

# Guidelines for the control of hepatitis A virus infection

NS Crowcroft, B Walsh, KL Davison, U Gungabissoon on behalf of PHLS Advisory Committee on Vaccination and Immunisation

**Summary:** *The PHLS Advisory Committee on Vaccination and Immunisation, following a review of the evidence on control measures for preventing hepatitis A virus (HAV) infection and widespread consultation, has prepared the following guidelines. They include a description of the current epidemiology of HAV infection in England and Wales, where most individuals are now susceptible to HAV. HAV infection is uncommon, with around 1000 infections notified per year in England and Wales. Clusters occur in families and in settings where potential for faecal/oral spread is high, e.g. day care centres, nurseries, primary schools. Larger outbreaks have been recorded in men who have sex with men and injecting drug users. Personal hygiene remains the cornerstone of measures for preventing HAV infection and its spread. Those with haemophilia, hepatitis B or C virus infection or liver cirrhosis, intravenous drug users and men who have sex with men should be offered HAV vaccination as a preventive measure. HAV vaccine should be used for preventing secondary cases and outbreaks provided that patients are informed that the latest date the vaccine is most likely to be effective in preventing disease in contacts is probably 7 days from onset of illness in the primary case. Human normal immunoglobulin (HNIG) should be offered in addition or in preference to vaccine for contacts who are more than 7 days from onset of illness in the primary case, and for those at risk of adverse outcome of HAV infection. Individuals at particular risk of an adverse outcome to infection include those more than 50 years old, with liver cirrhosis of any cause, or with pre-existing hepatitis B or C virus infection. HAV vaccine should be used to prevent infection for travellers to countries where HAV infection is a risk. HNIG is no longer indicated for travellers. Children travelling to such countries should be offered vaccine from 5 years and consideration should be given to vaccinating those aged 1-4 years.*

**Key words:**  
 hepatitis A virus (HAV)  
 hepatitis A vaccine  
 human normal immunoglobulin (HNIG)  
 outbreak  
 secondary cases  
 control of infection  
 guidelines  
 prevention

*Commun Dis Public Health* 2001; **4**: 213-27

## Scope and purpose of the guidance and methods of development

Public health policy and practice in controlling hepatitis A virus (HAV) infection has changed in many UK health districts, from use of human normal immunoglobulin for

contacts of cases of HAV infection to use of HAV vaccine. This has occurred because of concerns about using human blood products and the theoretical risk of transmission of variant Creutzfeldt Jacob Disease (vCJD). The changes have taken place without a review of the evidence base or the implications for this and other programmes.

NS Crowcroft, KL Davison, U Gungabissoon  
 Immunisation Division  
 PHLS Communicable Disease Surveillance Centre

B Walsh  
 Kingston and Richmond Health Authority

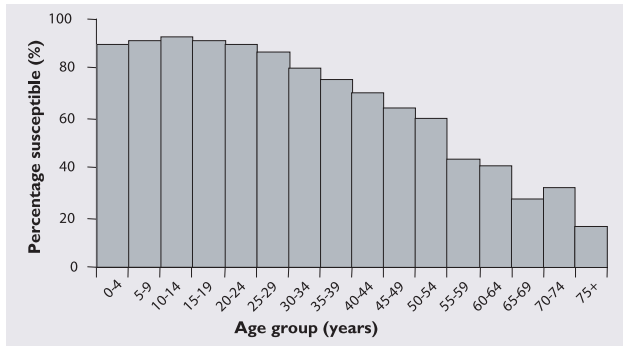
### Address for correspondence:

Dr Natasha S Crowcroft  
 Immunisation Division  
 PHLS Communicable Disease Surveillance Centre  
 61 Colindale Avenue  
 London NW9 5EQ  
 tel: 020 8200 6868 ext 4437  
 fax: 020 8200 7868  
 email: ncrowcroft@phls.org.uk

Because policy and practice now varies across the country, the PHLS Advisory Committee on Vaccination and Immunisation (ACVI) carried out an epidemiological analysis, literature review and consultation on control measures for HAV infection in the population, so that PHLS recommendations could be based on the best available evidence. These recommendations are graded using methods similar to those of the Scottish Intercollegiate Guidelines Network<sup>1</sup>.

The authors were asked by the Committee to produce guidance. PHLS CDSC Immunisation Division carried out an analysis of laboratory and clinical notifications and hospitalisation episode statistics to establish the current

**FIGURE 1 Susceptibility to hepatitis A virus by age group, England and Wales 1996<sup>10</sup>**



burden of HAV infection in England and Wales, and this was complemented by a review of the literature using Medline searches and a review of measures to control outbreaks carried out previously<sup>2</sup>.

Initial results of the epidemiological analysis and literature were presented and discussed at the Conference of Consultants in Communicable Disease Control (CsCDC) in November 2000. Further consultation on draft guidelines was carried out with members of the Public Health Medicine Environment Group (PHMEG) executive; PHLS ACVI; and Department of Health Advisory Group on Hepatitis (AGH) representing CsCDC, other public health specialists, epidemiologists and virologists working at local, regional and national level. Patient or lay views were not sought.

**Epidemiology of hepatitis A virus infection**

HAV infection causes a prodromal illness of fever, nausea, loss of appetite, abdominal pain, and mild gastrointestinal upset, followed by jaundice. HAV is an RNA virus in the family picornavirus.

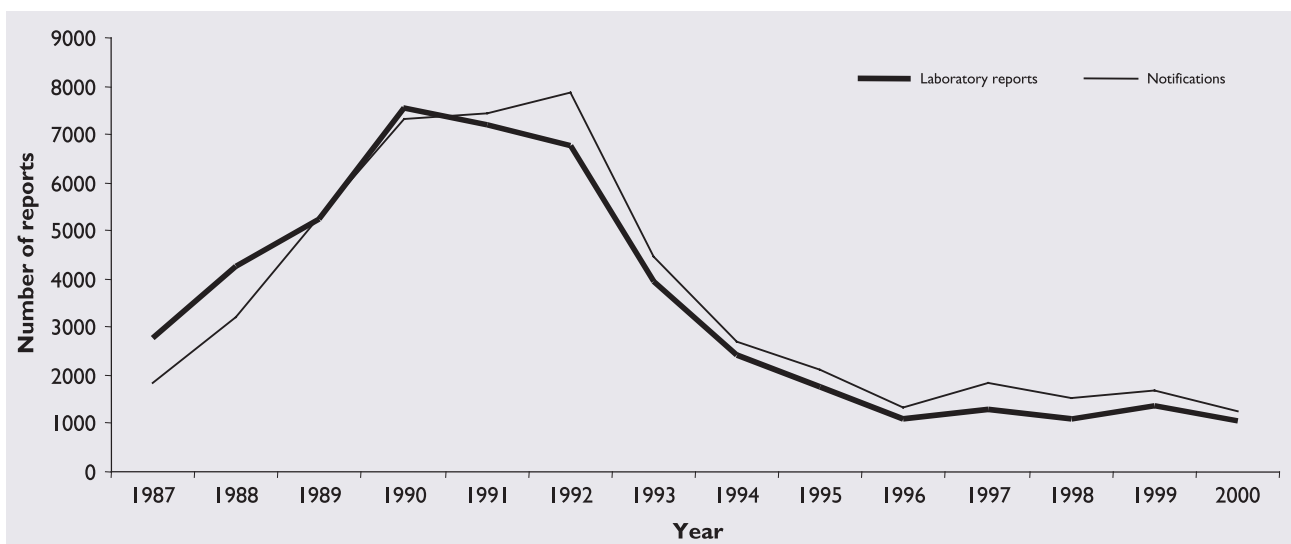
HAV is transmitted by the faecal-oral route. Person-to-person spread is the most usual method of transmission, although contaminated food or drink may sometimes be involved. Water-filtering shellfish and soft fruits have been the cause of recent outbreaks<sup>3,4</sup>. The mean incubation period is 28 days (range 15-50 days).

Asymptomatic and mild disease is common in children; the severity of infections increases with age. The majority of adults who become infected are symptomatic, with acute cholestatic jaundice<sup>5</sup>. Relapsing hepatitis is also recognised<sup>6</sup>. Fulminant hepatitis is the most severe form of infection. This is rare (less than 1% overall), but rates are higher with increasing age and with co-factors such as liver disease including chronic infection with hepatitis B or C viruses. Although children are at lower risk of symptomatic infection and of severe liver disease than adults, they occasionally develop liver failure necessitating liver transplantation or leading to death. The mean age at onset of fulminant hepatic failure in children is reported at 6.5 years in one series<sup>7</sup>.

