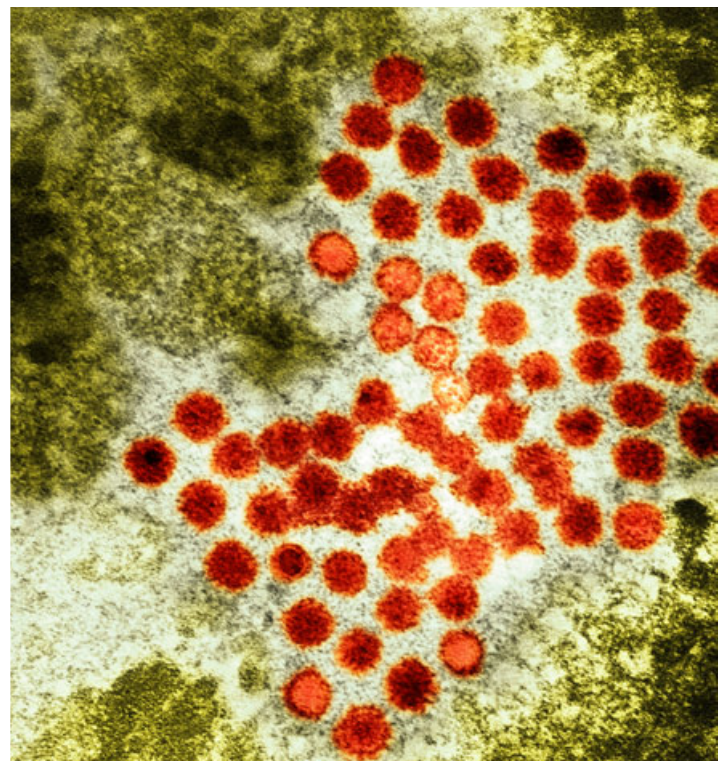


# Guidance for the Prevention and Control of Hepatitis A Infection



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## 1. 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 prevent and control outbreaks. The guidance has been developed based on a review of the current epidemiology of hepatitis A in England and Wales and a review of the literature on the efficacy of human normal immunoglobulin (HNIG) and hepatitis A vaccine for post-exposure prophylaxis.

The guidance contains the following recommendations:

### Management of the index case

- Advise on good hygiene practices
- Exclude from work, school or nursery until 7 days post onset of jaundice
- Identify possible source of infection

### Management of household and sexual contacts (see Box 6)

- **Household or sexual contacts seen within 14 days of exposure to index case**
  - Healthy contact aged 1-50 years
    - Offer hepatitis A vaccine
  - Healthy contact aged 2-12 months
    - Vaccinate carers to prevent tertiary infection OR offer hepatitis A vaccine to the infant (unlicensed) OR exclude from childcare
  - Healthy contact aged under 2 months
    - Offer vaccination to carers to prevent tertiary infection
  - Contact aged 50 years or over, or with chronic liver disease or chronic hepatitis B or C infection
    - Offer hepatitis A vaccine + HNIG
- **Household or sexual contacts seen more than 14 days post exposure**
  - More than one contact within the household and contacts seen within 8 weeks of exposure
    - Offer hepatitis A vaccine to prevent tertiary infection
  - 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 try to attenuate severity of disease
  - Contact is a food handler
    - Risk assessment of need for transfer to non-food-handling duties (see Box 4)

### Management of contacts beyond the household (specific settings)

- Index case is a food handler

- Risk assessment of need for post-exposure prophylaxis of contacts within work setting (see Box 5)
- Index case is a child cared for in a pre-school childcare setting
  - Treat contacts working in, or being cared for in, the same room as household contacts.
  - If contacts treated more than 14 days post exposure and or more than one case identified in the setting, offer vaccine to household contacts of exposed contacts to prevent tertiary infection
- Index case attends a primary school
  - If source of infection outside school not identified, assume infection acquired within school and offer hepatitis A vaccine to classroom contacts

## 2. Background Information

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<sup>1</sup>, while in countries with poor sanitation faeces-contaminated food and water are frequent sources of infection. Hepatitis A infection can also be spread during sexual intercourse and through injecting drug abuse, and there have been a number of recent outbreaks among men who have sex with men (MSM)<sup>2,3</sup> and injecting drug users (IDUs)<sup>4</sup> in the UK.

The average incubation period of hepatitis A is around 28 days (range 15–50 days). 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<sup>5</sup>. Severity of symptoms increases with age. Fulminant hepatitis occurs rarely (<1% overall), but rates are higher with increasing age and in those with underlying chronic liver disease, including those with chronic hepatitis B or C infection<sup>5</sup>. Hepatitis A does not appear to be worse in HIV-infected patients when compared to HIV-negative persons<sup>6</sup>, which may reflect the fact that the hepatic damage in hepatitis A is thought to be the result of host immune mechanisms<sup>7</sup>.

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<sup>8</sup>. Children may excrete the virus for longer than adults, although a chronic carrier 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<sup>9</sup>, 19% in Greece<sup>10</sup> and 25% in Kazakhstan<sup>11</sup>. Children under the age of 6 years are particularly effective transmitters of hepatitis A infection<sup>11,12</sup>. Transmission from children is also common, with secondary attack rates of between 2.6% and 27.6% reported in nurseries or day care centres<sup>11,13,14,15,16,17,18</sup> and secondary attack rates of between 2.9% and 50% reported in primary schools<sup>19,20,21</sup>.

Food borne outbreaks can occur due to the contamination of food at the point of service or due to contamination during growing, harvesting, processing or distribution. 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 food borne outbreaks<sup>22</sup>. 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<sup>22</sup>.

Infection is followed by lifelong immunity.

## **3. Recommendations for the prevention of Hepatitis A.**

(A detailed discussion on the evidence for these recommendations can be found at Annex D)

### **3.1 Primary Prevention**

#### **3.1.1 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. For travellers to countries of high and intermediate endemicity care should be taken to avoid exposure to hepatitis A through contaminated food and water.

#### **3.1.2 Vaccination**

There are four monovalent inactivated hepatitis A vaccines, one combined hepatitis A and hepatitis B vaccine and two combined hepatitis A and typhoid vaccines currently licensed for use in the UK<sup>23</sup>. 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 two doses are given prior to exposure<sup>24</sup>.

The following groups are recommended to receive pre-exposure vaccination. Further details are available in Immunisation against Infectious Disease<sup>23</sup> (the "Green Book") chap 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 should be encouraged to consider the travel vaccination needs of this group opportunistically.
2. Patients with chronic liver disease
3. Patients with haemophilia
4. Men who have sex with men
5. Injecting drug users
6. Individuals at occupational risk.

## **3.2 Prevention of secondary cases of hepatitis A infection**

### **3.2.1 Hepatitis A case definitions**

#### ***Confirmed case***

A case that meets the clinical case definition (an acute illness with a discrete onset of symptoms AND jaundice or elevated serum aminotransferase levels) AND is laboratory confirmed (IgM antibodies to hepatitis A virus (anti-HAV) positive).

#### ***Probable case***

A case that meets the clinical case definition (see above) and occurs in a person who has an epidemiological link with a person with laboratory confirmed hepatitis A (e.g. household or sexual contact during the 15-50 days before onset of symptoms).

#### ***Prompt notification***

Health Protection Units should work with local clinicians and microbiology or virology laboratories to ensure that cases of hepatitis A are promptly notified.

### **3.2.2 Management of the index case**

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

The index case and his or her family should receive verbal and written guidance on the importance of hand washing after using the toilet 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.

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.

An assessment should be carried out to try to identify the possible source of infection (e.g. history of travel to endemic country 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. In these circumstances, public health action may be required in that setting (see sections 3.2.4.2 and 3.2.4.3)

### 3.2.3 Management of household and sexual contacts

#### **Box 1 Definition of household-type contact:**

- 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. This would include extended family members who frequently visit the household and childminders and their families.
- A person who has *regularly* eaten food prepared by the index case during the infectious period, *or* who ate food prepared by the index case on a single occasion during the infectious period if there is concern about the hygiene practices of the index case or if the index case had diarrhoea at the time of food preparation.
- 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 during the infectious period.

#### **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. 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.

**Please refer to Appendix A for an algorithm for managing contacts of cases of acute hepatitis A.**

**A *Household and sexual contacts who have not previously received two doses of hepatitis A vaccine (or one dose within the past 6 months), do not have a history of laboratory-confirmed hepatitis A and are seen within 14 days of exposure to infection.***

#### **Box 2 Definition of time since exposure.**

- In the case of continuous exposure to the index case, this is defined as the number of days since the onset of the first symptoms \* in the index case.
- If a single exposure has occurred during the infectious period, time since exposure should be calculated as either the number of days since the onset of first symptoms in the index case or the number of days since exposure to the index case, whichever is the most recent.

\*The time since onset of first symptoms in the index case is used, rather than the time since onset of jaundice, as the evidence base for the post exposure efficacy of hepatitis A vaccine is based on its use within 14 days of first symptom onset in the index case.

#### **Box 3 Definition of infectious period in the index case**

The infectious period is taken from two weeks before the onset of symptoms to one week after the onset of symptoms

## **A.1 *Healthy persons aged 12 months to 50 years***

### **Recommendation**

A single dose of monovalent hepatitis A vaccine should be given to healthy household contacts aged 1-50 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 vaccination as pre-exposure prophylaxis, see section 3.1.2 above). Patients at continued risk of infection should be advised to receive a second dose of vaccine at 6-12 months after the first dose.

### **Summary of evidence base**

There is direct evidence from a randomised controlled trial of the efficacy of hepatitis A vaccine in preventing an estimated 79% of secondary cases of hepatitis A in healthy persons aged 2-40 years when given within 14 days of exposure to the index case.

There is good evidence from immunogenicity studies that hepatitis A vaccine produces a good immunogenic response in children from 12 months of age. In the UK hepatitis A vaccine is licensed for children from 12 months. It is therefore reasonable to extrapolate these findings 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 increased mortality rates being seen in the UK in patients over the age of 50 years. 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 50 years but not beyond this age.

