of over 80 year olds being admitted for over 2 days (See Figure 7). Episode has been used rather than total spell in hospital as it is specific for the duration of admission due to hepatitis A infection.

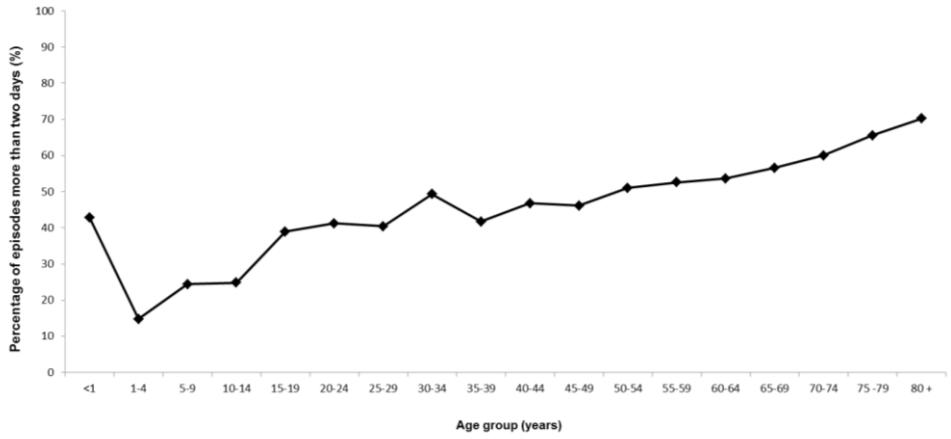
Figure 6. Mean annual admission rate for hepatitis A per 100,000 population by age group 2005-2014 in England[2]



Data source: Hosptial 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.

[2] **Assessing growth through time (Admitted patient care)** HES figures are available from 1989-90 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, e.g. 2012-13 includes activity ending between 1st April 2012 and 31st March 2013.

Figure 7. Percentage of all hepatitis A related hospital admissions which are for more than two days duration by age group 2005-2014 in England[2]



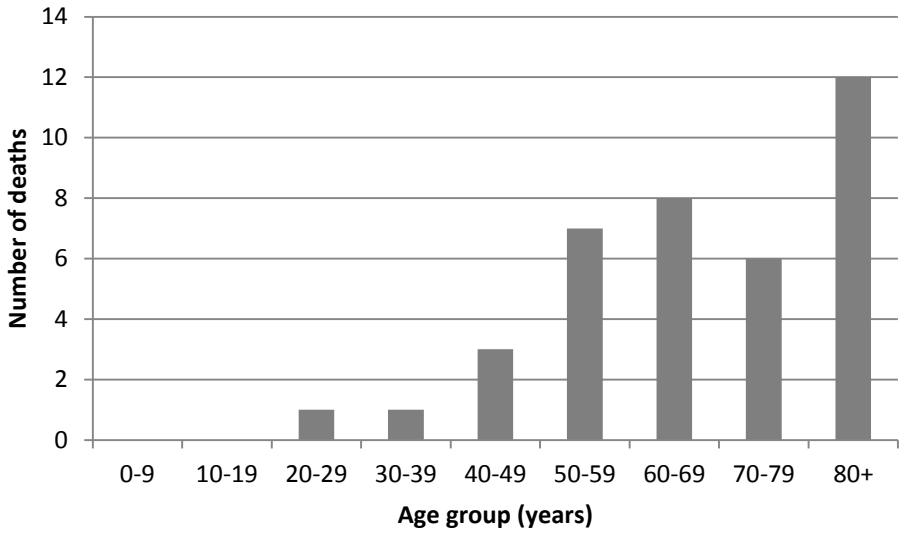
Data source: Hosptial Episode Statistics (HES), Health and Social Care Information Centre.

A further indication of severe morbidity can be derived from liver transplant data. In the 10 years from 2005-2014 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 10 years from 2005-2014 there were 38 deaths where hepatitis A was written as an underlying or contributing cause of death (Figure 8). Estimating deaths due to hepatitis A is difficult because of data accuracy; during this period 84 death certificates were noted to have hepatitis A coded as a contributing or underlying cause (this means 46 had hepatitis A coded but not written on the death certificate), and only 3 of these were confirmed on laboratory databases. In addition, of the 4463 episodes in HES, 143 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 8. Number of deaths in England and Wales between 2005-2014 where hepatitis A was written on the death certificate as an underlying or contributing cause of death.