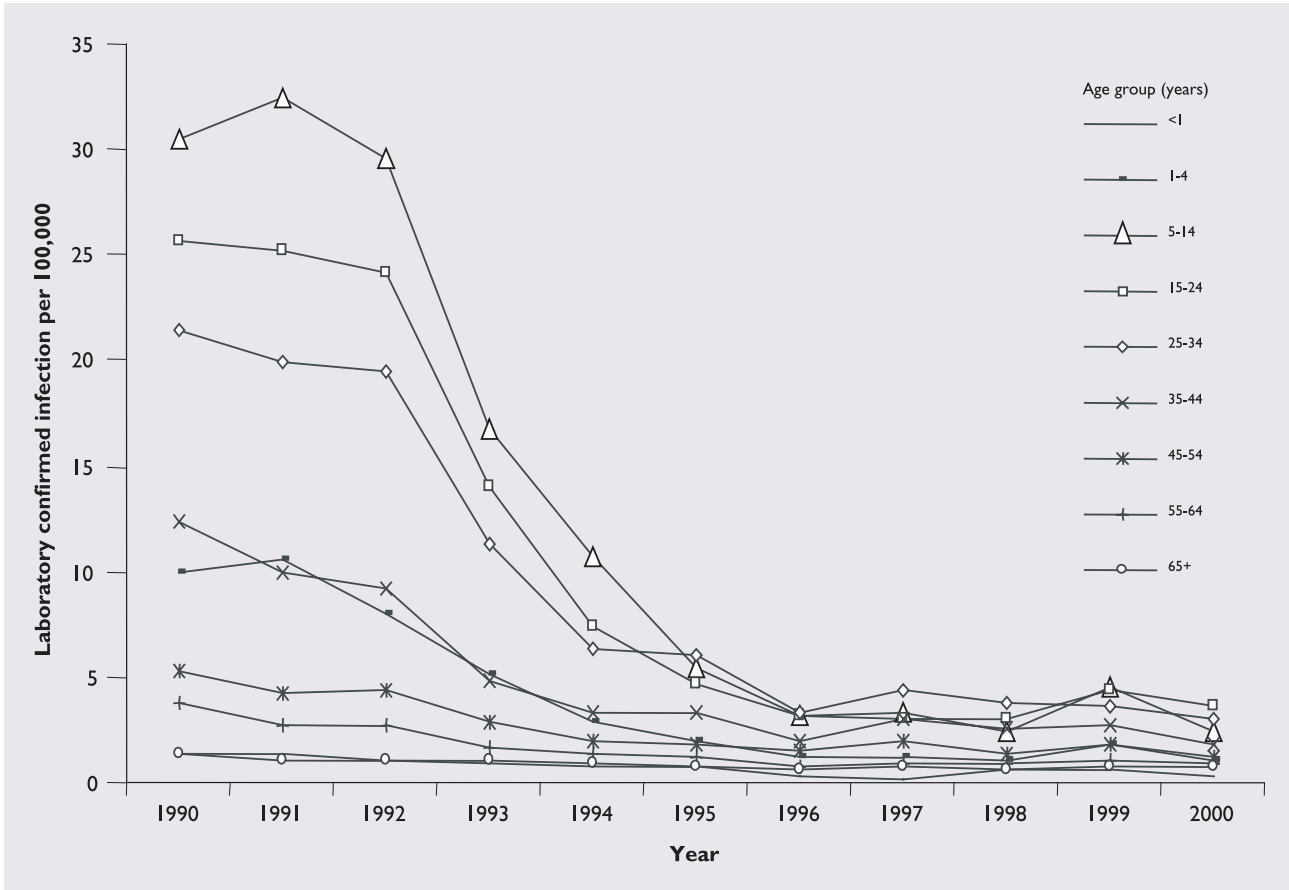
Peak infectivity occurs two weeks before onset of jaundice and falls rapidly thereafter. Children and infants may shed HAV longer than adults although chronic carriage does not occur. Immunity following infection protects against re-infection and appears to persist for life. The diagnosis is serological depending on the sensitivity of the assay used. IgM is detectable from the onset of symptoms (often before jaundice appears) and can persist for up to six months. HAV RNA can be detected in blood and stool early in infection. Sequencing of HAV RNA is available as a research tool for studying the molecular epidemiology of HAV.

The incidence of HAV infection has fallen progressively and the average age at infection has risen as standards of living have increased in the UK in the past century<sup>8</sup>. Similar trends have been observed in other countries. The majority of the UK population is now susceptible to HAV. The seroprevalence of antibodies to HAV in the general population has fallen considerably since 1986-87, when it ranged from 29.3% in 20-24 year olds to 55.3% in 40-44 year olds<sup>8</sup>. Only 25% of those over 40 years were found to be immune in one outbreak in 1997<sup>9</sup>. Seroprevalence data from 1996 indicate that a majority of those under 50 years of age are susceptible (figure 1)<sup>10</sup>. The situation is similar in other countries. Less than 10% of those under 35 years were found to be immune in a seroprevalence survey in the Netherlands in 1995-97<sup>11</sup>.

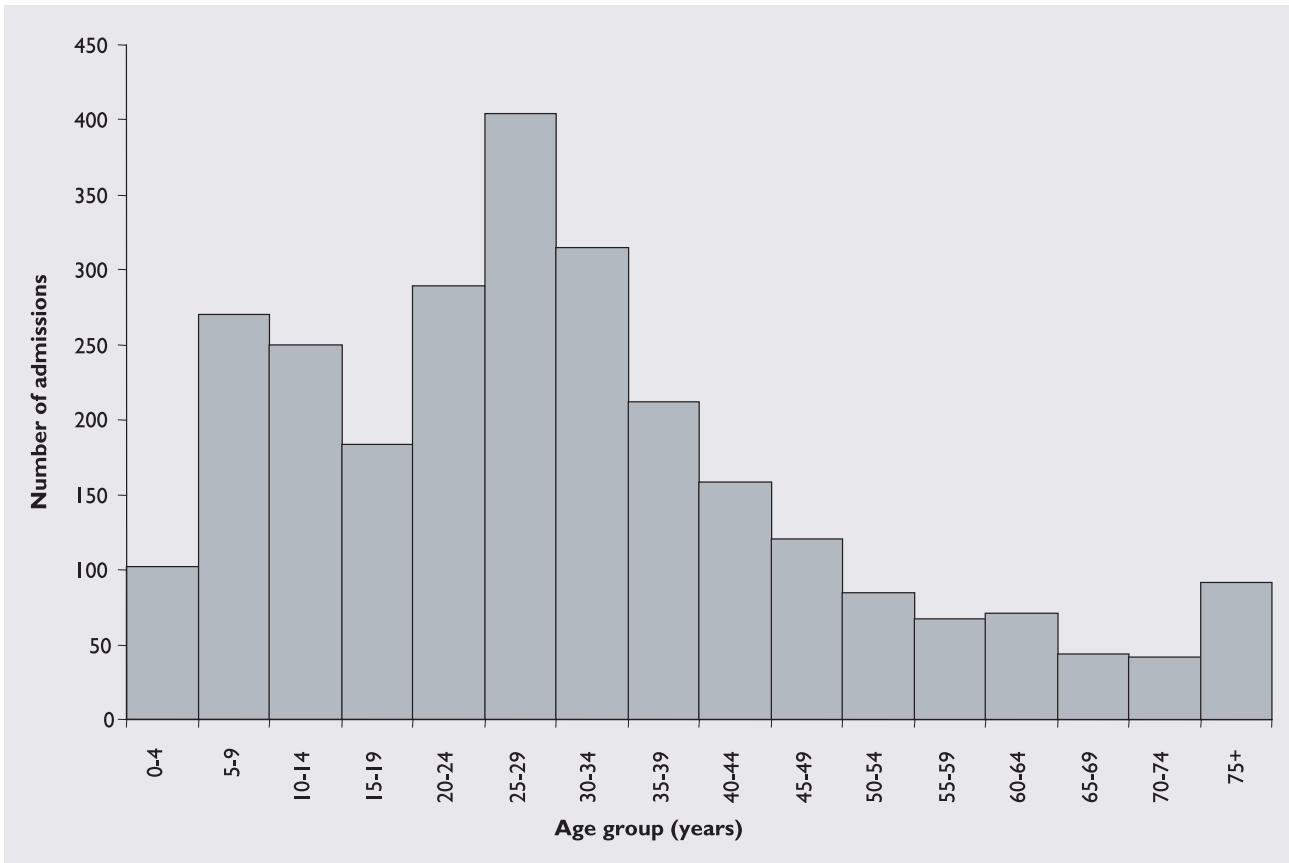
**FIGURE 2 Hepatitis A virus infection notifications and laboratory reports to PHLS CDSC, England and Wales 1987-2000**



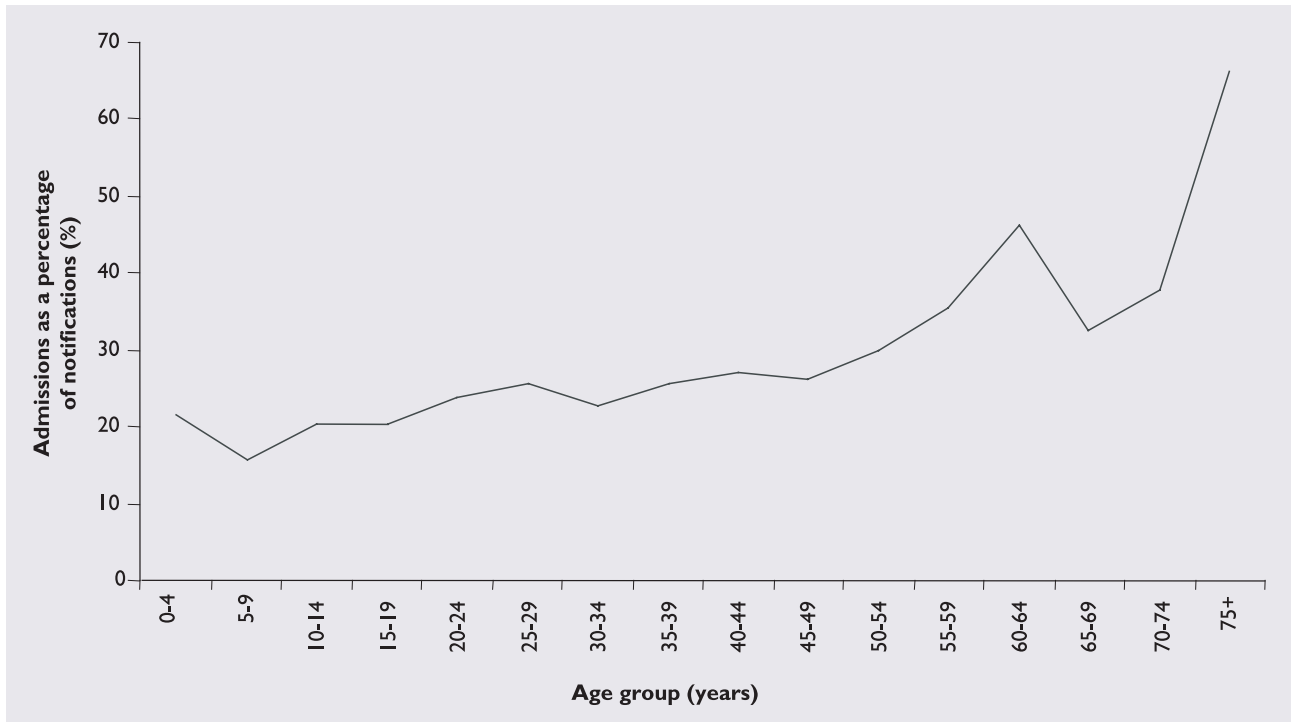
**FIGURE 3** Incidence of hepatitis A virus infection (laboratory confirmed cases) per 100,000 population of England and Wales by age group 1990-2000