## **A.2 *Healthy infants < 12 months***

### **Recommendation**

No post-exposure prophylaxis is required for healthy infants aged <12 months if all those involved in nappy changing are vaccinated against hepatitis A and thus protected against tertiary infection. Appropriate advice should be given on enhanced hygiene during infant care.

### **Summary of evidence base**

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 immunogenic response to vaccine in babies > 2 months, suggesting that the evidence on post-exposure efficacy can be extrapolated to infants in this age group.

If an infant attends nursery and it is not feasible to vaccinate all carers, or if there are other reasons to believe the child could become a source of infection to others, those aged  $\geq 2$  months should be vaccinated with monovalent hepatitis A vaccine or excluded from the childcare setting until 40 days post exposure.

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.

### **A.3 *Persons aged > 50 years***

#### **Recommendation**

Persons aged over 50 years should be offered HNIG in addition to monovalent hepatitis A vaccine. The patient should be referred to their GP for a second dose of hepatitis A vaccine at 6-12 months to ensure long-term protection.

#### **Summary of evidence base**

There is no direct evidence of the efficacy of vaccine in persons aged  $> 50$  years and there is evidence from immunogenicity studies of a lower and slower response to hepatitis A vaccine with increasing age.

The severity of hepatitis A infection increases with age, rising particularly after the age of 50 years. The use of HNIG in the secondary prevention of hepatitis A infection is established practice across all age groups.

### **A.4 *Persons with chronic liver disease, pre-existing chronic hepatitis B or C infection or HIV infection or immunosuppression.***

#### **Recommendation**

Patients with chronic liver disease, pre-existing chronic hepatitis B or C infection or HIV 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 at 6-12 months to ensure long-term protection.

#### **Summary of evidence base**

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 and evidence from immunogenicity studies of a poorer response to pre-exposure vaccination.

There is no evidence of more severe disease from hepatitis A infection in those with HIV infection. However there is evidence from immunogenicity studies of a poorer response to pre-exposure vaccination.

### **A.5 *Pregnant or breastfeeding women***

#### **Recommendation**

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

#### **Summary of evidence base**

There is no evidence of risk from vaccinating pregnant women or those who are breast-feeding with inactivated viral vaccines<sup>25</sup>.

### **B *Household contacts seen >14 days post exposure***

#### **B.1 *General advice for household contacts seen >14 days post exposure***

#### **Recommendation**

Consideration should be given to offering HNIG to household 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.

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

If a household contact who attends nursery or infant school does not receive vaccine within 14 days of exposure, hand washing should be supervised while at nursery or school to reduce the risk of asymptomatic transmission of infection.

#### **Summary of evidence base**

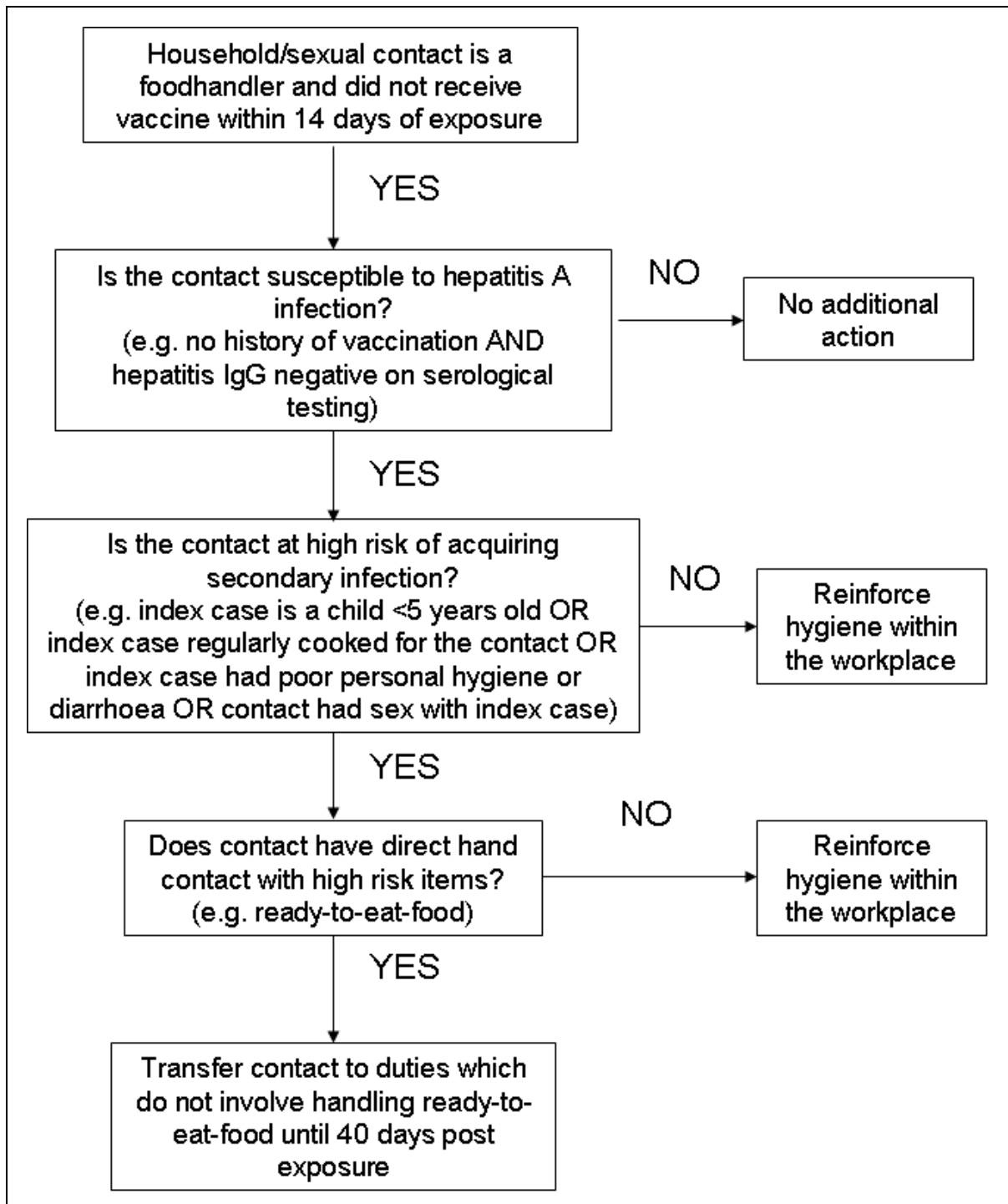
There is no clear evidence of the efficacy of either vaccine or HNIG in preventing secondary infection when given >14 days after exposure. However, there are theoretical grounds for believing that HNIG may attenuate the severity of disease if given during the incubation period. This would be of particular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

#### **B.2 *Household contacts who are food handlers and have not received vaccine within 14 days of exposure***

If it has not been possible to offer vaccine within 14 days of exposure to a food handler who has been a close contact of a person with hepatitis A, there is a risk of the food handler developing secondary hepatitis A infection and becoming a viral excreter before the onset of symptoms.

A risk assessment of the likelihood of developing secondary infection and the risk of onward transmission should be undertaken by the Health Protection Unit in conjunction with environmental health colleagues (see **Box 4**). This may require a visit to the workplace.

**Box 4. Risk assessment for contacts who are food handlers**

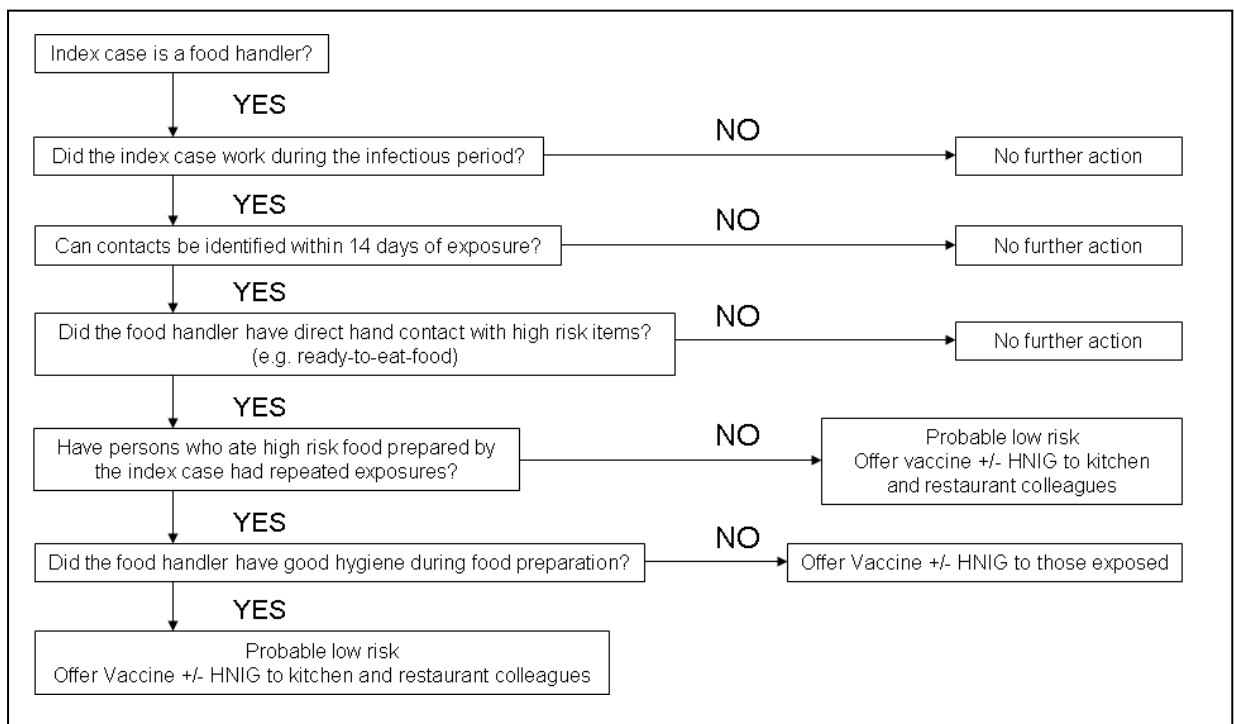


### 3.3 *Contacts beyond the household (specific settings)*

#### 3.3.1 Index case is a food handler

If a food handler is diagnosed with hepatitis A, health protection and environmental health professionals should carry out an assessment of the risk that transmission of infection may have occurred within the workplace (see Box 5). To carry out the risk assessment it is often helpful to visit the food establishment and interview the supervisors in addition to the index case. Factors to take into account include whether the food handler had bowel movements (especially diarrhoea) while at work, presence of medical conditions that might make hygiene more difficult to maintain, use of gloves, availability of hand washing facilities, standard of toilet facilities, hygiene training and previous hygiene assessments at the establishment. If individuals who have had repeated exposure to high-risk food items prepared by the index case are identified within 14 days of the last exposure, they should be offered vaccine, with or without HNIG as appropriate. Special consideration should be given to the risk to other kitchen and restaurant colleagues who may have eaten food prepared by the index case on multiple occasions in addition to sharing toilet and handwashing facilities (see Box 5)