Data source: Office for National Statistics

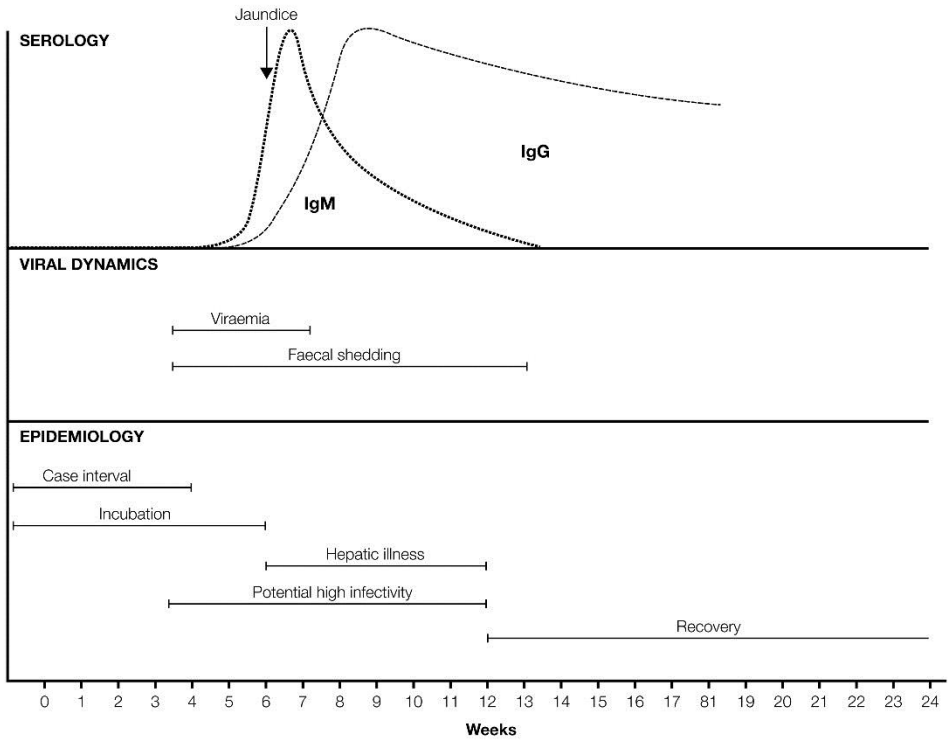
Of the 38 deaths in England and Wales in which hepatitis A was likely to have been a cause in the 10 years from 2005-2014, 22% (n=8) occurred in patients with chronic liver disease and an additional 5% (n=2) were noted to have had a liver transplant (although it was unclear if this was as a result of 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.

2.4 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 9 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 48-72 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 e.g. HAV RNA PCR on blood and faeces.

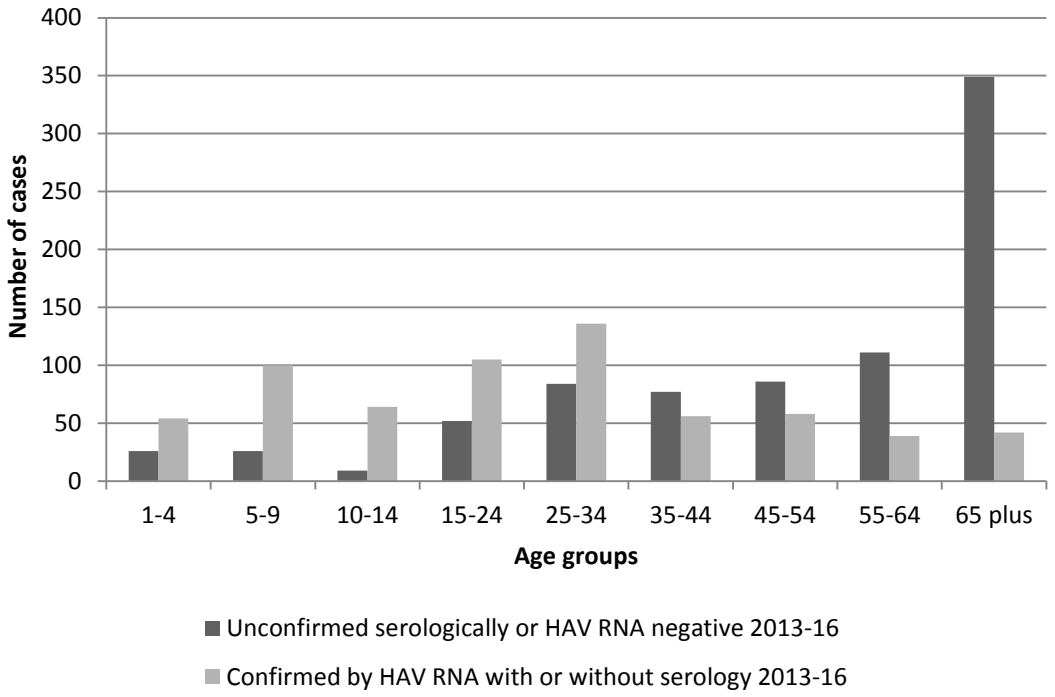
Figure 9. Immunological response to hepatitis A infection



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 2014 Annual Report on Hepatitis A, 28.5% of serum samples (59/207) reported as anti-HAV IgM positive on the Second Generation Surveillance System (SGSS) 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 10).