**FIGURE 4** Number of admissions for hepatitis A virus infection by age group April 1993 - March 1998



**FIGURE 5** Age specific hepatitis A admissions as a percentage of notifications 1993-98



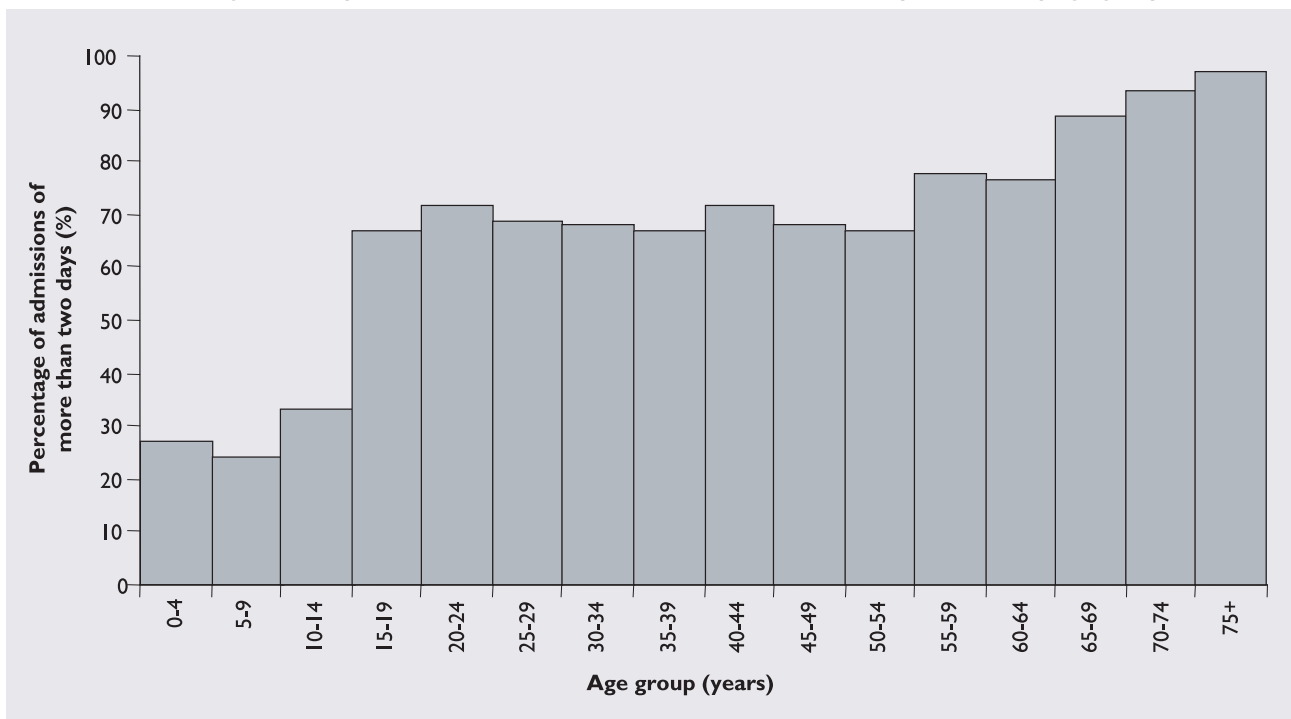
The incidence of HAV now shows a cyclical pattern in the UK. The most recent peak year was 1990 when 7,545 cases were reported to the Public Health Laboratory Service from England and Wales (figure 2). In 2000 there were 937 notifications and 1,274 laboratory reports to PHLS CDSC. The majority of outbreaks in England and Wales reported to the PHLS through the laboratory reporting system are small and occur in families. The last food-borne outbreak was in 1992, associated with shellfish consumption.

The fall in incidence has been seen most dramatically in the age group 5-14 years (figure 3).

HAV infection causes hospital admissions in all age groups. Between April 1993 and March 1998, 2707 admissions were recorded in Hospital Episode Statistics (HES). The number and length of admission varies by age, with two peaks in numbers of admissions occurring in children 5-14 and adults 20-34 years old (figure 4).

The likelihood of admission increases with age, with the ratio of admissions to notifications ranging from 20%

**FIGURE 6** Percentage of all hepatitis A admissions which are for more than two days duration by age group 1995-98



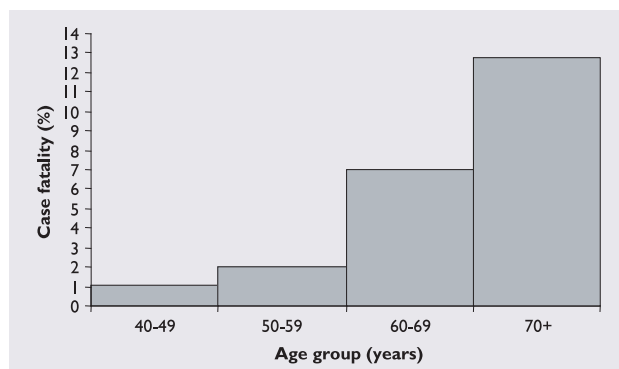
**TABLE 1** Deaths in England and Wales for which the certificate gives hepatitis A virus infection as the final underlying cause

Year of death	Number of deaths
1979	29
1980	21
1981	27
1982	22
1983	18
1984	11
1985	12
1986	10
1987	10
1988	12
1989	6
1990	14
1991	14
1992	11
1993	13
1994	10
1995	9
1996	5
1997	2
1998	0
1999	4
<i>Total</i>	<i>260</i>

to nearly 70% (figure 5). The degree of under-reporting of cases is greater in children than adults because they are much less likely to be symptomatic. Consequently, the percentage of cases requiring hospital admission is over-estimated in children and is likely to be significantly lower than 20%. Duration of admission increases with age, with 26% of children under 10 requiring admission for more than 2 days compared with 86% of those 65 years and over (figure 6). Half of those age 50 years and above required hospitalisation for more than 8 days.

HAV infection is an unusual cause of death with 260 cases certified as such between 1979 and 1999 in England and Wales (table 1). Hospital Episode Statistics recorded a total of 32 deaths in England during the five years between April 1993 and March 1998. This number is similar to the Office for National Statistics (ONS) mortality data where, in the five years 1993-97, 39 deaths

**FIGURE 7** Case fatality (%) hospitalised patients with hepatitis A virus infection in England by age group, April 1993 - March 1998



were recorded. One death from HAV occurred in all the cases under 40 years of age at admission, in a child aged between 10-14 years. In older adults the case fatality in those hospitalised increases progressively with age, with a case fatality of 2.0% in those aged 50-59, increasing to 12.8% in adults aged 70 years and above (figure 7).

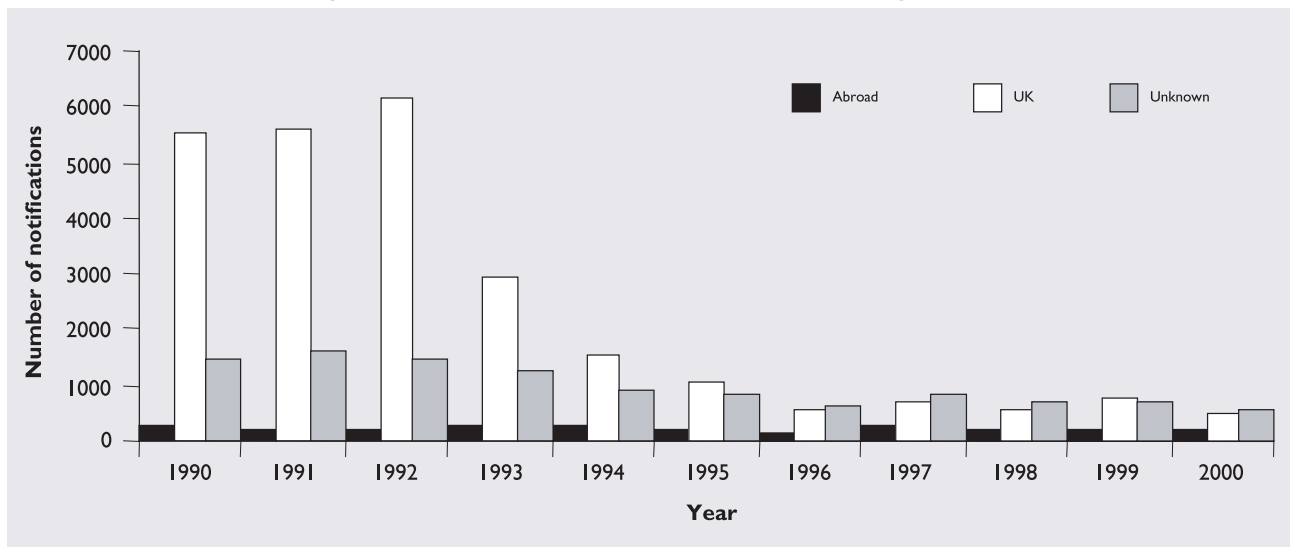
Imported cases occur through unvaccinated individuals travelling to countries with a high incidence of infection, particularly the Indian subcontinent and the Far East. Between 1990 and 2000, 8,952/35,542 (25%) individuals with laboratory confirmed HAV infections were reported to have travelled abroad. The country was reported for 2,968/8,952 cases. The most frequent destinations were India, with 450 cases (15.2%), Pakistan with 461 cases (15.5%) and Spain with 138 (4.6%). So many UK citizens travel to Spain every year that the absolute risk of infection in travellers is low<sup>12</sup>. The number of travel-related cases reported through laboratories to PHLS fell from 576 in 1990 to 96 in 1999. However, the percentage of reports with a complete travel history also fell in that time from 27.5% to 11.6%, making it difficult to interpret the apparent fall in cases. The number of travel related cases that have been notified has been quite stable in the same period (figure 8). The proportion of notified cases with a complete travel history is higher than that of laboratory reported cases at 55-60%, although this has also fallen from around 80% in 1990.