**Box 5. Risk assessment for index case who is food handler.** Adapted from Fiore, AE<sup>22</sup>



### **3.3.2 Index case attends a pre-school child-care setting**

Close contacts of a child cared for within a pre-school child-care setting such as a nursery or child minder (e.g. those working, or being cared for, in the same room as the index case) should be treated as household contacts. As asymptomatic infection is common in this age group, if vaccine cannot be administered within 14 days of exposure to the index case, or if more than one case occurs in this setting, the household contacts of exposed children aged < 5 years should also be offered hepatitis A vaccine to prevent tertiary infection.

### **3.3.3 Index case attends a primary school**

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. 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), 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 working within the same class as the index case, and other close friends within the school, may prevent continuing transmission.

### **3.3.4 Index case attends a secondary school, workplace, hospital**

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.

### **3.3.5 Use of prophylaxis for wider communities to control outbreaks**

#### **Recommendation**

Monovalent hepatitis A vaccine is the preferred prophylaxis for use in an outbreak setting. A second dose should be given at 6-12 months after the first dose if contacts are at continuing risk.

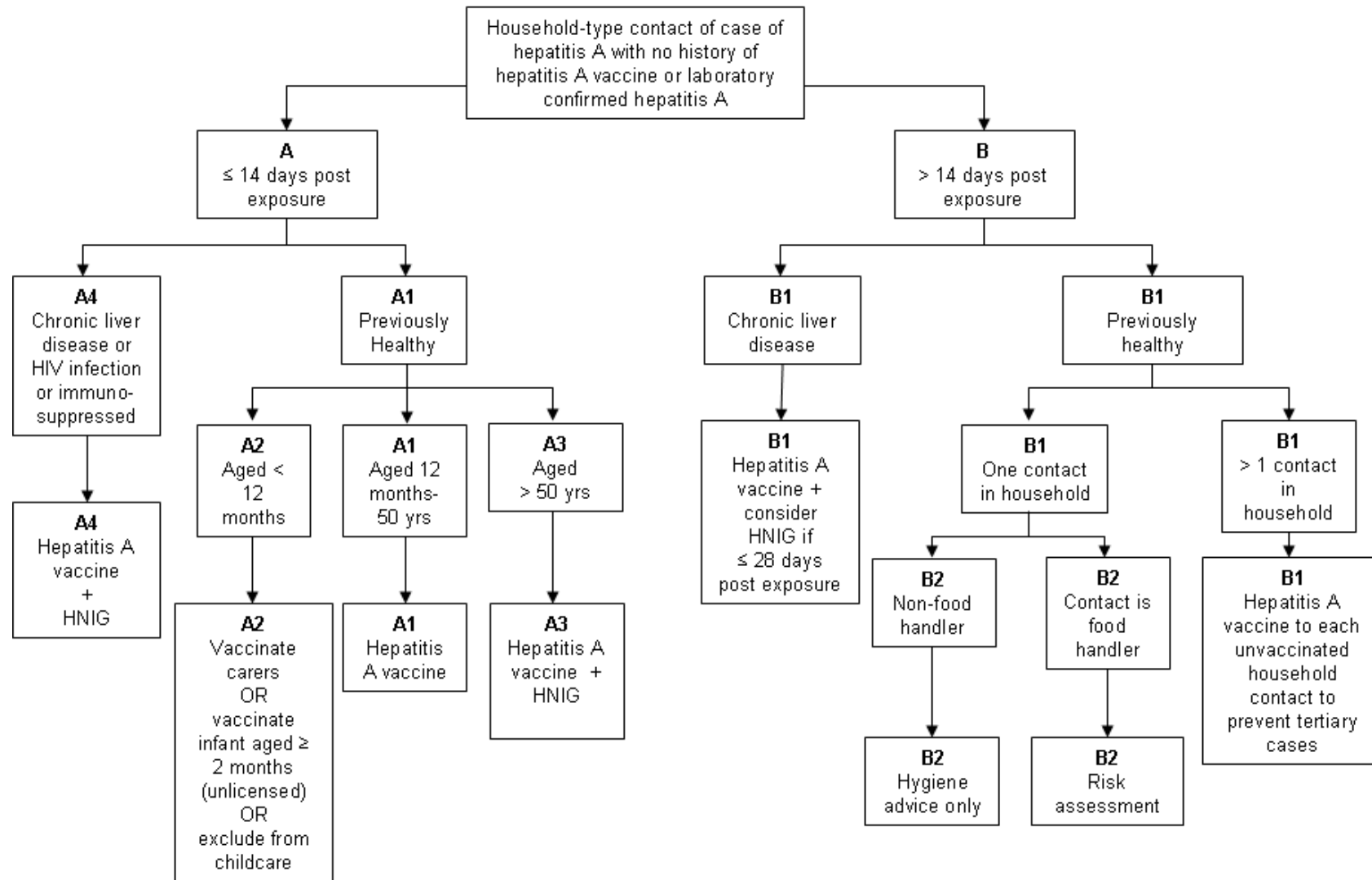
HNIG should be offered in addition to vaccine for those who are at particular risk of severe disease such as those with chronic liver disease or pre-existing chronic hepatitis B or C infection.

#### **Summary of evidence base**

Both hepatitis A vaccine and HNIG have been used successfully to control outbreaks in well-defined communities and in general population outbreaks. The effectiveness of either intervention depends on how well the community is defined, the coverage achieved with the intervention and the time elapsed since exposure to existing cases.

Widespread prophylaxis may have limited success in preventing secondary cases if exposure occurred more than 14 days before prophylaxis is given. However, vaccine is particularly useful at preventing tertiary infection and thus interrupting ongoing transmission.

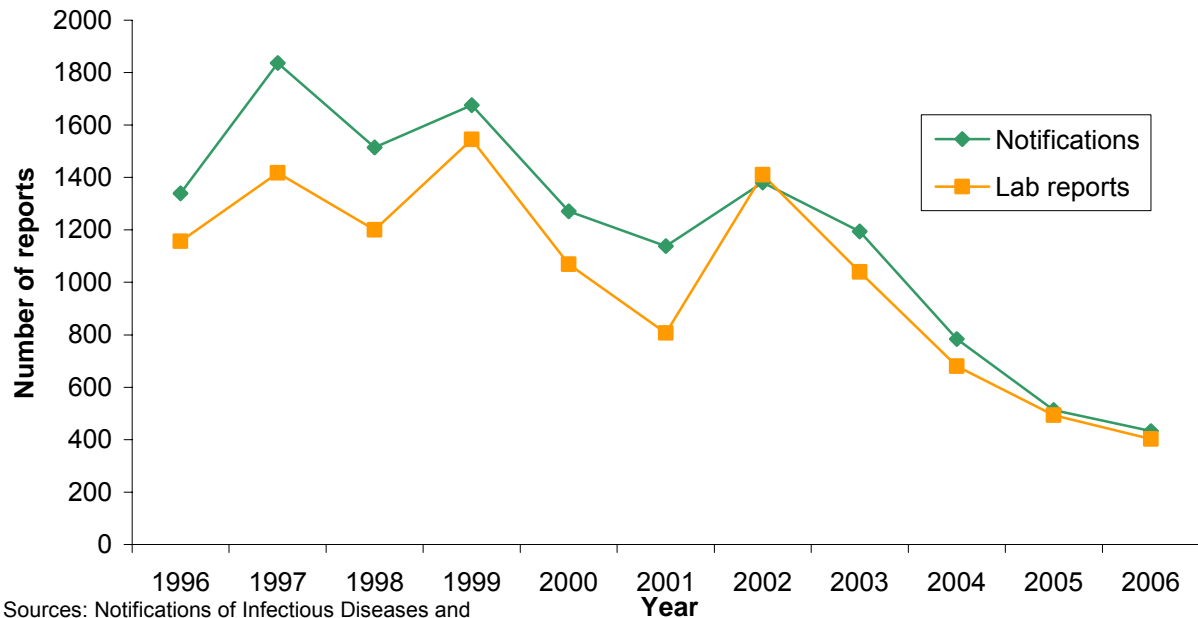
**Appendix A - Box 6. Algorithm for the management of household contacts of cases of acute hepatitis A**  
 (Please refer to section 3.2.3 of the main document for more detailed information on the algorithm)