Figure 10. False positivity of anti-HAV IgM positive serum samples referred to VRD for confirmatory testing 2013-16 from England and Wales.



Data source: PHE 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 (e.g. 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 (e.g. 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 notified that the oral fluids are being taken and who the index case in the household is. 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.

As part of on-going monitoring of the proficiency and quality assurance of oral fluid testing, PHE will request from time to time oral fluid sampling from cases of hepatitis A that have been diagnosed serologically. As this sampling does not affect their diagnosis, results will not be reported back to their GP or HPT.

2.5 Evidence Base for Recommendations

Human normal immunoglobulin

The current human normal immunoglobulin (HNIG) (Subgam) issued by Public Health England 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 IU/ampoule when reconstituted in 0.5.ml (98 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 – 86.8 IU/ml (65). Although these lower levels of antibody may be associated with protection, current PHE hepatitis A HNIG guidelines (63) recommend administering a larger volume to achieve a prophylactic effect (500mg to those under 10 years old and 750 mg to 10 year olds and over). Please consult the most up-to-date version of the Immunoglobulin Handbook (available via the PHE website at https://www.gov.uk/government/publications/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 1). 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 17/620 (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%. These data suggest 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 1. Efficacy of HNIG for post-exposure prophylaxis against Hepatitis A

Setting	Type of study	Protective efficacy / effectiveness
Outbreak, Children's summer camp, USA, 1944 (70)	Non-placebo controlled study of HNIG vs. no treatment	Against jaundice 87% Against clinical hepatitis 69%
Outbreak, Children's home, USA, 1945 (71)	Randomised non-placebo controlled study of HNIG vs. 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 vs. no treatment	93%
Outbreak, Institution for learning disabilities, USA, 1952 (73)	Randomised non-placebo controlled study, HNIG 0.05 ml/lb vs. no treatment	Against jaundice 86% No efficacy against non-icteric hepatitis
	Randomised non-placebo controlled trial, HNIG 0.01 ml/lb vs. no treatment	Against jaundice 80% No efficacy against non-icteric hepatitis
Household contacts aged 2-9 years within 14 days of exposure Israel, 1964 (74)	Randomised placebo-controlled trial of two different lots of HNIG (1953-4 vs. 1961)	46.9% (1953-4 IG) 87.5% (1961 IG)
Outbreaks, Schools, psychiatric hospitals, children's homes, England, 1966-68 (75)	Randomised non-placebo controlled trial	65.3%
Outbreak, household contacts in rural community, USA, 1970 (76)	Retrospective cohort	87%
Outbreak, Household contacts seen either within 2 weeks or greater than 2 weeks since exposure, USA, 1983-4 (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	Retrospective cohort	51 secondary cases

Setting	Type of study	Protective efficacy / effectiveness
setting, Slovakia 1993-1995 (79)		developed in 3,837 contacts given HNIG
Household contacts of cases 2002/05, Kazakhstan (80)	Randomised double-blind active-control noninferiority trial	84% see table 2 for more details
Household contacts of notified cases in Amsterdam 2004-12 (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 2008-10 (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 >14 days post exposure

There are 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 2-3 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 eight 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 (Havrix®, Vaqta®, and Avaxim®[4]), 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 (92-95). However, the contribution of IgM to protection within two 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 12-15 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 1-40 years showed an efficacy of vaccine in preventing infection of 82% (95% CI 20-96%), with an efficacy of 100% (9/207 versus 0/197) in preventing clinical hepatitis A (21).

[4] Epaxal® has now been discontinued by the manufacturer.

Table 2 summarises published efficacy data for post exposure hepatitis A vaccine.