### Prevention and recommendations for high-risk groups (box 1)

Good hygiene, particularly hand washing, is the cornerstone of prevention and should be promoted in settings and communities with higher rates or risk of infection. Clean facilities for hand washing should be universally available. These include nurseries; hostels for the homeless; and services for travellers, men who have sex with men, the homeless and intravenous drug users. People travelling to intermediate and high incidence countries should also be aware of the importance of good hygiene.

A selective routine vaccination policy is of benefit for certain groups with greater likelihood of infection. In the US, policy is to routinely vaccinate all communities with a high or moderate incidence of infection (i.e. rate over 20/100,000 population), and to focus prevention on areas with rates over 10/100,000 population<sup>13</sup>.

**FIGURE 8** Notifications of hepatitis A virus infection to the PHLs and travel history 1990-2000



**People with special needs living in residential institutions or attending day centres**

Sporadic cases and outbreaks have occurred in these settings<sup>14,15</sup>. Vaccination of residents may be justified. A local assessment of the ability of residents or attendees to maintain good standards of personal hygiene or a

previous history of an outbreak should help determine the need for vaccination. Similar considerations may apply to other institutions where hygiene may be difficult to maintain such as nurseries for pre-school children. However, good personal hygiene is effective in controlling most transmission of HAV, accounting for the dramatic

**Box 1 Summary of recommendations for high-risk groups and travellers**

**Prevention in high-risk groups**

- HAV vaccination should be considered for those individuals with special needs whose capacity to maintain good standards of hygiene is limited and for their carers, following a risk assessment. Occupational vaccination should be offered to laboratory workers working directly with HAV or with non-human primates and for sewage workers who are at high likelihood of regular direct contact with raw sewage.

Grade of evidence for recommendation: C

- People with haemophilia, hepatitis B or C virus infection or liver cirrhosis of any cause, and injecting drug users should be offered HAV vaccination as a preventive measure. Consideration should be given to vaccinating men who have sex with men especially where there is evidence locally of an increased incidence in this population. Where indicated, HAV vaccination can be combined with HBV vaccination.

Grade of evidence for recommendation: C

**Overseas travellers**

- HAV vaccine for all children aged 5 years and over and adults travelling to countries where they may be at risk of HAV infection
- For children aged 1-4 years the risks of morbidity are lower and judgement is required about immunisation. Clinicians should discuss with the child's parents the advantages for travelling and non-travelling contacts of vaccinating the child and the disadvantages of vaccination. There is no licensed vaccine for children < 1 year of age. If parents choose not to vaccinate children 1-4 years, extra care should be taken with hygiene by the child's contacts while travelling and when the child returns.
- HNIG is no longer used for travel purposes apart from in immunocompromised patients. Advice about the importance of good hygiene should be given and HAV vaccination considered, as above.

Grade of evidence base for recommendations: C and D

change in its epidemiology as standards of living have improved.

**Occupational exposure**

Staff working in residential or day centres for people with special needs may be at higher risk of HAV infection and may benefit from vaccination (see previous section). Routine vaccination of all child carers is not justifiable. Occasionally, outbreaks have occurred associated with food handlers, but these are not frequent enough to justify routine vaccination of all catering staff. There is no evidence that health care workers are at increased risk of HAV infection and routine immunisation is not recommended.

Sewage workers are not at increased risk of HAV infection unless they come into direct contact with raw sewage<sup>16,17</sup>. Therefore HAV vaccination is recommended for sewage workers who are at high likelihood of regular direct contact with raw sewage.

Immunisation is recommended for laboratory workers who are working directly with hepatitis A virus and for those working with non-human primates that are susceptible to HAV infection<sup>18</sup>. There is no evidence that other laboratory workers are at increased risk.

**Patients with chronic liver disease**

Patients with chronic liver disease and chronic infection with hepatitis B or C are at greater risk of severe disease should they become infected with HAV and should consequently be vaccinated<sup>19,20,21,22</sup>.

**Injecting drug users**

Several large outbreaks have occurred in injecting drug users (IDUs), sometimes linked epidemiologically to prisons<sup>23,24</sup>. Transmission occurs percutaneously in the

viraemic phase of the illness, through sharing injecting equipment and via faecal-oral routes because of poor living conditions<sup>25,26,27</sup>.

Vaccination of IDUs should be carried out, using combined HAV and hepatitis B virus (HBV) vaccine for individuals who have not been completely vaccinated for HBV. Combined vaccines will shortly be licensed for use in a hyperaccelerated (0, 7, 21 days) schedule. In order to achieve high coverage in this group, concerted action is required from all the agencies with which IDUs come into contact, including outreach services and prisons.

**Haemophilia**

People with haemophilia should be vaccinated against HAV. Transmission of HAV has been associated with the use of Factor VIII and Factor IX in the past when viral inactivation procedures did not destroy HAV<sup>28,29,30</sup>, and more recently from solvent/detergent treated products<sup>31</sup>. Moreover, many people with haemophilia are already chronically infected with hepatitis B virus and/or hepatitis C virus and so require vaccination because they risk having a severe outcome of HAV infection.

People with haemophilia should be immunised subcutaneously.

**Men who have sex with men**

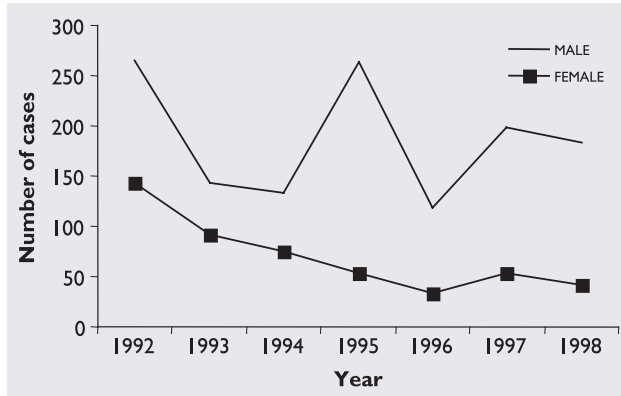
Several outbreaks have occurred amongst men who have sex with men<sup>32-43</sup>. The risk of infection following sex can be reduced by good personal hygiene after sex and through hygienic disposal of condoms, especially after anal intercourse.

Routine data on the incidence of HAV infection in men who have sex with men are limited, making it difficult to evaluate the potential benefit of selective vaccination. The

**TABLE 2** Number of laboratory reports of hepatitis A infection and incidence per 100,000 population per year in the London Region by age and sex 1992-98

Age group (years)	Number of cases in males 1992-98	Incidence per 100,000 per year	Number of cases in females 1992-98	Incidence per 100,000 per year
<1	4	1.1	1	0.3
01-04	20	1.4	16	1.2
05-09	74	4.3	68	4.1
10-14	63	4.1	46	3.2
15-24	185	5.4	90	2.7
25-34	512	11.0	126	2.8
35-44	240	5.9	54	1.4
45-54	98	3.4	33	1.1
45-55	1	0.0	0	0.0
55-64	24	1.5	15	0.8
65+	25	2.3	20	1.0

**FIGURE 9** Number of laboratory reports of hepatitis A virus infection in the London Region by sex in 1992-98



majority of young adults would now be expected to be susceptible to HAV. A recent study revealed a 23% seroprevalence of HAV antibody in gay men in London, likely to be higher than the general population<sup>44</sup>. Cases of HAV infection may not be detected through KC60 returns because such infections do not present to GUM clinics. Only one case was reported from Scotland in 1995<sup>45</sup>. Exposure and behavioural histories are incomplete in routine surveillance data. There are also difficulties estimating the denominator of men who have sex with men.

Routine data from the London Region can shed some light on possible risks, since there is a large gay community in London and there have been well documented outbreaks of HAV infection<sup>27,46</sup>. CDSC Labbase reports from the London NHS Region between 1992-98, mention homosexuality as a possible risk factor in only 180/1838 (9.8%) cases of HAV infection. During this same period, 1307/1838 (71.1%) of all cases were male, a sex imbalance that is unlikely to be explicable solely through other recognised risks such as travel to high-incidence countries, homelessness or intravenous drug use. These 776 extra cases in males compared with females occurred over seven years. The highest incidence is seen in males aged 25-34 (table 2).

Recommendations in the US identify communities with high and intermediate rates of HAV infection as those with rates typically peaking in epidemic periods at more than 700 cases and 50-200 cases per 100,000 population respectively<sup>13</sup> and states requiring concerted action to address HAV infection as those with rates of 20 cases per 100,000. None of the age groups in the London data reach these thresholds. However, during an outbreak, the incidence can approach this level (figure 9). In 1995, for instance, the incidence in men aged 25-34 in London was 17.8/100,000. This rate is calculated using the total population of men in London, whereas the incidence and hence risk in gay men must have greatly exceeded the threshold of 20 per 100,000. The total population of gay men in London may be around 118,000<sup>47</sup>; thus if the 776 extra cases of HAV infection seen in males compared with females all occurred in gay men, the incidence would be 94 cases per 100,000 population per year, well above the threshold for routine selective vaccination.

Data from the London Region were used for this analysis because of the large gay community living in the city, but the results from the London Region are likely to be applicable to gay men living throughout the country. Vaccination will benefit only those whose behaviour puts them at risk of HAV infection. However, in practice it is not easy to use reported behaviour as a criterion for recommending vaccination. A vaccination programme for all men who have sex with men may be more effective, and would be particularly indicated when there is evidence locally of an increased rate in this population.

### Recommendations for overseas travellers (box 1)

Individuals who have lived for most of their lives in low endemicity countries and who visit countries where the HAV incidence is not low are at increased risk of HAV infection<sup>12,48,49,50</sup>. Areas for which vaccination is not indicated are Australia, New Zealand, Japan, North America, northern and Western Europe. Travellers should be advised to take precautions against food and water borne disease including avoiding untreated water, ice and uncooked shellfish and also uncooked or unwashed fruit or vegetables. Consideration should be given to offering travellers HAV vaccine following current travel guidance<sup>50</sup>. Vaccine is likely to be effective even if given shortly before departure<sup>51</sup>. HNIG is no longer recommended for routine prophylaxis. HNIG may be indicated for immunocompromised patients if they are unlikely to make an adequate antibody response to vaccine.