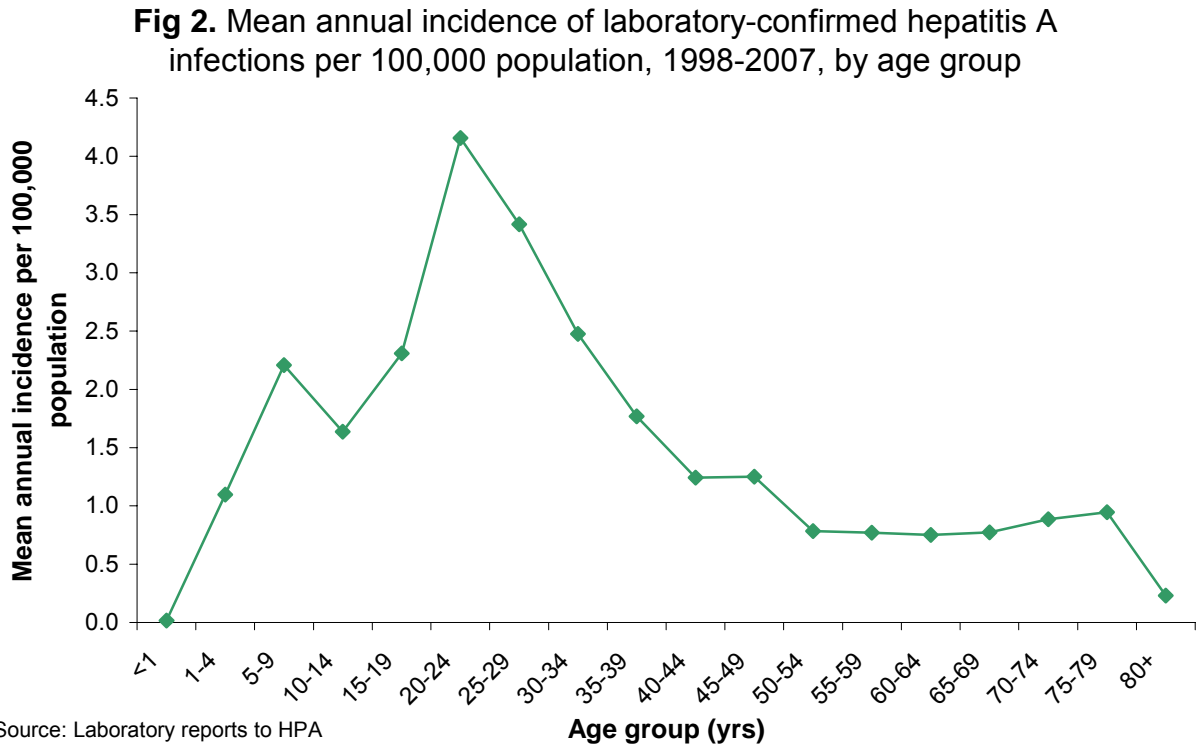
## Appendix B - Epidemiology of hepatitis A in England and Wales

As in other developed countries, the incidence of hepatitis A in England and Wales has fallen dramatically over the past 10 years. The number of statutory notifications of hepatitis A has fallen from 1,838 in 1997 to 334 in 2007 and the number of laboratory confirmed cases of hepatitis A infection reported to the Health Protection Agency each year has shown a similar downward trend (Fig 1). However, as with other notifiable diseases, there is significant underreporting of hepatitis A infection<sup>26</sup>.

**Fig 1.** Hepatitis A notifications and laboratory reports , England and Wales 1996-2006



The incidence of laboratory confirmed cases of hepatitis A shows an age-related trend, with no reported cases in children under one year, a rise in early childhood to a peak incidence of just over 4/100,000 in young adults aged 20-25 yrs, followed by a progressive decline with increasing age (see Fig 2).



The absence of reported cases in children under one year and the low incidence in children under five reflects the fact that infection is more likely to be asymptomatic or mild in this age group. The high incidence in young adults will be influenced by a number of outbreaks in MSM and IDUs in this period. The decline in incidence with age, from early adulthood, is likely to reflect the increase in seroprevalence (and thus decline in susceptibility) with age.

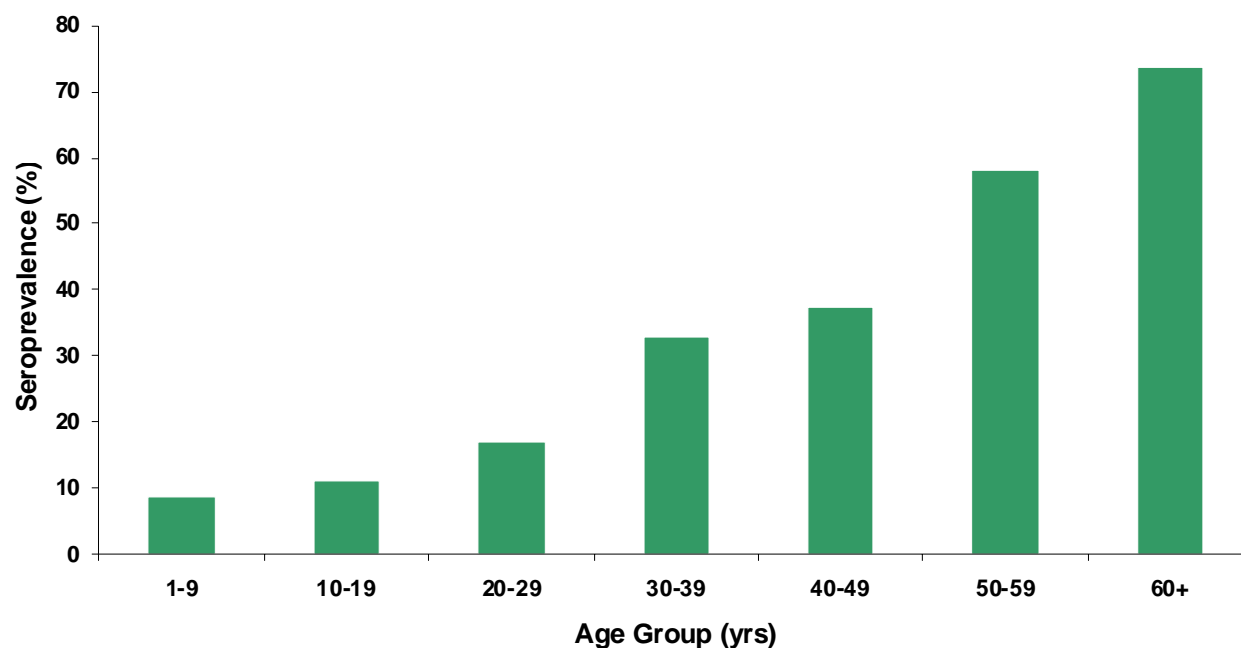
Routine data from statutory notifications and laboratory reports contain very little information on risk factors for disease acquisition. However, a study on routine laboratory reports between 1992 and 2004 found that rates of infection were more than double in persons with names indicating a South Asian ethnic origin<sup>27</sup>. 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 dramatically in the past 10 years, from 27% in 1996 to 1% in 2007, so it is not possible to establish whether there are any trends in travel-associated disease.

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 (Fig 3)<sup>28</sup>.

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 4% in those aged 1-4 years to 26% in those aged 25-44 years<sup>29</sup>. 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 the risk of natural HAV infection (seropositivity in non-

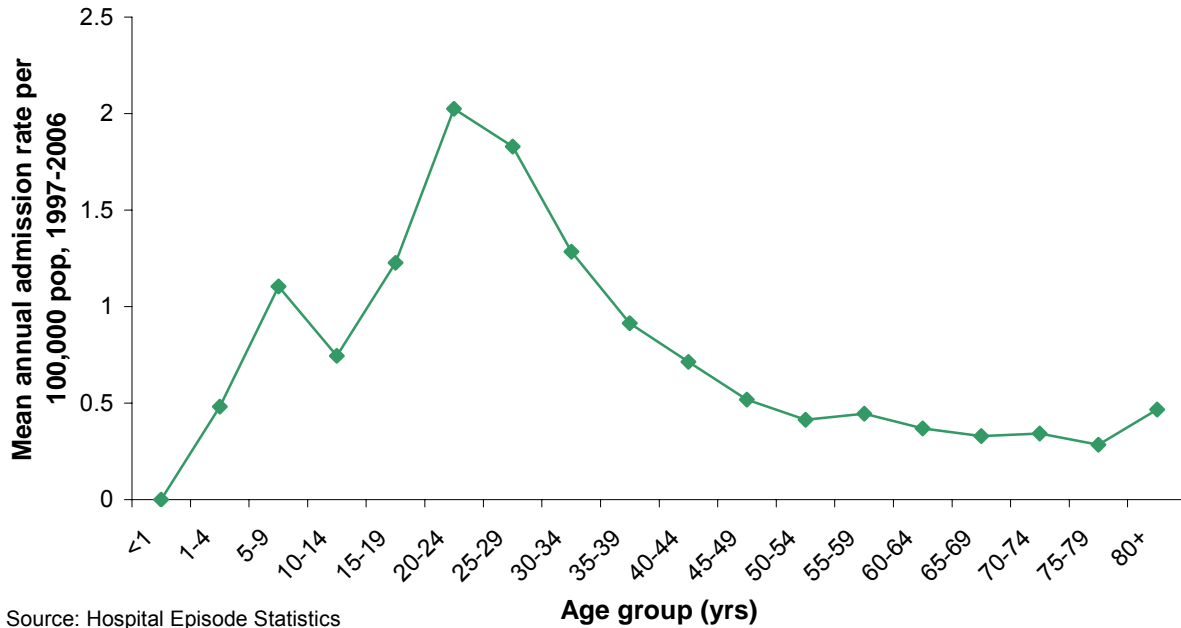
vaccinees) was independently associated with South Asian and mixed ethnic groups on logistical regression analysis. A smaller study based on oral-fluid testing of 257 children aged 7-12 years in an ethnically diverse region of northwest England found a similar raised seroprevalence in Indian (54.1%) ethnic groups and in children born outside the UK (54.1%)<sup>30</sup>.

**Fig 3.** Age specific seroprevalence of hepatitis A in England and Wales in 1996<sup>25</sup>



Hepatitis A infection causes hospital admissions in all age groups over the age of one year. In the ten years from 1997-2006 the hospital admission rate for persons with hepatitis A as one of their recorded diagnoses per 100,000 population was greatest in young adults aged 20-34 years (Fig 4).