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

Setting	Type of study	Protective efficacy / effectiveness
Outbreak in a Jewish community, USA, vaccine given to children age 2-16 years 1991 (101)	Double-blind, placebo-controlled trial	100%
Household contacts of sporadic cases in Naples, 1997 (21)	Randomised controlled trial of vaccine vs no treatment	82%
Ten outbreaks, school setting, Slovakia 1993-1995 (79)	Retrospective cohort	16 secondary cases developed in 2,171 vaccinated contacts
Household contacts of cases 2002/05, Kazakhstan (80)	Randomised double-blind active-control noninferiority trial	79%
Household contacts of notified cases in Amsterdam 2004-12 (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 2008-10 (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 are 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 1090 susceptible contacts aged 2-40 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 3). 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 3. Secondary attack rates and estimated efficacy of hepatitis A vaccine vs. HNIG when given within 14 days of exposure, Almaty, Kazakhstan, 2002-5 (80)

	Secondary attack rate when administered 1-7 days post exposure (95% CIs)	**Estimated efficacy 1-7 days post exposure (95% CIs)**	**Secondary attack rate when administered 8-14 days post exposure (95% CIs)**	**Estimated efficacy 8-14 days post exposure (95% CIs)**	**Overall estimated efficacy 1-14 days post exposure (95% CIs)**
Hepatitis A vaccine	4/79 = **5.1%** (1.4%, 12.5%)	76% (51 - 100%)	21/489**=4.3%** (2.7%, 6.5%)	80% (68 - 91%)	79% (68% - 90%)
Immuno-globulin	2/68 = **2.9%** (0.4%, 10.2%)	86% (66 - 100%)	15/454=**3.3%** (1.9%, 5.4%)	84% (74 - 94%)	84% (75% - 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 <30, or, 30-50 years and vaccinated <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, 8/112 (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 >40 years of age. In healthy contacts immunised per-protocol <8 days post-exposure, relative risk of secondary infection in those >40 years was 12.0 (95% CI 1.3-106.7). This is based on secondary infection in 3/10 contacts aged over 40 years who received vaccine per-protocol and 4/90 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 1/260 (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 <40 year olds and ≥ 40 year olds. Both studies found reduced seroconversion rates 15 days post immunisation in the ≥ 40 year old group; seroconversion rates (≥ 10 mIU/ml of anti-HAV) of 77% in persons aged 40-62 years compared to 97% in persons aged 20-39 years in one study (102), and seroconversion rates (≥ 20 mIU/ml) of 23% in patients aged 40-65 years compared to 60% in those aged 18-39 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 (mean age 47.0) compared with 92.3 (84.0-97.1) of 20-30 (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 20-30 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 40-49 year olds after one HAV vaccine, 54% (n=37) and 81% (n=42) of 50-59 year olds, and 30% (n=10) and 50% (n=10) of ≥60s 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 <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 <2 years old.

Several immunogenicity studies have evaluated the use of hepatitis A vaccine in children <12 months (108-111). 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 three-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 (≥ 33 mIU/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 were 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 50–95% overall, but range from 9% at CD4 counts <200 cells/mm^3 to 95–100% at CD4 counts >300–500 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 (115-120). The duration of protection in HIV-infected people is unknown, but may be shorter than in HIV-negative persons. There are 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 two 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 three women with acute hepatitis A which identified antibodies in breastmilk, and HAV RNA was detected in two specimens, however none of the three infants acquired clinical hepatitis A infection, therefore mothers should not be encouraged to discontinue breastfeeding (125).

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

There are no studies examining the efficacy of hepatitis A vaccine used >14 days post exposure. There is weak anecdotal evidence that hepatitis A vaccine given >14 days post exposure may attenuate clinical illness. In one study three 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 three 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 (127-130). 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 in older patients

It is well established that severity of disease increases with increasing age (12). Three large studies (with 256-770 patients) have identified increasing age as being associated with increasing severity of disease (131-133); however several small studies (each with less than 100 patients) have not found age to be statistically significantly associated with disease severity (134-138). 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 (139-141). 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 256-770 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 (131-133). 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 (144-146), primary schools (35-37), 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, three 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 (R_0) which varies according to country, e.g. 1.1 -1.5 in USA (153) and 2.2 in Italy pre-vaccine introduction (154). In England R_0 is more likely to be similar to the US. Therefore even taking the upper estimate for R_0 of 1.6, a modest immunisation coverage of 40% in a susceptible population is likely to make the effective reproductive number, $R_e < 1$ 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 4. 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 nursery/schools. Oral fluid testing was used in three outbreaks to understand the transmission dynamics (table 4). Mass immunisation was carried out in 16 of the 19 outbreaks (see table 5), mainly in educational (nursery/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 5).