Opinions differ as to whether children should receive HAV vaccine when travelling. Vaccine is licensed for those over 1 year of age but infection is unlikely to cause significant morbidity in pre-school children. In view of the morbidity associated with infections in primary school children (figure 4), vaccination is of probable benefit for children five years of age and older. In other words, the benefit of vaccination to the individual is probably significant from 5 years of age, whereas before this age there may be benefit to unvaccinated household contacts as well as to the community in preventing outbreaks on a child's return from travel, particularly if the child attends nursery or childcare. The options should be discussed with parents for children under 5 years.

### Management of close contacts of sporadic cases of HAV infection and outbreaks (box 2) Hygiene

Advice on good hygiene, principally careful hand washing, should be part of the response to every identified case of HAV infection. HAV is inactivated instantaneously in boiling water, by pasteurisation, or household bleach (surfaces).

### Close contacts of cases of HAV infection

Prophylaxis should be considered for close contacts of a confirmed case of HAV infection irrespective of their age since there are significant hospitalisation rates in all age groups. Close contacts include household and sexual contacts. Health-care workers caring for patients in the

**Box 2 Summary of recommendations for use of prophylaxis for contacts of cases and outbreaks**

HAV vaccine should be used for preventing secondary cases and outbreaks provided that:

- Patients are informed that vaccine should be given as close to the time of exposure as possible and the latest time that the vaccine is likely to be effective in preventing disease is probably 7 days from onset of disease in the primary case. Use of vaccine after this time may be considered to prevent tertiary infections.
- Specimens from suspected cases are collected, processed and reported urgently.
- Arrangements are in place for early reporting by microbiologists of IgM confirmed cases of acute HAV infection to the Consultant in Communicable Disease Control (CCDC).
- Same- or next-day vaccination is given to family and household contacts considered at risk from exposure to the primary case.
- The patient information leaflet included with HAV vaccine is given to each recipient and/or parent so that they are informed about the advantages and disadvantages of vaccine.
- Arrangements are in place for surveillance of secondary cases and vaccine failures so that the policy and practice can be properly audited.

Grade of evidence for recommendations: C or D

Human Normal Immunoglobulin (HNIG) should be offered in addition or in preference to vaccine if the following applies:

- The exposed person is at particular risk of adverse outcome of HAV infection, e.g. is more than 50 years old, has liver cirrhosis, or has pre-existing Hepatitis B or C virus infection.
- To protect close contacts who are identified too late to be protected by vaccine (8 days or more from exposure). The window of opportunity for HNIG to prevent a secondary case is 14 days post-exposure, but HNIG may modify disease severity if given after 14 days. In general it is probably not worth considering much after 28 days from exposure.
- The patient information leaflet included with HNIG has been given to the person to ensure they are informed about the advantages and disadvantages of HNIG.

Grade of evidence for recommendations: C

prodromal phase of the illness are also at risk if appropriate infection control measures are not taken<sup>52</sup>. The choices for prophylaxis are between human normal immunoglobulin (HNIG), HAV vaccine or using both together. HNIG can be administered simultaneously with HAV vaccine, but this may reduce the long-term efficacy of vaccine<sup>53</sup>.

HAV vaccine is increasingly being used for contacts in place of HNIG because of concerns about use of human blood products and transmission of prions and other agents. However, the evidence base for deciding upon the best prophylaxis to use is currently limited for choosing between HAV vaccine and HNIG since no direct comparison has been carried out. Current UK supplies of HNIG are derived from US plasma and there have been no cases of vCJD in the US. Prion transmission to humans from HNIG has not been reported and remains a theoretical risk.

HNIG is a well-established intervention with good efficacy at preventing disease when given within two

weeks of exposure (tables 3a and 3b). After two weeks, HNIG may modify disease severity. As would be expected from the mechanism of action, serological studies show that administration of HNIG produces protective levels of antibody within hours. Antibody levels following vaccination take longer to become detectable (12-15 days), but protection may be provided before antibody can be detected by current assays. Where vaccine has been given to contacts close to exposure, secondary cases have occurred within 7-10 days from vaccination<sup>54</sup>. Small studies in animals indicate that HAV vaccine reduces excretion of virus when given immediately post-exposure<sup>55,56</sup>. In practice, vaccine is not usually given as close to exposure as this, and failures of vaccine to control transmission have been reported<sup>57</sup>. Where the timing of exposure was unknown, cases have occurred up to 21 days<sup>58</sup> or longer<sup>59</sup> after vaccination. Vaccine may have to be given close to the time of the contact's first significant exposure to have similar post-exposure efficacy because of the inherent delay in

**TABLE 3a Comparative post-exposure efficacies of HNIG and hepatitis A vaccine**

Intervention	Protective efficacy	Time between onset in primary case and administration of prophylaxis	Setting	Country
HNIG	47-87%	≤ 14 days	Household contacts	Israel <sup>60</sup>
	68-87%	≤ 14 days	Children's summer camp	US <sup>61</sup>
	63%	NK	Community	US <sup>62</sup>
Vaccine	79% (95% CI 7-95%)	≤ 8 days	Household contacts	Italy <sup>63</sup>

antibody production with active vaccination. HNIG provides faster protection but of shorter duration compared with vaccine. In general, for pragmatic reasons, HNIG may not be considered worthwhile more than 28 days from exposure.

The extra protection offered by the rapidity of action of HNIG may be particularly important for adult contacts, or those at increased risk of severe disease, such as the elderly or those with chronic liver disease, especially if there has been some delay in identifying them. If a contact is at ongoing risk of HAV infection because of their lifestyle or for any other reason, they should be offered vaccine irrespective of whether they are offered HNIG.

If public health departments base prophylaxis upon HAV vaccine alone, they need to ensure that systems are in place for HAV cases to be detected rapidly so that contacts can receive the vaccine within 7 days of exposure. This requires awareness in GPs, hospital physicians and microbiologists of the need rapidly to inform public health departments of suspected and confirmed cases of HAV infection. In view of the lack of evidence about how vaccine efficacy compares with HNIG, contacts should be actively followed up and vaccine failures documented.

Prophylaxis need not be extended to all previously unvaccinated staff and children when a single case occurs in a school or workplace (including hospital) where the case was most likely infected outside that institution. Prophylaxis is not required for individuals who have received one dose of vaccine in the past year or two doses in the previous ten years.

The 'number needed to treat' with prophylaxis to prevent one case of infection depends upon the prevalence of susceptibility, the secondary attack rate following exposure, the effectiveness of the intervention and the rate of clinical disease in the age group exposed. Nearly all members of households in the UK are likely to be susceptible. Secondary attack rates in households range between 6-30% with higher rates in children, and are usually well in excess of 10% (table 4). This makes the number needed to receive prophylaxis to prevent one infection less than 20 within the range of reported efficacies of HNIG or vaccine (figure 10). In settings where secondary attack rates are likely to be of the order of 20%, the number needed to receive prophylaxis to prevent infection is less than ten. In young children the number needed to receive prophylaxis to prevent disease will be considerably greater than the number needed to prevent infection because most infections are asymptomatic.

**TABLE 3b Comparative efficacies of HNIG and hepatitis A vaccine in populations experiencing outbreaks or high incidence with no documented exposure**

Intervention	Protective efficacy	Setting	Country
HNIG	89% (95% CI 78-95%)	Religious community outbreak	US <sup>64</sup>
Vaccine	96%	School outbreak	Slovakia <sup>11</sup>
	83% in a single region (19% of cases in all 3 regions occurred in vaccinated)	Community outbreak (<34 years)	US <sup>59</sup>
	95% (95% CI 82-99%)	Community outbreak (<17 years)	Thailand <sup>65</sup>
	0% at < 21 days after vaccine admin. 100% at >21 days after vaccine admin.	Religious community outbreak	US <sup>58</sup>

**TABLE 4** Estimates of secondary attack rates

Secondary attack rate	Year	Setting	Country
5.8%	1997	Household	Italy <sup>63</sup>
9.0%	1996	Household	Italy <sup>54</sup>
19.6%	1993	Military field station	US <sup>66</sup>
51.0%	1986	Children (<16) in household	Italy <sup>67</sup>
25% uncorrected for prior immunity	1984	Household	US <sup>68</sup>
31.0%	1982	Household	Germany <sup>69</sup>
20.0%	1996	Household	US <sup>70</sup>
27.6%	1994	Household	US <sup>71</sup>