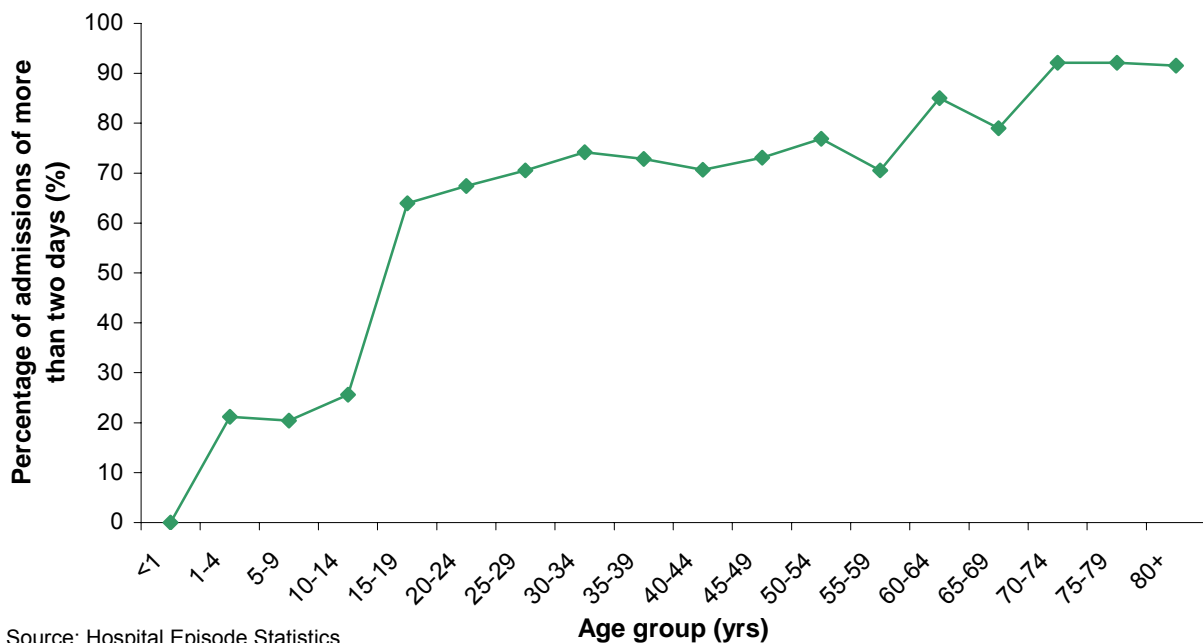
**Fig 4.** Mean annual admission rate for hepatitis A per 100,000 population by age group, 1997-2006



Source: Hospital Episode Statistics

The duration of hospital admission (as a proxy for severity of disease) increases with age. During the 10 years from 1997-2006 less than 25% of patients aged under 15 years admitted with hepatitis A as one of the recorded diagnoses were hospitalised for more than 2 days compared with over 60% for those aged 15-19 years, rising to over 90% for those aged 70 years and over (fig 5).

**Fig 5.** Percentage of all hospital admissions which are for more than two days duration by age group

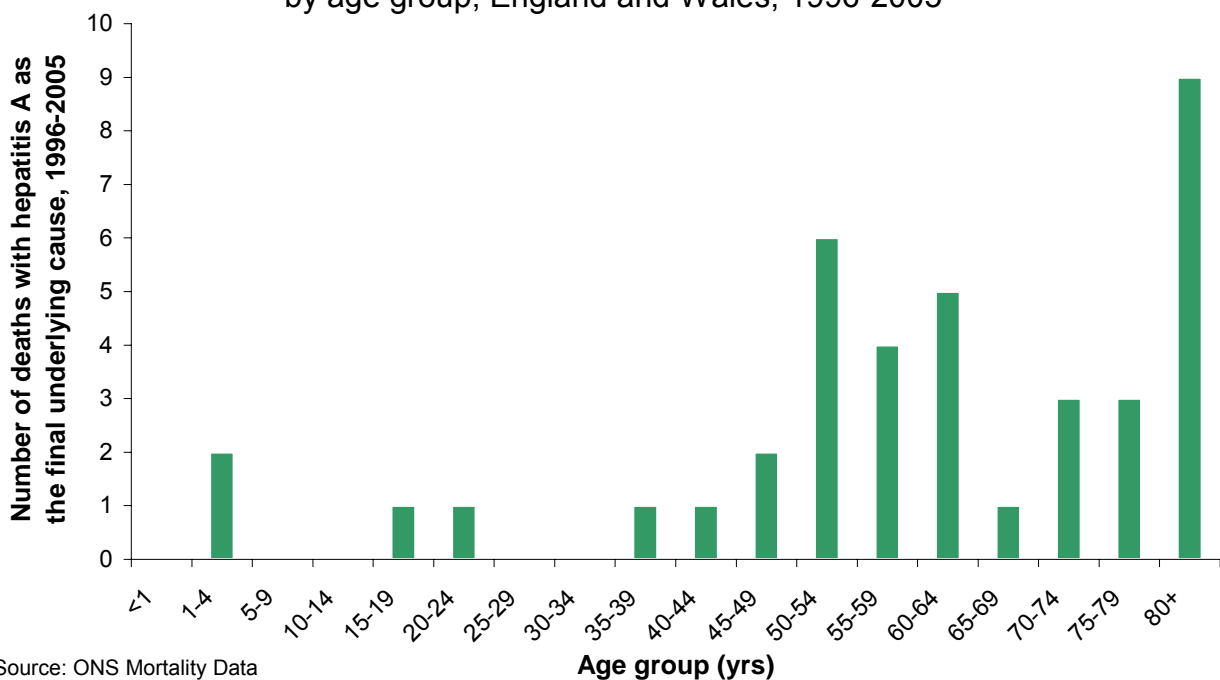


Source: Hospital Episode Statistics

A further indication of severe morbidity can be derived from liver transplant data. In the 10 years from 1997-2006 inclusive, the UK Transplant database recorded 5 liver transplants performed on patients with hepatitis A recorded as their primary liver disease at registration. These patients were aged 3-64 years (median 32 years) and all were female.

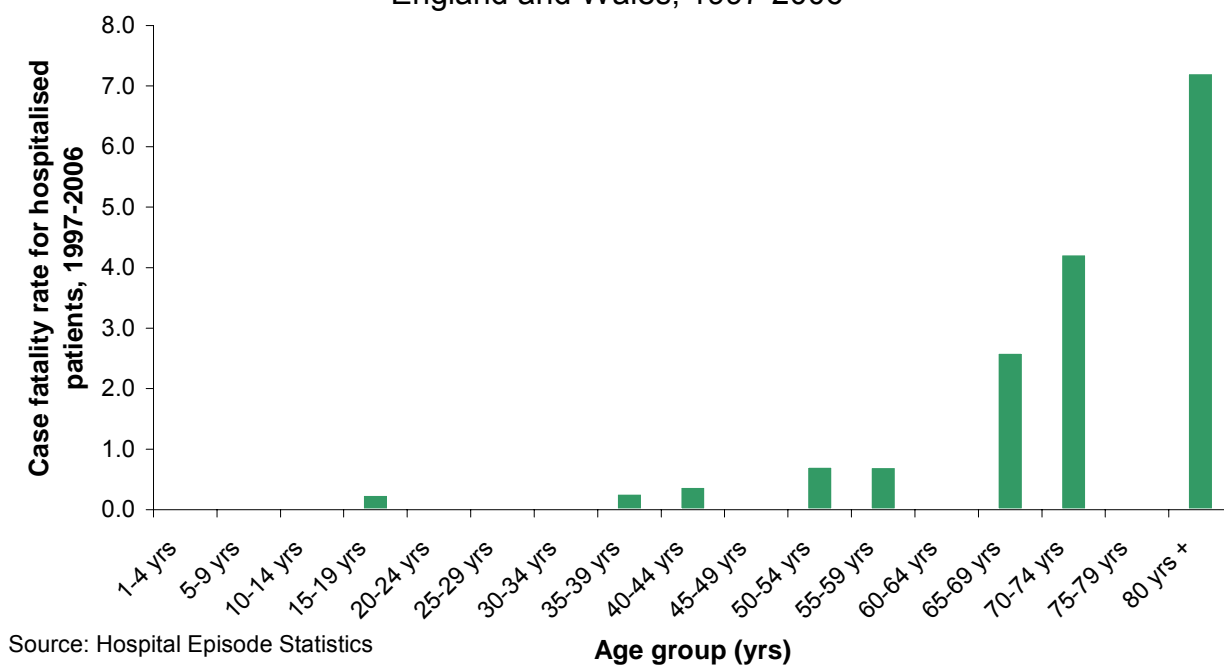
Hepatitis A is a very rare cause of death in England and Wales. In the 10 years from 1996-2005 there have been 39 deaths in which hepatitis A was either the underlying cause of death or a contributory cause of death (Office for National Statistics (ONS) Mortality Statistics) (Fig 6). The majority of these deaths (79%) were in persons aged  $\geq 50$  years. Over a third (38%) were in patients with pre-existing chronic liver disease and an additional 29% were in patients with other chronic or serious acute medical conditions. However, it is important to note that in this 10 year period two children (one aged 4 and one aged 16 years) and one young adult (aged 20 years) with no other recorded medical conditions on the death certificate died of fulminant hepatic failure following hepatitis A infection.

**Fig 6.** Number of deaths with hepatitis A as the final underlying cause by age group, England and Wales, 1996-2005



Hospital episode statistics recorded 17 deaths of patients with hepatitis A infection in the 10 years 1997-2006. The case-fatality rate for hospitalised patients increased considerably with age (Fig 7)

**Fig 7. Case-fatality rate in hospitalised patients by age group, England and Wales, 1997-2006**



## Appendix C - 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. Ideally laboratory testing for hepatitis A IgM (anti-HAV IgM) (for diagnosis of acute infection) and hepatitis A IgG antibody (anti-HAV IgG) (for checking immune status where relevant) 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.

### 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<sup>31</sup>. 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<sup>32</sup>.

Testing of anti-HAV IgG at the same time as IgM is desirable as it can help interpretation; a high IgG level in the presence of weak IgM reactivity should raise doubts as to the specificity of the IgM reactivity.