Table 4. Summary of hepatitis A clusters and incidents characteristics, in England, 2011-2015 (N=19)

Median delay onset of symptoms to HPT notification (N=15 clusters).	15 days, range: 8-51
Median delay onset of jaundice to notification to the HPT (N=17 clusters).	7 days (range: 2-17)
Median age of index cases (N=16 clusters)	9.5 years (range: 2-52)

Genotype (N= 10 clusters)	1A: 30%
	1B 70%
Oral fluid testing used	3 clusters
Median number of household contacts	5 (range: 1-46)
HNIG offered	6 clusters , 53 contacts (all contacts >50 year old)
Median number of linked cases by outbreak (N=17 clusters , total 63 cases)	2 (range: 1-17)
Median age of all secondary cases (N= 5 clusters, 39 cases).	9.5 years (range: 0-58)
Sex of secondary cases: (N=4 clusters, 19 cases)	12 (63%) : female
Cluster settings	Combined (household and school/nursery): 3
	Household: 4
	School/nursery: 7
	Other: 2 (1 choir trip and 1 care home)

Table 5. Summary of hepatitis A wider immunisation in response to outbreaks in England, 2011-2015 (16 clusters)

Cluster setting (N=16)	Primary schools: 10
	Nursery: 4
	Care home: 1
	Choir: 1
Extent of immunisation in educational settings (school/nursery) (N=10 clusters)	Same class/room: 1
	Same year: 1
	Whole structure: 6
	All groups sharing toilet/or specific area with index case: 2
Total number of people immunised	2508
Median number of immunisations per cluster	90 (range: 27-1000)
Median immunisation uptake	80% (range 49-100%)
Immunisations (N=10 clusters)	School/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 HAV guidance working group

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Abbreviations

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
IHBSD	Immunisation, Hepatitis and Blood Safety Department
MMR	Measles, Mumps, Rubella
MSM	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
US	United States
vCJD	variant Creutzfeldt–Jakob Disease
VRD	Virus Reference Department
WHO	World Health Organization

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Appendices

Appendix 1: Information Sheet

HEPATITIS A Information Sheet

What is hepatitis A?
Hepatitis A is a disease caused by the hepatitis A virus which affects the liver. Hepatitis means inflammation of the liver and viruses are a common cause.

How is hepatitis A spread?
The hepatitis A virus is caught by eating or drinking food or water which is contaminated with the virus. The infection can also be spread by close contact with an infected person. The virus is spread by poor personal or public hygiene. It can be caught where standards of hygiene are low in this country and abroad.

How do I know if I or someone else has it?
The illness usually begins with a sudden onset of fever (temperature), feeling unwell, loss of appetite, tiredness, nausea and stomach pain which may be followed within a few days by jaundice - a yellow discolouration of the whites of the eyes and often the skin. Severity of symptoms increases with age. Young children may have mild infections without jaundice or other symptoms and many may have no symptoms at all.

Is hepatitis A infectious?
Yes, the infection is most commonly spread from person to person by infected faeces (stools) and poor hygiene. Transmission within households is very common. The faeces from infected people are infectious for two weeks before the person becomes ill and for about a week after the jaundice appears. Children without symptoms may be infectious for several weeks longer. People travelling abroad to countries where sanitation is poor are at risk of becoming infected. It is always advisable to seek travel health advice from your GP before undertaking any foreign travel. A vaccine against hepatitis A is available and can be obtained from a GP/travel health clinic before travelling to countries where hepatitis A is common.

How do you get hepatitis A?
You can be infected with the hepatitis A virus by:

- eating food prepared by someone with the infection who hasn't washed their hands properly or washed them in water contaminated with sewage
- drinking contaminated water (including ice cubes)
- eating raw or undercooked shellfish from contaminated water
- close contact with someone who has hepatitis A
- having sex with someone who has the infection (this is particularly a risk for men who have sex with men) or injecting drugs using contaminated equipment

How can the spread of hepatitis A infection be avoided?
Young children often have infection without having symptoms. The most important steps to prevent the spread of the infection are:-

- Good hand washing; especially after using the toilet, after changing nappies, after helping a child with toileting and before eating and preparing food, is the most effective way to prevent hepatitis A spreading.

- Toilets (handles and seats) should be kept clean; this should include the use of normally available cleaning agents found in most supermarkets/shops.

Is there a vaccine to prevent hepatitis A infection?
Hepatitis A can be prevented by vaccination. The hepatitis A vaccine is an inactivated vaccine (not a live virus) and cannot cause the illness it protects against. The vaccine is usually offered to household contacts of infected people to prevent transmission. The vaccine is very safe and effective but may not prevent infection in all cases but may lessen the symptoms of the disease. Side effects are usually mild and the commonest reactions are transient soreness at the injection site. The full immunisation schedule involves being given two doses of hepatitis A. The first dose of vaccine will give short term protection (lasting approximately 6 months). A second dose of hepatitis A vaccine given 6 to 12 months after the first dose provides long term protection (lasting at least 25 years). People should be vaccinated against hepatitis A before travelling to countries where hepatitis A is common. Seek advice from your GP or travel health clinic.