**Resources**

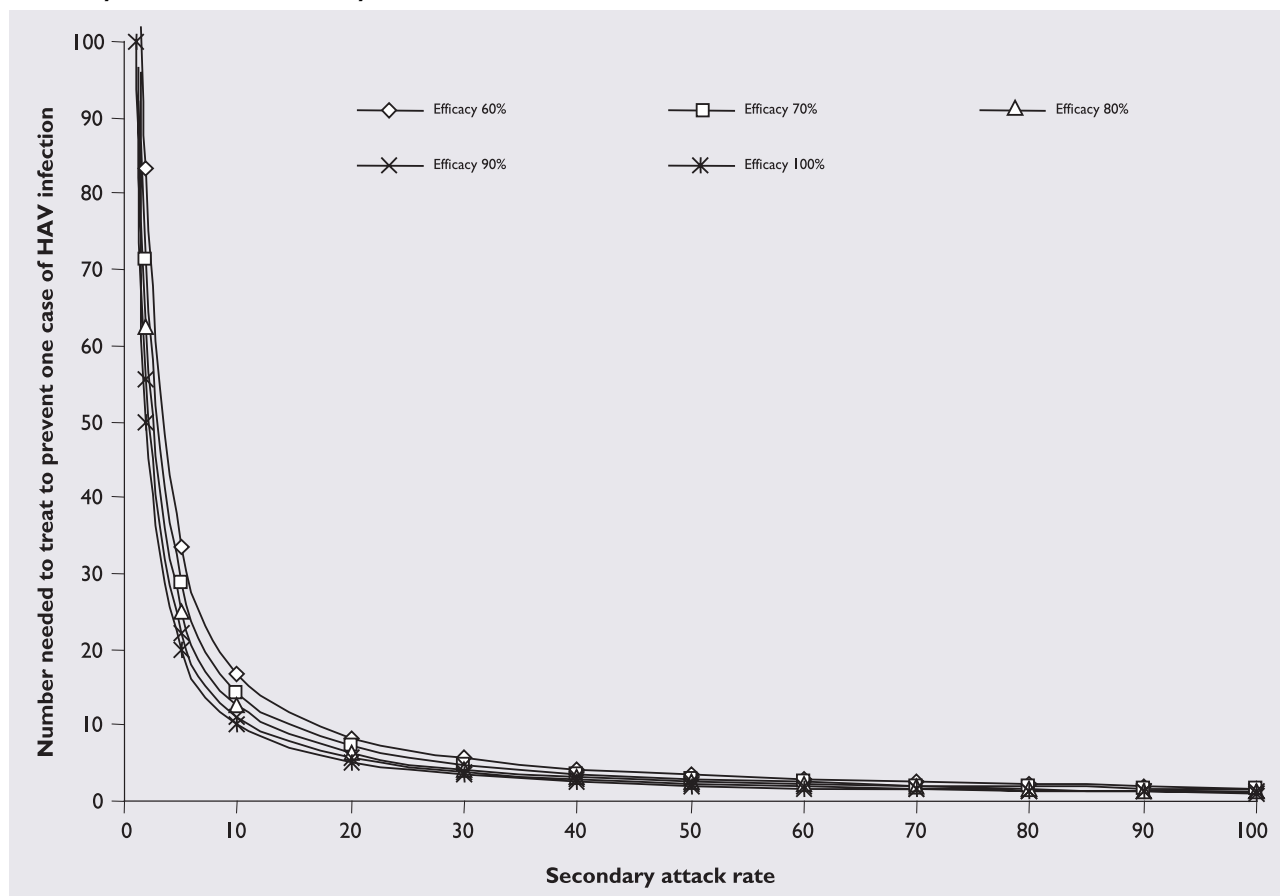
HNIG has increased in price since becoming sourced from non-UK donors and the cost of prophylaxis with HNIG or vaccine is now about the same. Assuming a post-exposure vaccine efficacy of 80% and secondary attack rates in household contacts greater than 10%, the number needed to treat to prevent one case of HAV infection is less than 20. At a cost per individual of £20, the current cost of using either vaccine or HNIG per case prevented is less than £400. The cost of using both HNIG and vaccine is double this amount. This is for the cost of the prophylaxis alone and excludes other

costs such as of identifying contacts and administering vaccine. The cost of HNIG is borne centrally (HNIG is currently supplied by PHLS) and that of vaccine locally.

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

When an outbreak occurs in a community such as a school, all close contacts of cases should be managed as indicated previously. The rest of this section deals with management of other members of the community experiencing the outbreak.

**FIGURE 10** The number needed to receive prophylaxis (HNIG or vaccine) to prevent one secondary case, according to secondary attack rate and efficacy of the intervention



The effectiveness of either HNIG or vaccine in controlling outbreaks depends on how well the community is defined and the coverage achieved with the intervention, as well as the efficacy of the intervention at individual level. HNIG has been used successfully to control outbreaks in well-defined or closed communities such as schools<sup>5,72-78</sup>, although it may have no impact on clinical cases if given late in the incubation period<sup>79,80</sup> or if the whole population at risk is not included in the intervention<sup>81,82</sup>. Vaccine has been used successfully as well to control outbreaks in well-defined communities<sup>83,84,85</sup>.

Outbreaks in the general population have also been successfully controlled by widespread use of HNIG<sup>64,86</sup> or vaccine<sup>9,87</sup>. Likewise HNIG has failed in such settings, particularly when the community has been poorly defined so that transmission continued beyond the period of protection<sup>88</sup>. Vaccination too has been either partly successful or delayed in effectiveness at controlling outbreaks<sup>54,59,89,90,91</sup>. If vaccine succeeds where HNIG has failed in controlling an outbreak, it does not follow that vaccine would have been successful if used from the outset. As with any new intervention that is initially taken up with enthusiasm, vaccine requires careful evaluation.

Outbreaks often occur in communities with a high incidence of HAV infection and a targeted vaccination programme may prevent both a sustained high incidence of infection and further outbreaks. Outbreaks in communities of injecting drug users, street homeless and men who have sex with men have proved difficult to control and this underlines the importance of achieving high uptake if selective vaccination programmes are to succeed.

## Product details

### Human normal immunoglobulin (HNIG)

Human normal immunoglobulin (HNIG) is prepared from pooled non-UK sourced donors' plasma. The plasma is derived from blood from donors screened for HIV, Hepatitis B and Hepatitis C and the processing of the plasma ensures that such viruses would be inactivated. There is a remote risk of transmission of vCJD, as for all blood products. The licensure includes a requirement that HNIG contains an adequate level of anti-HAV antibody.

HNIG offers short-term protection (up to about four months) against infection with HAV. It should be given within two weeks of exposure, preferably within 72 hours. If given within 2 weeks, efficacy has been estimated at 85%<sup>60,61,92</sup> while later administration may reduce the severity of disease rather than preventing infection.

For contacts of cases, the dose of HNIG should be 250mg for children under 10 years and 500mg for those 10 years and older.

HNIG should be administered intramuscularly into the deltoid or gluteal muscle except for haemophilia patients who should be injected subcutaneously. Anaphylaxis has been reported in those with IgA deficiency. It is safe in pregnancy and breastfeeding.

### Safety of HNIG

Patients should be given the patient information leaflet, which accompanies the product.

### Supplies of HNIG

HNIG is available for contacts of cases and control of outbreaks from:

- PHLs Communicable Disease Surveillance Centre, tel: 020 8200 6868
- Scottish Centre for Infection and Environmental Health, Glasgow, tel: 0141 211 3600.

### HAV vaccine

HAV vaccine is a formaldehyde-inactivated vaccine prepared from either the 'GBM' or the 'HM 175' strains of HAV grown in human diploid cells. Bovine albumin from BSE-free herds is used in its production. It is supplied as a suspension in pre-filled syringes.

The vaccine should be stored at 2°C to 8°C but not frozen, and should be protected from light. It should not be diluted or mixed with other vaccines in the same syringe.

The primary course of HAV vaccine is a single dose followed by a booster 6-12 months later. Immunogenicity studies show that levels of antibody produced after a primary course of vaccine administered intramuscularly are well in excess of those found after HNIG. Antibody persistence is prolonged up to 10 years by administration of the booster dose of vaccine a minimum of 6-12 months after the initial dose. Vaccine efficacy after 2 doses has been estimated at around 95%<sup>58</sup>.

Adult and child preparations containing differing amounts of antigen are available from the different manufacturers. All are given into the deltoid muscle (not gluteal region).

HAV vaccine can also be delivered for convenience in combination with Hepatitis B vaccine and with polysaccharide typhoid vaccine.

### Infants and pregnant women

The vaccine is not licensed for use in children <1 year of age and is not recommended for use in pregnancy by the manufacturers. If the risks of infection are high, however, prophylaxis may be indicated for a pregnant woman. While no vaccine can be considered completely safe in pregnancy, the risks of acquiring HAV infection in pregnancy may outweigh any likely risk of prophylaxis. As it is an inactivated vaccine, it is safe to use in immunocompromised patients although they should be warned that they may not produce an adequate immune response. It is safe for HIV-infected individuals<sup>93</sup>.

### Testing for immunity prior to vaccination

In general, testing for immunity is inadvisable. For certain groups who are likely to be already immune, testing prior to vaccination may be cost effective. This may include anyone born before 1945. For some individuals, such as injecting drug users, prior testing may significantly reduce the likelihood of vaccination being carried out at all and should not be a reason for delaying vaccination.

Testing is not recommended before giving post-exposure prophylaxis as this introduces unacceptable delay.

## Audit and research needs

Local and regional audit of control measures for HAV would enhance evaluation of the guidance. Notifications vary considerably between districts and regions. In 2000 this ranged from 63 to 276 cases reported from different English regions. The number at district level can be very small making it difficult for CsCDC to evaluate the impact of interventions in reducing secondary cases. Regional audits of HAV control may yield important information in this respect.

Although useful information would be gained from a head-to-head comparison of HNIG and vaccine for household contacts and for controlling outbreaks, this would require a large sample size and would be difficult to carry out in low incidence countries. Studies comparing the serological response to vaccine and HNIG would be feasible. Descriptive studies could also be carried out to estimate efficacy of HAV vaccine and HNIG in a large number of close contacts and in larger outbreaks.

## Acknowledgements

The authors wish to thank Mary Ramsay, Marianne Morris, Douglas Harding, Henry Prempeh and the Public Health Medicine Environment Group, Philip Mortimer, Noel Gill, Nick Andrews, Pauline Kaye, Norman Begg, and Henri Laurichesse.

Membership of the PHLS Advisory Committee on Vaccines and Immunisation, from 1996 to March 2001: Dr Elizabeth Miller (PHLS CDSC), Chairman; Dr David Brown (Director ERVL, CPHL); Professor Keith Cartwright (Group Director, PHLS South West); Dr Mike Corbel (NIBSC); Dr Natasha Crowcroft (PHLS CDSC); Dr Robert George (Director RSIL, CHPL); Dr David Goldblatt (Scientific Secretary, Institute of Child Health); Dr Philip Minor (NIBSC); Professor Peter Morgan-Capner (Medical Director, Chorley & South Ribble District General Hospital); Dr Mary Ramsay (PHLS CDSC); Dr Andrew Robinson (General Project Manager, CAMR); Dr David Salisbury (Principal Medical Officer, Department of Health); Dr James Stuart (Regional Epidemiologist, CDSC); Dr Barry Walsh (CCDC, Kingston and Richmond Health Authority); Dr Julius Weinberg (Pro-vice Chancellor for Research, City University).