Interpretation of results requires clinical details, including liver function tests, together with information on the age of the patient (false IgM results are more common 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)<sup>33</sup>.

Negative 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.

Positive IgM results consistent with recent hepatitis A should be promptly flagged up by the testing laboratory to the local HPU. Results of doubtful significance should be reported by laboratories with suitable interpretive comments.

### 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 vaccination. A negative anti-HAV IgG test should be interpreted with caution in vaccinated individuals, as

anti-HAV IgG levels conferring immunity (10 IU/ml) are not reliably detected by conventional laboratory assays.

## **Appendix D - Evidence base for interventions to prevent secondary cases of hepatitis A infection**

### ***Human normal immunoglobulin***

The current human normal immunoglobulin (HNIG) (Subgam) issued by Health Protection Agency and NHS laboratories is prepared by Bio Products Limited (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<sup>34</sup>. The WHO second international standard for anti-hepatitis A immunoglobulin is 49 IU/ampoule when reconstituted in 0.5 ml (98 IU/ml)<sup>35</sup>. 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<sup>36</sup>. Although these lower levels of antibody may be associated with protection, current HPA hepatitis A HNIG guidelines<sup>37</sup> 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 HPA Immunoglobulin Handbook (available via the HPA website at [www.hpa.org.uk](http://www.hpa.org.uk)) 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.

**Table 1. Efficacy of HNIG for post-exposure prophylaxis against Hepatitis A**

<b>Setting</b>	<b>Type of study</b>	<b>Protective efficacy / effectiveness</b>
Outbreak, Children's summer camp, USA, 1944 <sup>38</sup>	Non-placebo controlled study of HNIG vs. no treatment	Against jaundice 87%  Against clinical hepatitis 69%
Outbreak, Children's home, USA, 1945 <sup>39</sup>	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 <sup>40</sup>	Retrospective cohort, HNIG vs no treatment	93%
Outbreak, Institution for learning disabilities, USA, 1952 <sup>41</sup>	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 yrs within 14 days of exposure Israel, 1964 <sup>42</sup>	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 <sup>43</sup>	Randomised non-placebo controlled trial	65.3%
Outbreak, household contacts in rural community, USA, 1970 <sup>44</sup>	Retrospective cohort	87%
Outbreak, Household contacts seen either within 2 weeks or greater than 2 weeks since exposure, USA, 1983-4 <sup>45</sup>	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 <sup>46</sup>	Retrospective cohort	80%

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<sup>47, 48</sup> has led some to doubt the adequacy of protective anti-HAV levels in HNIG that has anti-HAV titres below the WHO standard<sup>49, 50</sup>. 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<sup>11</sup> 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.

### **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 do 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<sup>41</sup>. 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<sup>44</sup>. 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<sup>51</sup>. 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<sup>52</sup>.

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<sup>47, 49, 53</sup>. 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<sup>54</sup> 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<sup>55</sup>.

In summary, there is no convincing evidence to suggest that HNIG given late in the incubation period (past 14 days exposure) prevents infection, 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<sup>56</sup>. Studies from the 1950s<sup>57</sup> found nearly identical incidences of biochemically-diagnosed hepatitis in children treated with HNIG and untreated controls, and more recently a serological study of 108 susceptible household contacts who received prophylactic HNIG found that although only 12 developed clinical disease, 64 (34%) had acquired a secondary infection<sup>58</sup>. However, the recent randomised controlled trial of HNIG versus vaccine conducted in Khazakstan 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<sup>68</sup>.

## ***Hepatitis A Vaccine***

Four hepatitis A monovalent vaccines are currently available (Haverix, Vaqta, Avaxim and Epaxal), prepared from different strains of the hepatitis A virus; all are grown on human diploid cells (MRC5). These vaccines can be used interchangeably<sup>59</sup>.

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 vaccination<sup>60, 61</sup>. 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 vaccination<sup>62</sup>.

The combined vaccine containing purified hepatitis A virus and purified recombinant hepatitis B surface antigen (Twinrix) may provide a slower immunogenic response and so is not recommended for post-exposure prophylaxis<sup>23</sup>.

Mathematical models based on up to 12 years of follow up data predict that antibodies will persist for at least 25 years<sup>63</sup>. Hepatitis A vaccine induces immunological memory so it will provide protection far beyond the duration of anti-HAV antibodies<sup>64</sup>. It is therefore not considered necessary to provide a booster dose after full primary immunisation<sup>65</sup>. 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<sup>64</sup>.

### **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 vaccination<sup>66</sup>.

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 yrs 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<sup>9</sup>.

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<sup>67</sup>. 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 vaccination group were not vaccinated 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 (RCT) 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)<sup>68</sup>. 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 1). 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 numbers treated in the first week was low and the study was not powered to answer this question.

**Table 1. Secondary attack rates and estimated efficacy of hepatitis A vaccine vs. HNIG when given within 14 days of exposure, Almaty, Kazakhstan, 2002-5**

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

**Efficacy of hepatitis A vaccine in patients > 40 years**

Direct evidence of the efficacy of hepatitis A vaccine in preventing secondary cases of hepatitis A in persons over the age of 40 is lacking. The two efficacy trials of hepatitis A vaccine as post-exposure prophylaxis were both conducted in healthy populations under the age of 40. This age cut-off was chosen as the majority of people over that age were not susceptible to hepatitis A in the population studied.

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<sup>69</sup>, 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<sup>70</sup>). The only study to look at immunogenicity rates across 10 year age bands found an overall tendency to slightly lower geometric mean titres with age<sup>71</sup>. All those aged 60 years and younger had seroprotective levels of anti-HAV (≥ 10 mIU/ml) one month post vaccination 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 may be lower than had previously been thought.

### **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<sup>72, 73, 74, 75</sup>. These studies generally show that hepatitis A vaccine induces seroprotective levels of anti-HAV antibodies 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 ( $\geq 33$  mIU/ml) one month later<sup>73</sup>. In a study in which the first dose was given at 4 months of age 85.4% achieved anti-HAV levels  $\geq 10$  mIU/ml one month later<sup>74</sup>. A study in which the first dose was either given at 6, 12 or 15 months of age found seroprotective levels ( $\geq 33$  mIU/ml) one month after vaccination in 54%, 60% and 73% of infants respectively<sup>75</sup>.

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 illness. An immunogenicity study of hepatitis A vaccine in patients with chronic liver disease demonstrated a lower seroconversion rate one month post vaccination 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 vaccination<sup>76</sup>.

Hepatitis A infection causes more severe disease in patients with underlying chronic liver disease. Of the 39 deaths in England and Wales in which hepatitis A was the underlying cause of death or a contributory cause of death in the 10 years from 1996-2005, 38% occurred in patients with pre-existing chronic liver disease (see section 4.1)

### **Efficacy of hepatitis A vaccine in HIV positive and immunosuppressed patients**

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<sup>77</sup>. Rates are 50–95% overall, but range from 9% at CD4 counts <200 cells/mL to 95–100% at CD4 counts >300–500 cells/mL. Highly active antiretroviral therapy (HAART) is associated with improved anti-HAV antibody levels<sup>78</sup>. 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 that both HNIG and vaccine be administered as post exposure prophylaxis in HIV positive individuals<sup>79</sup>. Similar considerations are likely to apply to other people with immunosuppression.

A number of studies have used three dose strategies, with the recent HEPAVAC study suggesting improved responses with a three dose schedule in the HIV positive group<sup>80</sup>.

### **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 vaccinated recruits required significantly fewer days hospitalisation and had significantly lower average maximal liver enzyme levels than three non-vaccinated colleagues<sup>81</sup>.

### **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<sup>82, 83, 84, 85</sup>. 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<sup>82, 83</sup>. 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<sup>86</sup>. 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.

**Table 2. Advantages and disadvantages of HNIG and hepatitis A vaccine**

<b>HNIG</b>	
<b>Disadvantages</b>	<b>Advantages</b>
HNIG is a blood product which carries theoretical risks of transmission of unidentified infectious agents.	HNIG is quick acting, leading to peak antibody levels within 4 days of administration
HNIG is of unclear effectiveness at preventing sub-clinical infection and may not interrupt onward transmission.	If HNIG prevents clinical disease, but not subclinical infection, it may allow natural immunity to develop in some recipients (so called active-passive immunity)
Availability of HNIG with known potency levels is limited, and supplies have to be issued on a named patient basis by the HPA or certain NHS laboratories	
Passive immunity acquired following HNIG is short-lived, lasting about 4 months. Those at ongoing risk of hepatitis A infection will require additional active immunisation with hepatitis A vaccine	

<b>Hepatitis A Vaccine</b>	
<b>Disadvantages</b>	<b>Advantages</b>
Vaccine takes longer to achieve protective antibody levels; the exact time taken is unknown	Vaccine achieves longer lasting immunity: with a second dose at 6-12 months it gives long term protection
	Vaccine is more effective at interrupting outbreaks in which multiple exposures may occur over a long time period
	Hepatitis A vaccine is widely available and so can usually be administered rapidly.

## Appendix E - Table of Quality of Evidence for Recommendations

Strongly recommended on the basis of >2 consistent, well-conceived, well-executed studies with control groups or longitudinal measurements.

Recommended on the basis of >1 well-conceived, well executed, controlled, or time-series study; or >3 studies with more limited execution.

Indicated on the basis of previous scientific observation, and theoretic rationale, but case controlled or prospective studies do not exist.