Is there treatment for hepatitis A?
There is no specific treatment for hepatitis A. Symptoms for the infection are treated as they appear. Individuals may need to be hospitalised as a result of their illness. There is a small risk of death during the acute phase of infection particularly in those aged 60 and over.
A person can return to their work/ school roughly seven days after the illness (jaundice) begins if they feel well enough.
Once a person has recovered from hepatitis A infection they will be immune (protected from reinfection) for life.

What should I do if I think a member of my household has the illness?
Seek advice from your GP.

Appendix 2: Case/ Close contact oral fluid test letter

Service/team
First address line
Second address line
Town/city Postcode

T +44 (0)20 7000 1234
F +44 (0)20 7000 1234

www.gov.uk/phe

00 Month 20XX

Dear ***[Name of case or close contact / parent or guardian]***

Your doctor has recently notified the local health protection team of Public Health England (PHE) that you have been diagnosed with hepatitis A OR are a close contact of someone with a diagnosis of hepatitis A. Hepatitis A is a viral illness spread by the consumption of contaminated food or water. Your doctor is legally obliged to report all such cases, in confidence, to PHE who are responsible for the investigation and control of infectious diseases.

Hepatitis A is now an uncommon infection in the U.K and many cases are related to travel overseas. Symptoms include flu-like symptoms and jaundice (yellowing of the skin) which gradually clears over time. Often hepatitis A does not cause any symptoms, particularly in children, who may be unaware that they have had the infection. Most people recover and have no long term problems. Hepatitis A can be passed from person-to-person, particularly between close contacts and those living in the same household. Spread of infection can be prevented by good hygiene, especially hand washing, and immunisation. It is therefore important that close contacts of cases receive hepatitis A vaccine.

We also recommend **oral fluid** (**saliva) samples** are taken from close contacts of children diagnosed with hepatitis A to test for recent hepatitis A infection only. In addition, we are requesting oral fluid samples from a small number of people diagnosed with hepatitis A (also known as cases of hepatitis A) to compare this oral fluid test against the usual blood test for hepatitis A.

The sample is very simply taken by gently brushing the teeth and gums with a sponge swab and is therefore, painless - even in young children. The sample can be taken by you, a parent or guardian, or a doctor or nurse. If you are willing to help, please take your oral fluid sample as soon as possible.

If you are a close contact and have been advised to receive hepatitis A vaccine please take this oral fluid sample preferably BEFORE OR AT THE SAME TIME that you receive hepatitis A vaccine from your GP/Practice nurse. **If you have been diagnosed with hepatitis A**, please take this sample even if you have had a blood test for hepatitis A.

We have enclosed a special oral fluid collecting kit with instructions and a short form to fill out; these can then be posted to the laboratory using the pre-paid addressed bag. If you are unable or uncomfortable with taking your sample yourself, please contact your GP who can arrange taking the sample for you. For close contacts, the results will be available from your GP within a few weeks. For people already diagnosed with hepatitis A, results will not be sent back to your GP as it does not change your original diagnosis.

If, for any reason, you do not want the test, this will not affect the care you receive from your doctor.
Thank you for your help with this important investigation. If you want to learn more about hepatitis A please visit: http://www.nhs.uk/conditions/Hepatitis-A/Pages/Introduction.aspx

If you have any queries, you can talk to a doctor or nurse at your local PHE Centre on ***xxxxxxxx.***

Yours sincerely

Position
Team
employee.email@phe.gov.uk

REQUEST FORM FOR ORAL FLUID CONFIRMATION OF HEPATITIS A To be completed by case of hepatitis A or close contact Please complete a separate form for each case or close contact in a household	For laboratory use only Project code: **SUHAV** For PHE centre only Name of HP team / PHE centre:
DETAILS OF PATIENT HAVING SWAB TAKEN	**DETAILS OF PATIENT DIAGNOSED WITH HEPATITIS A**
Name: Sex: M ☐ F ☐ Date of birth: _____/_____/_____ Postcode:_____ Is patient a case of hepatitis A?: Yes ☐ No ☐ Is patient a close contact of a hepatitis A case?: Yes ☐ No ☐ Date saliva sample taken: _____/_____/____	Name of patient diagnosed with hepatitis A in the household (if not already given): _____ Date of birth (if not already given): _____/_____/_____ Date of onset of symptoms (if any) in case: _____/_____/_____ If case has /had symptoms, date of onset of jaundice (yellowing eyes and skin): _____/_____/_____
VACCINATION HISTORY	**GP DETAILS**
Hepatitis A vaccine: Yes ☐ No ☐ If yes, date of vaccination: ____/_____/_____	GP name, full address including surgery name and postcode: Practice Name: Address: Postcode:

Instructions for taking and posting the swab:

1. In this package you should have the following items:
   - a blue swab (A) inside a clear tube (B) (both in a sealed paper packet)
   - a green screw top container (C) inside a cardboard box (D),
   - a request form (E) and
   - a pre-paid plastic envelope (F), and
   - a pictogram of how to take the swab
2. Open the paper packet, remove the top from the clear tube (B) and pull out the blue swab using the handle. **Rub the blue sponge swab all along the gums and teeth** (if present), a bit like using a toothbrush, for one to two minutes.
3. Place the wet swab (A) back inside the clear tube (B), and replace the white cap. Please print the name, date of birth and today's date on the label on the clear tube.
4. Please now wash your hands.
5. Place the labelled tube containing the swab inside the green screw top container (C).
6. Please complete the request form (E), ensuring that the patient's name and the GP name and address are correct.
7. Place both the completed request form and the green screw top container back into the cardboard box (D), and then into the pre-paid plastic envelope (F).
8. Seal the envelope. Post as soon as you can in a Royal Mail post box – a stamp is not required.
9. The results should be available from your doctor within a few weeks.

Thank you

If you are unclear about these instructions you can phone 0208 327 6442 within office hours. IF THE PAPER PACKET HAS BEEN OPENED, DO NOT USE THE SWAB, BUT STOP AND RING THE NUMBER ABOVE.

Appendix 3: Contact immunisation letter to GP

Service/team
First address line
Second address line
Town/city Postcode

T +44 (0)20 7000 1234
F +44 (0)20 7000 1234

www.gov.uk/phe

GP Surgery name
Street name
Town
Postcode

00 Month 20XX

Dear Doctor/Practice Nurse

Re: Immunisation for hepatitis A contacts

The ***xxxxxxxx*** team has been notified that the above patient has been diagnosed with acute hepatitis A with symptom onset ***<ENTER DATE>.*** We have identified ***<ENTER NUMBER>*** contact(s) of this case who are registered at your practice and require hepatitis A immunisation.

The vaccine should be administered without delay as it is known to be effective at reducing the risk of secondary infection when given within 14 days of symptom onset in the case. Hepatitis A vaccine given >14 days post exposure is still beneficial in households with more than one contact to help in the prevention of tertiary cases. Completion of the hepatitis A schedule to provide longer term protection of at least 25 years requires a second dose after 6-12months.

Please refer to the Green Book, chapter 17 for further information:
https://www.gov.uk/government/publications/hepatitis-a-the-green-book-chapter-17

If any of the contacts are aged 60 years and over, have chronic liver disease, confirmed hepatitis B or C infection or are immunosuppressed, please contact us urgently on the number above for further advice regarding additional prophylaxis with Human Normal Immunoglobulin (HNIG).

Please do not hesitate to contact us at the ***xxxxxxxx*** team on ***xxxxxxxx*** should you require any further information.

Contact(s) of acute Hepatitis - A case registered with your practice requiring vaccine

Name	Date of Birth	Address	Type of contact (e.g. household, sexual etc.)

Yours sincerely

Position
Team
employee.email@phe.gov.uk

Appendix 4: School staff immunisation letter

Service/team
First address line
Second address line
Town/city Postcode

T +44 (0)20 7000 1234
F +44 (0)20 7000 1234

www.gov.uk/phe

School/college
Street name
Town
Postcode

00 Month 20XX

Dear member of staff,

We have been notified that there has been a confirmed case of hepatitis A at the school. Hepatitis A is a viral illness spread by the consumption of contaminated food or water. Infection can spread from a person with the infection to others in the same environment, for example if they share toilets or if food which is touched by a person with the infection is consumed by people who do not have immunity. Hepatitis A is now an uncommon infection in the U.K and many cases are related to travel overseas; however, in this case we cannot identify a link to overseas travel or a source elsewhere.

The decision has been made to vaccinate **all children / children in years *xyz*** at the school in order to protect them from developing this infection.

You are advised to take this letter to your GP and arrange for immunisation. You will not need to pay your GP to have this immunisation. The **attached** factsheet gives information about hepatitis A vaccine. If you or your GP have any queries, please call ***xxxxxxxx*** Health Protection Team on ***xxxxxxxx.***

It is important to make yourself aware of the symptoms of hepatitis A, given the small risk that you may go on to develop the infection even if you receive immunisation. Symptoms include flu-like symptoms and jaundice (yellowing of the skin) which gradually clears over time. Often hepatitis A does not cause any symptoms, particularly in children, who may be unaware that they have had the infection. Most people recover and have no long term problems.