No author has any conflict of interest to declare.

## References

- Grilli R, Magrini N, Penna A, Mura G, Liberati A. Practice guidelines developed by specialty societies: the need for a critical appraisal. *Lancet* 2000; **355**: 103-106.
- Communicable Disease Surveillance Centre. *Managements of hepatitis A outbreaks; a review of the evidence*. 1998; (UnPub).
- Anonymous. Hepatitis A associated with consumption of frozen strawberries - Michigan, March 1997. *MMWR* 1997; **46**: 288-295.
- Conaty S, Bird P, Bell G, Kraa E, Grohmann G, McAnulty JM. Hepatitis A in New South Wales, Australia from consumption of oysters: the first reported outbreak. *Epidemiol Infect* 2000; **124**: 121-130.
- Lednar WM, Lemon SM, Kirkpatrick JW, Redfield RR, Fields ML, Kelley PW. Frequency of illness associated with epidemic hepatitis A virus infections in adults. *Am J Epidemiol* 1985; **122**: 226-233.
- Ciocca M. Clinical course and consequences of hepatitis A infection. *Vaccine* 2000; **18 Suppl 1**: S71-S74.
- Debray D, Cullufi P, Devictor D, Fabre M, Bernard O. Liver failure in children with hepatitis A. *Hepatology* 1997; **26**: 1018-1022.
- Gay NJ, Morgan-Capner P, Wright J, Farrington CP, Miller E. Age-specific antibody prevalence to hepatitis A in England: implications for disease control. *Epidemiol Infect* 1994; **113**: 113-120.
- Irwin DJ, Millership S. Control of a community hepatitis A outbreak using hepatitis A vaccine. *Commun Dis Public Health* 1999; **2**: 184-187.
- Morris MC, Gay NJ, Hesketh LM, Morgan-Capner P, Miller E. *The changing epidemiological pattern of hepatitis A in England and Wales*. 2001; (UnPub).
- Termorshuizen F, Dorigo-Zetsma JW, de Melker HE, van den Hof S, Conyn-Van Spaendonck MA. The prevalence of antibodies to hepatitis A virus and its determinants in The Netherlands: a population-based survey [In Process Citation]. *Epidemiol Infect* 2000; **124**: 459-466.
- Behrens RH, Collins M, Botto B, Heptonstall J. Risk for British travellers of acquiring hepatitis A. *BMJ* 1995; **311**: 193-193.
- Anonymous. Prevention of hepatitis A through active or passive immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 1999; **48**: 1-37.
- Szmunn W, Purcell RH, Dienstag JL, Stevens CE. Antibody to hepatitis A antigen in institutionalized mentally retarded patients. *JAMA* 1977; **237**: 1702-1705.
- Ang LH. Outbreak of hepatitis A in a special needs school in Kent: 1999. *Commun Dis Public Health* 2000; **3**: 139-140.
- Donoghue AM, Hancox B. Hepatitis A vaccination for sewage workers [letter; comment]. *N Z Med J* 1995; **108**: 235-236.
- Brugha R, Heptonstall J, Farrington P, Andren S, Perry K, Parry J. Risk of hepatitis A infection in sewage workers. *Occup Environ Med* 1998; **55**: 567-569.
- Hinthorn DR, Foster MTJ, Bruce HL, Aach RD. An outbreak of chimpanzee associated hepatitis. *J Occup Med* 1974; **16**: 388-391.
- Akriviadis EA, Redeker AG. Fulminant hepatitis A in intravenous drug users with chronic liver disease. *Ann Intern Med* 1989; **110**: 838-839.
- Vento S, Garofano T, Renzini C, Cainelli F, Casali F, Ghironzi G, et al. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. *N Engl J Med* 1998; **338**: 286-290.
- Williams I, Bell B, Kaluba J, Shapiro CN. Association between chronic liver disease and death from hepatitis A, United States, 1989-92 [Abstract A39]. *IX Triennial International Symposium on Viral Hepatitis and Liver Disease. Rome, Italy*. 1996; (Abstract).
- Keeffe EB. Is hepatitis A more severe in patients with chronic hepatitis B and other chronic liver diseases? *Am J Gastroenterol* 1995; **90**: 201-205.
- Harkess J, Gildon B, Istre GR. Outbreaks of hepatitis A among illicit drug users, Oklahoma, 1984-87. *Am J Public Health* 1989; **79**: 463-466.
- Hutin YJ, Bell BP, Marshall KL, Schaben CP, Dart M, Quinlisk MP, et al. Identifying target groups for a potential vaccination program during a hepatitis A communitywide outbreak [published erratum appears in Am J Public Health 1999 Aug; **89**(8): 1274] [see comments]. *Am J Public Health* 1999; **89**: 918-919.
- Grinde B, Stene-Johansen K, Sharma B, Hoel T, Jensenius M, Skaug K. Characterisation of an epidemic of hepatitis A virus involving intravenous drug abusers—infection by needle sharing? *J Med Virol* 1997; **53**: 69-75.
- Shaw DD, Whiteman DC, Merritt AD, el-Saadi DM, Stafford RJ, Heel K, et al. Hepatitis A outbreaks among illicit drug users and their contacts in Queensland, 1997. *Med J Aust* 1999; **170**: 584-587.
- Hutin YJ, Sabin KM, Hutwagner LC, Schaben L, Shipp GM, Lord DM, et al. Multiple modes of hepatitis A virus transmission among methamphetamine users. *Am J Epidemiol* 2000; **152**: 186-192.