Recommendation	Level of Evidence
Susceptible close contacts to be offered Hepatitis A vaccine for post exposure prophylaxis up to 14 days post exposure	Recommended
HNIG as well as Hepatitis A vaccine to be offered for contacts over 50 or with chronic liver disease as post exposure prophylaxis up to 14 days post exposure	Indicated
Susceptible close contacts to be offered HNIG and Hepatitis A vaccine post exposure prophylaxis up to 28 days after exposure if they have chronic liver disease	Indicated
Hepatitis A vaccine for close contacts to prevent tertiary cases (i.e. pre-exposure prophylaxis)	Strongly recommended
Hepatitis A vaccine as post exposure prophylaxis under two years	Indicated
Index case should not prepare food for 14 days after onset and if necessary exclusion from work	Indicated
Susceptible close contacts who are food handlers not given post exposure prophylaxis within 14 days should be regarded as potential secondary cases and appropriate risk assessment undertaken. As far as practicable, food handling should be discouraged for up to 40 days after onset of illness in index case unless immunity demonstrable by serology	Indicated
Hepatitis A vaccine as post exposure prophylaxis up to 14 days after onset of illness in index case in breast feeding and pregnant women	Indicated

## References

- <sup>1</sup> Bell BP, Shapiro CN, Alter MJ et al. The diverse patterns of hepatitis A epidemiology in the United States – implications for vaccination strategies. *Journal of Infectious Diseases* 1998; 178: 1579-84
- <sup>2</sup> Cotter SM, Sansom S and Long T et al. Outbreak of hepatitis A among men who have sex with men: implications for hepatitis A vaccination strategies. *Journal of Infectious Disease* 2003; 187:1235–1240.
- <sup>3</sup> Bell A, Ncube F, Hansell A et al. An outbreak of hepatitis A among young men associated with having sex in public venues. *Communicable Disease and Public Health*. 2001;4:163-70
- <sup>4</sup> Crowcroft N. Hepatitis A infections in injecting drug users. *Communicable Disease and Public Health*, 2003; 6:82-84.
- <sup>5</sup> World Health Organisation Department of Communicable Disease Surveillance and Response. Hepatitis A. 2000. WHO/CDS/CSR/EDC/2000.7. Available online. <http://www.who.int/csr/disease/hepatitis/whocdscsredc2007/en/>
- <sup>6</sup> Fonquernie L, Meynard JL, Charrois A, Delamare C, Meyohas MC, Frottier J. Occurrence of acute hepatitis A in patients infected with human immunodeficiency virus. *Clinical Infectious Diseases*. 2001; 32: 297–299.
- <sup>7</sup> Stapleton JT. Host immune response to hepatitis A virus. *Journal of Infectious Diseases*, 1995,171(Suppl 1):S9-S14.
- <sup>8</sup> Tassopoulos NC, Papaevangelou GJ, Ticehurst JR and Purcell RH. Fecal excretion of Greek strains of hepatitis A virus in patients with hepatitis A and in experimentally infected chimpanzees . *Journal of Infectious Diseases*, 1986; 154:231-7
- <sup>9</sup> Sagliocca L, Amoroso P, Stroffolini T, Adamo B, Tosti ME, Lettieri G et al. Efficacy of hepatitis A vaccine in prevention of secondary hepatitis A infection: a randomized trial. *Lancet* 1999; 353: 1136–9.
- <sup>10</sup> Roumeliotou A, Papachristopoulos A, Alexiou D, Papaevangelou V, Stergiou G, Papaevangelou G. Intrafamilial clustering of hepatitis A. *Infection*. 1994;22:96-8.
- <sup>11</sup> Victor J C, Surdina TY, Suleimenova SZ, Favorov MO, Bell BP and Monto AS. Person-to-person transmission of hepatitis A virus in an urban area of intermediate endemicity: implications for vaccination strategies. *American Journal of Epidemiology* 2006; 163 204–10.
- <sup>12</sup> Smith PF, Grabau JC, Werzberger A, Gunn RA, Rolka HR, Kondracki SF, Gallo RJ, Morse DL The role of young children in a community-wide outbreak of hepatitis A. *Epidemiol Infect*. 1997;118:243-52
- <sup>13</sup> Panella H, Bayas JM, Maldonado R, Cayla JA, Vilella A, Sala C, Carbo JM, Bruguera M. Epidemic outbreak of hepatitis A related to a day care centre. *Gastroenterol Hepatol* 1998; 21: 319-323
- <sup>14</sup> Arce Arnaez A, Roder Garaduno I, Inigo Martinez J et al. Hepatitis A outbreak in a day care center and household transmission. *An Pediatr (Barc)* 2004, 60:222-227
- <sup>15</sup> Bonanni P, Colombai R, Franchi G, Lo Nostro A, Comodo N and Tiscione E. Experience of hepatitis A vaccination during an outbreak in a nursery school in Tuscany, Italy. *Epidemiology and Infection* 1998; 121:377-380
- <sup>16</sup> Severo CA, Abensur P, Buisson Y, Lafuma A, Detournay B, Pechevis M. An outbreak of hepatitis A in a French day-care center and efforts to combat it. *European Journal of Epidemiology* 1997; 13:139-144
- <sup>17</sup> Stuart JM, Majeed FA, Cartwright KA, Room R, Parry JV, Perry KR and Begg NT. Salivary antibody testing in a school outbreak of hepatitis A. *Epidemiology and Infection* 1992; 109:161-166
- <sup>18</sup> Garcia Puga JM, Toledano Cantero E and Ballesta Rodriguez M. Outbreak of hepatitis A in day nursery: diagnosis and follow-up in a pediatric clinic. *Aten Primaria* 1989; 6:484-485
- <sup>19</sup> Taylor-Robinson DC, Regan M, Crowcroft N, Parry JV and Dadamissis E. Exploration of cost effectiveness of vaccination in the control of a school outbreak of hepatitis A in a deprived community in the United Kingdom. *Euro Surveill*. 2007; 12:E5-6
- <sup>20</sup> Leoni E, Bevini C, Degli Esposti S and Graziano A. An outbreak of intrafamilial hepatitis A associated with clam consumption: epidemic transmission to a school community. *European Journal of Epidemiology*. 1998; 14: 187-192
- <sup>21</sup> Rajaratnam G, Patel M, Parry JV, Perry KR and Palmer SR. An outbreak of hepatitis A: school toilets as a source of transmission. *Journal of Public Health medicine*. 1992; 14: 72-77
- <sup>22</sup> Fiore AE. Hepatitis A transmitted by food. *Clinical Infectious Diseases*, 2004; 38:705-715
- <sup>23</sup> Department of Health. Immunisation Against Infectious Disease, 2006. Hepatitis A. [http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_079917](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_079917)

- <sup>24</sup> Demicheli V and Tiberti D. The effectiveness and safety of hepatitis A vaccine: a systematic review. *Vaccine*, 2003; 21: 2242-2245
- <sup>25</sup> Plotkin SA and Orenstein WA (eds) (2004) *Vaccines*, 4<sup>th</sup> Edition. Philadelphia: WB Saunders Company.
- <sup>26</sup> Matin N, Grant A, Granerod J and Crowcroft N. Hepatitis A surveillance in England – how many cases are reported and does it really matter? *Epidemiology and Infection*, 2006; 134: 1299-1302
- <sup>27</sup> Gungabisson U, Andrews N and Crowcroft NS. Hepatitis A virus infection in people of South Asian origin in England and Wales: analysis of laboratory reports between 1992 and 2004. *Epidemiology of Infection*; 2007: 549-554
- <sup>28</sup> Morris MC, Gay NJ, Hesleth LM, Morgan-Capner P and Miller E. The changing epidemiological pattern of hepatitis A in England and Wales. *Epidemiology and Infection*, 2002; 128:457-463
- <sup>29</sup> Morris-Cunnington MC, Edmunds WJ, Miller E and 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
- <sup>30</sup> Morris-Cunnington M, Edmunds WJ and Miller E. Immunity and exposure to hepatitis A virus in pre-adolescent children from a multi-ethnic inner city area. *Communicable Disease and Public Health*, 2004; 7: 134-137
- <sup>31</sup> HPA Standard Methods VSOP27 Hepatitis A virus acute infection serology (<http://www.hpa-standardmethods.org.uk/documents/vsop/pdf/vsop27.pdf>).
- <sup>32</sup> Dembek ZF, Hadler JL, Castrodale L, Funk B, Fiore AE, Openo K et al. Positive test results for acute hepatitis A virus infection amongst persons with no recent history of acute hepatitis – United States, 2002-2004. *MMWR Weekly*, 2005; 54: 453-456
- <sup>33</sup> HPA Standard Methods VSOP6 Hepatitis, jaundice and abnormal LFTs (<http://www.hpa-standardmethods.org.uk/documents/vsop/pdf/vsop6.pdf>)
- <sup>34</sup> Health Protection Agency Immunoglobulin Handbook 2007. [http://www.hpa.org.uk/web/HPAwebFile/HPAweb\\_C/1194947358556](http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947358556)
- <sup>35</sup> Ferguson M, Sands D and Lelie N. Hepatitis A immunoglobulin: an international collaborative study to establish the second international standard. *Biologicals*, 2000; 28: 233-240.
- <sup>36</sup> Bio Products Laboratory. Certificates of Analysis for Subgam 750mg Nov 2007-July 2008
- <sup>37</sup> Health Protection Agency. Immunoglobulin Handbook. January 2007. [http://www.hpa.org.uk/web/HPAwebFile/HPAweb\\_C/1194947358556](http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947358556)
- <sup>38</sup> Stokes J and Neefe JR. The prevention and attenuation of infectious hepatitis by gamma globulin. *JAMA* 1945; 127: 144-145
- <sup>39</sup> Havens WP and Paul JR. Prevention of infectious hepatitis with gamma globulin. *JAMA* 1945; 129: 270-273
- <sup>40</sup> Ashley A. Gamma globulin. Effect on secondary attack rates in infectious hepatitis. *New England Journal of Medicine* 1954; 250:412-417
- <sup>41</sup> Drake ME and Vineland CM. Gamma globulin in epidemic hepatitis: comparative value of two dosage levels, apparently near the minimal effective level. *JAMA* 1954; 155: 1302-1305
- <sup>42</sup> Mosley JW, Reisler DM, Brachott et al. Comparison of two lots of immune serum globulin for prophylaxis of infectious hepatitis. *American Journal of Epidemiology* 1968; 87: 539-550
- <sup>43</sup> PHLS. Assessment of British gammaglobulin in preventing infectious hepatitis. *BMJ*, 1968; 3: 451-454.
- <sup>44</sup> Landrigan PJ, Huber DH, Murphy GD et al. The protective efficacy of immune serum globulin in hepatitis A; a statistical approach. *JAMA* 1973; 223: 74-75
- <sup>45</sup> Shaw FE, Sudman JH, Smith SM et al. A community-wide epidemic of hepatitis A in Ohio. *American Journal of Epidemiology* 1986; 123: 1057-1065
- <sup>46</sup> Pavia AT, Nielsen L, Armington L et al. A community-wide outbreak of hepatitis A in a religious community: impact of mass administration of immune globulin. *American Journal of Epidemiology* 1990, 131: 1085-1093
- <sup>47</sup> Thorpe R, Minor P and Wood D. Hepatitis A concentrations in immunoglobulin preparations. *The Lancet*, 1991; 337: 497
- <sup>48</sup> Stapleton JT, Jansen R and Lemon S. Neutralizing antibody to hepatitis A virus in immune serum globulin and in the sera of human recipients of immune serum globulin. *Gastroenterology*, 1985; 89: 637-642
- <sup>49</sup> Taliani G and Gaeta GB. Hepatitis A: post-exposure prophylaxis. *Vaccine*, 2003: 2234-2237
- <sup>50</sup> Zaaijer HL, Leentvaar-Kuijpers A, Rotman H and Lelie PN. Hepatitis A antibody titres after infections and immunisation: implications for passive and active immunisation. *Journal of Medical Virology* 1993: 22-27