If you develop any of the symptoms above in the coming 2-6 weeks, please go to your GP and inform both ourselves and the school. Persons with suspected hepatitis A infection should be excluded from school until their doctor advises that it is safe to return. This is usually for a period of one week.

If you want to learn more about hepatitis A please visit http://www.nhs.uk/conditions/Hepatitis-A/Pages/Introduction.aspx

Yours sincerely

Position
Team
employee.email@phe.gov.uk

Appendix 5: Parent information letter

Service/team
First address line
Second address line
Town/city Postcode

T +44 (0)20 7000 1234
F +44 (0)20 7000 1234

www.gov.uk/phe

School/college
Street name
Town
Postcode

00 Month 20XX

Dear parent/ guardian,

I am writing to inform you that there has been a case of confirmed hepatitis A infection in a pupil in year ***xyz*** at ***xyz*** School. ***Xxxxxxxx*** Public Health England Centre, the NHS in xxxxxxxx area and ***xxxxxxxx*** council have reviewed the risk posed by this infection and have recommended the immunisation of all children and staff in year xyz as a precautionary measure. No other children, staff or visitors to the school will be offered the vaccine as the risk of exposure to them is very low.

Parents of pupils from Year ***xyz*** will be contacted separately with further details about the immunisation.

Hepatitis A is a viral infection of the liver which can be commonly transmitted via poor hygiene, through person to person spread or through contaminated foods or water. Symptoms can include fever, abdominal pain, loss of appetite, nausea, vomiting and sometimes leading to jaundice. Hepatitis A infection can sometimes spread within families but the most common cause in the UK is due to foreign travel to countries where sanitation is poor.

Young children with hepatitis A often have mild or no symptoms at all but can pass the infection to others. If your child, or a member of your family, develops jaundice (yellowish tinge to the whites of the eyes) or other symptoms of Hepatitis A (fever, tiredness, loss of appetite, nausea, abdominal discomfort or dark urine) please contact your GP (Out of hours contact NHS 111) for advice and further investigation.

This information is being given as a precaution to parents and staff of all year groups for information and as a reminder that good hygiene, especially after helping a child with toileting, offers protection. We have no other information to suggest that there is spread of the infection in other years in the school and would like to reassure you that we will continue to monitor this infection over the coming weeks.

For more information about hepatitis A please type ‘Hepatitis A and NHS choices’ into your internet search engine. http://www.nhs.uk/conditions/Hepatitis-A/Pages/Introduction.aspx
Yours sincerely

Position
Team
employee.email@phe.gov.uk

Appendix 6: Parent immunisation consent letter

Service/team
First address line
Second address line
Town/city Postcode

T +44 (0)20 7000 1234
F +44 (0)20 7000 1234

www.gov.uk/phe

School/college
Street name
Town
Postcode

00 Month 20XX

Dear Parent

Re: confirmed case of hepatitis A at _____

There has been **<ENTER NUMBER>** case(s) of confirmed hepatitis A in a child attending the ***xyz school / nursery.***

Hepatitis A is a viral infection which causes a range of illness from nausea and vomiting through to liver inflammation and jaundice. In the UK it is usually spread by poor hygiene after using the toilet (the faecal-oral route) but can also be spread through contaminated food and water. Infection is prevented by good hygiene; especially hand washing, and safe drinking water and food. Infected children under 6 years of age easily transmit the virus to others who are susceptible.

Hepatitis A vaccine reduces the risk of infection if given within 2 weeks of exposure to someone with hepatitis A infection.

To reduce the risk of your child acquiring the infection, the ***xxxxxxxx*** team is working with NHS xxx and advise that all the staff and children in ***xyz*** class be offered hepatitis A vaccine.

An immunisation session will take place, in school, on _____ at ____am. It is important for your child to be immunised with hepatitis A vaccine so that s/he will be personally protected. If you wish to accompany your child to the immunisation session, you may do so.

Please complete the attached consent form and return it to the school nurse by _____ in the envelope provided.

A second dose of hepatitis A vaccine in 6 -12months will give protection beyond 25 years if this is required.

If you require further information on hepatitis A please call NHS 111 or refer to the NHS choices website http://www.nhs.uk/Conditions/Hepatitis-A/Pages/Introduction.aspx or see https://www.gov.uk/government/collections/hepatitis-a-guidance-data-and-analysis

Yours sincerely

Position
Team
employee.email@phe.gov.uk