28. Mannucci PM, Gdovin S, Gringeri A, Colombo M, Mele A, Schinaia N, et al. Transmission of hepatitis A to patients with hemophilia by factor VIII concentrates treated with organic solvent and detergent to inactivate viruses. The Italian Collaborative Group. *Ann Intern Med* 1994; **120**: 1-7.
29. Mah MW, Royce RA, Rathouz PJ, Wang JG, White GC, Janco RL, et al. Prevalence of hepatitis A antibodies in hemophiliacs: preliminary results from the Southeastern Delta Hepatitis Study. *Vox Sang* 1994; **67 Suppl 1**: 21-22.
30. Soucie JM, Robertson BH, Bell BP, McCaustland KA, Evatt BL. Hepatitis A virus infections associated with clotting factor concentrate in the United States. *Transfusion* 1998; **38**: 573-579.
31. Chudy M, Budek I, Keller-Stanislawski B, McCaustland KA, Neidhold S, Robertson BH, et al. A new cluster of hepatitis A infection in hemophiliacs traced to a contaminated plasma pool. *J Med Virol* 1999; **57**: 91-99.
32. Anonymous. Hepatitis A among homosexual men - United States, Canada and Australia. *MMWR* 1992; **41**: 155-164.
33. Walsh B, Sundkvist T, Maguire H, Young Y, Heathcock R, Iverson A. Rise in hepatitis A among gay men in the Thames regions 1995 and 1996 [letter]. *Genitourin Med* 1996; **72**: 449-450.
34. Anonymous. Hepatitis A vaccination of men who have sex with men - Atlanta, Georgia, 1996-1997. *MMWR Morb Mortal Wkly Rep* 1998; **47**: 708-711.
35. Anonymous. From the Centers for Disease Control. Hepatitis A among homosexual men - United States, Canada, and Australia. *JAMA* 1992; **267**: 1587-1588.
36. Stokes ML, Ferson MJ, Young LC. Outbreak of hepatitis A among homosexual men in Sydney. *Am J Public Health* 1997; **87**: 2039-2041.
37. Henning KJ, Bell E, Braun J, Barker ND. A community-wide outbreak of hepatitis A: risk factors for infection among homosexual and bisexual men. *Am J Med* 1995; **99**: 132-136.
38. Christenson B, Brostrom C, Bottiger M, Hermanson J, Weiland O, Ryd G, et al. An epidemic outbreak of hepatitis A among homosexual men in Stockholm. Hepatitis A, a special hazard for the male homosexual subpopulation in Sweden. *Am J Epidemiol* 1982; **116**: 599-607.
39. Corey L, Holmes KK. Sexual transmission of hepatitis A in homosexual men: incidence and mechanism. *N Engl J Med* 1980; **302**: 435-438.
40. Coutinho RA, Albrecht-van LP, Lelie N, Nagelkerke N, Kuipers H, Rijdsdijk T. Prevalence and incidence of hepatitis A among male homosexuals. *Br Med J (Clin Res Ed)* 1983; **287**: 1743-1745.
41. Villano SA, Nelson KE, Vlahov D, Purcell RH, Saah AJ, Thomas DL. Hepatitis A among homosexual men and injection drug users: more evidence for vaccination. *Clin Infect Dis* 1997; **25**: 726-728.
42. Katz MH, Hsu L, Wong E, Liska S, Anderson L, Janssen RS. Seroprevalence of and risk factors for hepatitis A infection among young homosexual and bisexual men. *J Infect Dis* 1997; **175**: 1225-1229.
43. Communicable Disease Surveillance Centre. Hepatitis A in homosexual men. *Comm Dis Rep CDR Wkly* 1996; **6**: 247.
44. Young Y, Heathcock R, Walsh B, Maguire H. Seroprevalence of hepatitis A at Gay Pride Festival, London, 1996. 1996; (UnPub).
45. PHLS, DHSS&PS, ISD, SCIEH, MSSVD. Trends in sexually transmitted infection in the United Kingdom 1990-1999. Table 3. 2001.
46. Sundkvist T, Johansson B, Widell A. Rectum carried drugs may spread hepatitis A among drug addicts. *Scand J Infect Dis* 1985; **17**: 1-4.
47. Hickson F, Hartley M, Weatherburn P. London Counts; HIV prevention needs and information amongst gay and bisexual men in the 16 London Health Authorities. London Sigma Research, 2001.
48. Steffen R, Kane MA, Shapiro CN, Billo N, Schoellhorn KJ, Van Damme P. Epidemiology and prevention of hepatitis A in travelers. *JAMA* 1994; **272**: 885-889.
49. Steffen R, Rickenbach M, Wilhelm U, Helminger A, Schar M. Health problems after travel to developing countries. *J Infect Dis* 1987; **156**: 84-91.
50. Department of Health, National Assembly for Wales, Scottish Executive Health Department, DHS PS (Northern Ireland), Public Health Laboratory Service Communicable Disease Surveillance Centre. Disease risks and recommendations by continental group and country. In: Lea G, Leese J, eds. *Health Information for Overseas Travel*. London: The Stationary Office, 2001; 8-91.
51. Communicable Disease Surveillance Centre. Human normal immunoglobulin (HNIG): lack of availability for travellers. *Comm Dis Rep CDR Wkly* 2000; **10**: 301-301.
52. Krober MS, Bass JW, Brown JD, Lemon SM, Rupert KJ. Hospital outbreak of hepatitis A: risk factors for spread. *Pediatr Infect Dis* 1984; **3**: 296-299.
53. Green MS, Cohen D, Lerman Y, Sjogren M, Binn LN, Zur S, et al. Depression of the immune response to an inactivated hepatitis A vaccine administered concomitantly with immune globulin. *J Infect Dis* 1993; **168**: 740-743.
54. Bonanni P, Colombai R, Franchi G, Lo NA, Comodo N, Tiscione E. Experience of hepatitis A vaccination during an outbreak in a nursery school of Tuscany, Italy. *Epidemiol Infect* 1998; **121**: 377-380.
55. Robertson BH, D'Hondt EH, Spelbring J, Tian H, Krawczynski K, Margolis HS. Effect of postexposure vaccination in a chimpanzee model of hepatitis A virus infection. *J Med Virol* 1994; **43**: 249-251.
56. D'Hondt E, Purcell RH, Emerson SU, Wong DC, Shapiro M, Govindarajan S. Efficacy of an inactivated hepatitis A vaccine in pre- and postexposure conditions in marmosets. *J Infect Dis* 1995; **171 Suppl 1**: S40-S43.
57. Flehmig B, Normann A, Bohnen D. Transmission of hepatitis A virus infection despite vaccination [letter]. *N Engl J Med* 2000; **343**: 301-302.
58. 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 [see comments]. *N Engl J Med* 1992; **327**: 453-457.
59. McMahon BJ, Beller M, Williams J, Schloss M, Tanttila H, Bulkow L. A program to control an outbreak of hepatitis A in Alaska by using an inactivated hepatitis A vaccine. *Arch Pediatr Adolesc Med* 1996; **150**: 733-739.
60. Mosley JW, Reisler DM, Brachott D, Roth D, Weiser J. Comparison of two lots of immune serum globulin for prophylaxis of infectious hepatitis. *Am J Epidemiol* 1968; **87**: 539-550.
61. Stokes J, Neefe JR. The prevention and attenuation of infectious hepatitis by gamma globulin: preliminary note. *JAMA* 1945; **127**: 144-145.
62. Shaw FEJ, Sudman JH, Smith SM, Williams DL, Kapell LA, Hadler SC, et al. A community-wide epidemic of hepatitis A in Ohio. *Am J Epidemiol* 1986; **123**: 1057-1065.
63. 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 randomised trial [published erratum appears in *Lancet* 1999; **353**: (Jun 12) (9169): 2078]. *Lancet* 1999; **353**: 1136-1139.
64. Pavia AT, Nielsen L, Armington L, Thurman DJ, Tierney E, Nichols CR. A community-wide outbreak of hepatitis A in a religious community: impact of mass administration of immune globulin. *Am J Epidemiol* 1990; **131**: 1085-1093.
65. Innis BL, Snitbhan R, Kunasol P, Laorakpongse T, Poopatanakool W, Kozik CA, et al. Protection against hepatitis A by an inactivated vaccine. *JAMA* 1994; **271**: 1328-1334.
66. Rubertone MV, DeFraitte RF, Krauss MR, Brandt CA. An outbreak of hepatitis A during a military field training exercise. *Mil Med* 1993; **158**: 37-41.
67. Greco D, De Giacomo G, Piersante GP, Bibby L, Nicastro M, Cavalcanti P. A person to person hepatitis A outbreak. *Int J Epidemiol* 1986; **15**: 108-111.
68. Noble RC, Kane MA, Reeves SA, Roeckel I. Posttransfusion hepatitis A in a neonatal intensive care unit. *JAMA* 1984; **252**: 2711-2715.
69. Gmelin K, Doerr HW, Severin R, Bommer J, von Ehrlich-Treuenstatt B, Ritz E, et al. Presumable non-A, non-B hepatitis in hemodialysis. *Zentralbl Bakteriol Mikrobiol Hyg [B]* 1982; **176**: 28-38.
70. Staes CJ, Schlenker TL, Risk I, Cannon KG, Harris H, Pavia AT,

- et al. Sources of infection among persons with acute hepatitis A and no identified risk factors during a sustained community-wide outbreak [In Process Citation]. *Pediatrics* 2000; **106**: E54.
71. 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. *Eur J Epidemiol* 1997; **13**: 139-144.
  72. Drusin LM, Sohmer M, Groshen SL, Spiritos MD, Senterfit LB, Christenson WN. Nosocomial hepatitis A infection in a paediatric intensive care unit. *Arch Dis Child* 1987; **62**: 690-695.
  73. Hall WT, Madden DL, Mundon FK, Brandt DE, Clarke NA. Protective effect of immune serum globulin (ISG) against hepatitis A infection in a natural epidemic. *Am J Epidemiol* 1977; **106**: 72-75.
  74. Hadler SC, Erben JJ, Matthews D, Starko K, Francis DP, Maynard JE. Effect of immunoglobulin on hepatitis A in day-care centers. *JAMA* 1983; **249**: 48-53.
  75. Bull AR, Kimmance KJ, Parry JV, Perry KR. Investigation of an outbreak of hepatitis A simplified by salivary antibody testing. *Epidemiol Infect* 1989; **103**: 371-376.
  76. Hanna J. Hepatitis A outbreak in a rural town, Atherton Tablesland, Queensland, 1992. *Commun Dis Intell* 1993; **17**: 70-72.
  77. Hanna J. Hepatitis A in a child-care centre. *Commun Dis Intell* 2001; **17**: 73-75.
  78. Davidson R, El-Saadi O, Longhurst D, Kassulke D. An outbreak of hepatitis A in a childcare centre. *Commun Dis Intell* 1996; **20**: 276-278.
  79. Tassopoulos NC, Roumeliotou-Karayannis A, Sakka M, Ticehurst J, Mihalik K, Stephanou T, et al. An epidemic of hepatitis A in an institution for young children. *Am J Epidemiol* 1987; **125**: 302-307.
  80. Green MS, Dotan K. Efficacy of immune serum globulin in an outbreak of hepatitis A virus infection in adults. *J Infect* 1988; **17**: 265-270.
  81. Hatazawa T, Abo W, Sakai Y, Seki K, Doi T, Tachibana N, et al. An outbreak of hepatitis A in a day-care center: immunoprophylaxis with human immunoglobulin. *Acta Paediatr JPN* 1998; **40**: 244-246.
  82. Rajaratnam G, Patel M, Parry JV, Perry KR, Palmer SR. An outbreak of hepatitis A: school toilets as a source of transmission. *J Public Health Med* 1992; **14**: 72-77.
  83. Deshaies D, Dion R, Valiquette L, Auger N. Immunization against hepatitis A during an outbreak in a Jewish Orthodox community-Quebec, 1997-1998. *Can Commun Dis Rep* 1998; **24**: 145-151.
  84. Hockin J, Isaacs S, Kittle D, Brimmer G, Bailey N, Tamblyn S. Hepatitis A outbreak in a socially-contained religious community in rural southern Ontario. *Can Commun Dis Rep* 1997; **23**: 161-166.
  85. Laurichesse H, Peigue-Lafeuille H, Rabanel JR, Henquell C, Beytout J, Rey M. Une épidémie d'hépatite A dans un établissement pour handicapés rapidement enrayée par la séro-vaccination des résidents et du personnel [Abstract 286/P15]. *13th Réunion Interdisciplinaire de Chimiothérapie Anti-Infectieuse (RICAI), Paris 2-3 Décembre 1993*. 1993.
  86. Gildon B, Makintube S, Istre GR. Community-wide Outbreak of Hepatitis A Among an Indian population in Oklahoma. *Southern Medical Journal* 1992; **85**: 9-13.
  87. Poovorawan Y, Tieamboonlers A, Chumdermpadetsuk S, Gluck R, Cryz SJJ. Control of a hepatitis A outbreak by active immunization of high-risk susceptible subjects [letter]. *J Infect Dis* 1994; **169**: 228-229.
  88. Aszkenasy OM. A community outbreak of hepatitis A in a religious community in Indiana: failure of immune serum globulin to prevent the spread of infection. *Epidemiol Infect* 2000; **124**: 309-313.
  89. Prikazsky V, Olear V, Cernoch A, Safary A, Andre FE. Interruption of an outbreak of hepatitis A in two villages by vaccination. *J Med Virol* 1994; **44**: 457-459.
  90. Craig AS, Sockwell DC, Schaffner W, Moore WLJ, Skinner JT, Williams IT, et al. Use of hepatitis A vaccine in a community-wide outbreak of hepatitis A. *Clin Infect Dis* 1998; **27**: 531-535.
  91. Averbhoff F, Shapiro CN, Hyams I, Burd L, Ward C, Ellena G, et al. Use of inactivated hepatitis A vaccine (VAQTA) to interrupt a community wide hepatitis A outbreak [Abstract H73]. *1996 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), American Society of Microbiology* 1996; 176-176.
  92. Kluge T. Gamma-globulin in the prevention of viral hepatitis: a study on the effect of medium-size doses. *Acta Med Scand* 1963; **174**: 467-477.
  93. Bodsworth NJ, Neilsen GA, Donovan B. The effect of immunization with inactivated hepatitis A vaccine on the clinical course of HIV-1 infection: 1-year follow-up. *AIDS* 1997; **11**: 747-749.