- 
- <sup>51</sup> Winokpur PL and Stapleton JT. Immunoglobulin prophylaxis for hepatitis A. *Clinical Infectious Diseases* 1992; 14:580-586
- <sup>52</sup> Shaw FE, Sudman JH, Smith SM et al. A community-wide epidemic of hepatitis A in Ohio. *American Journal of Epidemiology* 1986; 123: 1057-1065
- <sup>53</sup> Lednar W, Lemon SM, Kirkpatrick JW, Redfield RR, Fields ML and Kelley PW. Frequency of illness associated with epidemic hepatitis A virus infections in adults. *American Journal of Epidemiology* 1985; 122:226-233
- <sup>54</sup> Brachott D, Lifschitz I, Mosley JW, Kendrick MA and Sgouris JT. Potency of fragmented IgG: two studies of postexposure prophylaxis in type A hepatitis. *Journal of Clinical and Laboratory Medicine*, 1975; 85: 281-286
- <sup>55</sup> Green MS and Dotan K. Efficacy of immune serum globulin in an outbreak of hepatitis A virus infection in adults. *Journal of Infection* 1988; 17:265-270
- <sup>56</sup> Purcell RH, D'Hondt E, Bradbury R, Emerson Su, Govindarajan S and Binn L. Inactivated hepatitis A vaccine: active and passive immunoprophylaxis in chimpanzees. *Vaccine*, 1992; 10: S148-151
- <sup>57</sup> Krugman S. The clinical use of gamma globulin. *New England Journal of Medicine*, 1963; 269:198-201
- <sup>58</sup> Sonder GJB, van Steenberghe JE, Boove LPMJ, Peerbooms PGH, Coutinho RA and van den Hoek A. Hepatitis A immunity and seroconversion among contacts of acute hepatitis A in Amsterdam, 1996-2000: an evaluation of current policy. *American Journal of Public Health*, 2004; 94: 1620-1626
- <sup>59</sup> Soysal A, Gokce I, Pehlivan T and Bakir M. Interchangeability of a hepatitis A second dose: Avaxim 80 following a first dose of Vaqta 25 or Haverix 720 in children in Turkey. *European Journal of Paediatrics* 2207; 166:533-539
- <sup>60</sup> Jilg W, Bittner R, Bock HL et al. Vaccination against hepatitis A: comparison of different short-term immunisation schedules. *Vaccine* 1992; 10 (Suppl 1): S126-128
- <sup>61</sup> Van Damme P, Mathei C, Thoelen S, Meheus A, Safary A and Andre FE. Single dose inactivated hepatitis A vaccine: rationale and clinical assessment of the safety and immunogenicity. *Journal of Medical Virology*, 1994; 44: 435-441
- <sup>62</sup> Irwin DJ and Millership S. Antibody response to hepatitis A vaccine in healthy adults. *Communicable Disease and Public Health*, 2001; 4: 139-140
- <sup>63</sup> Van Herck K and Van Damme P. Inactivated hepatitis A vaccine-induced antibodies: follow-up and estimates of long-term protection. *Journal of Medical Virology*, 2001; 63:1-7
- <sup>64</sup> Van Damme P and Van Herck K. A review of the long-term protection after hepatitis A and B vaccination. *Travel Medicine and Infectious Disease*, 2007; 5:79-84
- <sup>65</sup> Van Damme P, Banatvala J, Fay I, Iwarson S, McMahon B, Van Herck K et al. Hepatitis A booster vaccine: is there a need? *The Lancet*, 2003; 5:79-84
- <sup>66</sup> Werzberger A, Mensch B, Kuter B, Brown L, Lewis J, Sitrin R et al. A controlled trial of a formalin-inactivated hepatitis A vaccine in healthy children. *The New England Journal of Medicine*, 1992; 327:453-457
- <sup>67</sup> Kohl I, Nemecek V, Summerova M, Chlibek R, Nad'ova K and Minarikova O. Long-term protective effect of post-exposure Havrix administration during viral hepatitis Type A outbreaks. *European Journal of Epidemiology*, 2006; 21: 893-899
- <sup>68</sup> Victor JC, Monto AS, Surdina TY, Suleimenova SZ, Vaughan G, Nainan OV et al. Hepatitis A vaccine versus immune globulin for postexposure prophylaxis. *The New England Journal of Medicine*, 2007; 357:1685-94.
- <sup>69</sup> Brien H and Safary A. Immunogenicity and safety in adults of hepatitis A virus vaccine administered as a single dose with a booster 6 months later. *Journal of Medical Virology* 1994; 44: 443-445
- <sup>70</sup> Reuman PD, Kubilis P, Hurni W, Brown L and Nalin D. The effect of age and weight on the response to formalin inactivated alum-adsorbed hepatitis A vaccine in healthy adults. *Vaccine*, 1997; 15: 1157-1161
- <sup>71</sup> D'Acromont V, Herzog C and Genton B. Immunogenicity and safety of a virosomal hepatitis A vaccine (Epaxal) in the elderly. *Journal of Travel Medicine*, 2006; 13: 78-83
- <sup>72</sup> Piazza M, Safary A, Vegnente A et al. Safety and immunogenicity of hepatitis A vaccine in infants: a candidate for inclusion in the childhood vaccination programme. *Vaccine*. 1999; 17: 585-588
- <sup>73</sup> Dagan R, Amir J, Mijalovsky A et al. Immunization against hepatitis A in the first year of life: priming despite the presence of maternal antibody. *Pediatric Infectious Disease Journal*. 2000; 19:1045-1052
- <sup>74</sup> De Silvestri A, Zara F, Terulla V et al. Immunogenicity of hepatitis A-inactivated vaccine administered to seronegative infants, and serological follow-up 12 months after the second dose. *Acta Paediatrica*. 2006; 95: 1582-1585

- 
- <sup>75</sup> Bell BP, Ngus S, Plotnik AE, et al. Immunogenicity of an inactivated hepatitis A vaccine in infants and young children. *Pediatric Infectious Disease Journal*. 2007; 116-122
- <sup>76</sup> Keefe EB, Iwarson S, McMahon BJ, Lindsay KL, Koff RS, Manns M, Baumgarten R, Wiese M, Fourneau M, Safary A, Clemens R, Krause DS. Safety and immunogenicity of hepatitis A vaccine in patients with chronic liver disease. *Hepatology*. 1998 Mar;27(3):881-6.
- <sup>77</sup> Shire NJ, Welge JA, Sherman KE. Efficacy of inactivated hepatitis A vaccine in HIV-infected patients: a hierarchical Bayesian meta-analysis. *Vaccine* 2006; 24: 272–279.
- <sup>78</sup> Rimland D, Guest JL. Response to hepatitis A vaccine in HIV patients in the HAART era. *AIDS* 2005; 19: 1702–1704.
- <sup>79</sup> British HIV Association guidelines for immunization of HIV-infected adults 2008. <http://www.bhiva.org/cms1191554.asp>
- <sup>80</sup> Launay O, Grabar S, Gordien E, Desaint C, Jegou D, Abad S et al. Immunological efficacy of a three-dose schedule of hepatitis A vaccine in HIV-infected adults: HEPAVAC study. *Journal of Acquired Immune Deficiency Syndrome*, 2008; 49: 272-275
- <sup>81</sup> Mimouni D, Bar-Zeev Y, Davidovitch N and Zarka S. Disease-modifying effects of postexposure hepatitis A active immunisation. *Military Medicine*, 2006; 171: 1196-1197
- <sup>82</sup> Green, M, Cohen, D, Lerman Y et al. Depression of the immune response to an inactivated hepatitis A vaccine administered concomitantly with immune globulin. *Journal of Infectious Diseases*; 1993: 168:740-743
- <sup>83</sup> Leentvaar-Kuijpers A, Coutinho RA, Brulein V and Safary A. Simultaneous passive and active immunisation against hepatitis A. *Vaccine* 1992; 10 Suppl 1: S138-41
- <sup>84</sup> Wagner G, Lavancy D, Adrioli R, Pecoud A, Brulein V, Safary A and Frei PC. Simultaneous active and passive immunization against hepatitis A studied in a population of travellers. *Vaccine*, 11: 10: 1027-1032
- <sup>85</sup> Zanetti A, Pregliasco F, Andreassi A, Pozzi A, Vigano P, Cargnel A, Briantais P and Vidor E. Does immunoglobulin interfere with the immunogenicity to Pasteur Merieux inactivated hepatitis A vaccine. *Journal of Hepatology*, 1997; 26: 25-30
- <sup>86</sup> Van Damme P, Banatvala J, Fay O *et al.* (2003) Hepatitis A booster vaccination: is there a need? *Lancet* 362: 1065–71.

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