A community outbreak of hepatitis A in a religious community in Indiana: failure of immune serum globulin to prevent the spread of infection

O. M. ASZKENASY

Community Child Health Department, West Lane Hospital, Acklam Road, Middlesbrough TS5 4EE

SUMMARY

An outbreak of hepatitis A occurred in a religious community in Indiana, USA. Sixty-nine cases were ascertained among the 4466 residents over a year, and the highest attack rate was in children. The management of the outbreak included the widespread use of prophylactic immune serum globulin (ISG). Despite this, further cases occurred. To guide further ISG administration, a survey was undertaken to ascertain what proportion remained susceptible to HAV infection. From a random sample of 600 people in the affected community 440 saliva specimens (73%) were obtained. Of these, 12·5% were found to be immune (95% confidence intervals from 9–16%). No changes were made to the ISG administration policy. There was no evidence to suggest that administration of ISG had any effect on the duration of the outbreak. There was a low rate of symptomatic infection among young children (less than 10 years); as ISG does not prevent the spread of the virus its use is not recommended in future outbreak situations.

INTRODUCTION

Community outbreaks of hepatitis A pose challenging management problems for public health departments. Cases notified to health departments are likely to represent only the tip of the iceberg of all infected individuals. This is because attack rates are usually highest in the young [1–3], in whom the majority of cases are asymptomatic [4–6] and who therefore constitute a reservoir for the transmission of infection to adults who usually have symptomatic disease [5].

In this study, a serological survey of oral fluid samples from a selected cohort of a religious community in northern Indiana, USA, was undertaken to determine anti-HAV total and IgM positivity rates. This was in response to an outbreak of HAV infection in this religious community in 1991–2.

METHODS

Investigations were undertaken by environmental health officers to try to identify likely sources of the outbreak. This included site visits to affected families and testing of local water supplies and food samples. The community had a practice of large social gatherings at which home-prepared food was distributed, and some water supplies were from hand-pumped open wells. However, the distribution of cases could not be linked statistically or microbiologically to any one specific factor.

After liaison with community leaders and encouraging results from a pilot study, in December 1992 oral fluid specimens were collected from a random sample of the population. A directory compiled by one of the community members was identified as a suitable sampling frame. Names and addresses were entered onto a computer, and a random sample of the population was obtained. The results of a previous small serological survey of HAV antibody status in a religious community with similar family size to those found in this religious community [7], suggested a sample of 360. A sample of 600 was chosen (90 families), on the basis of an anticipated 60% response rate. Families were invited by post to participate in the
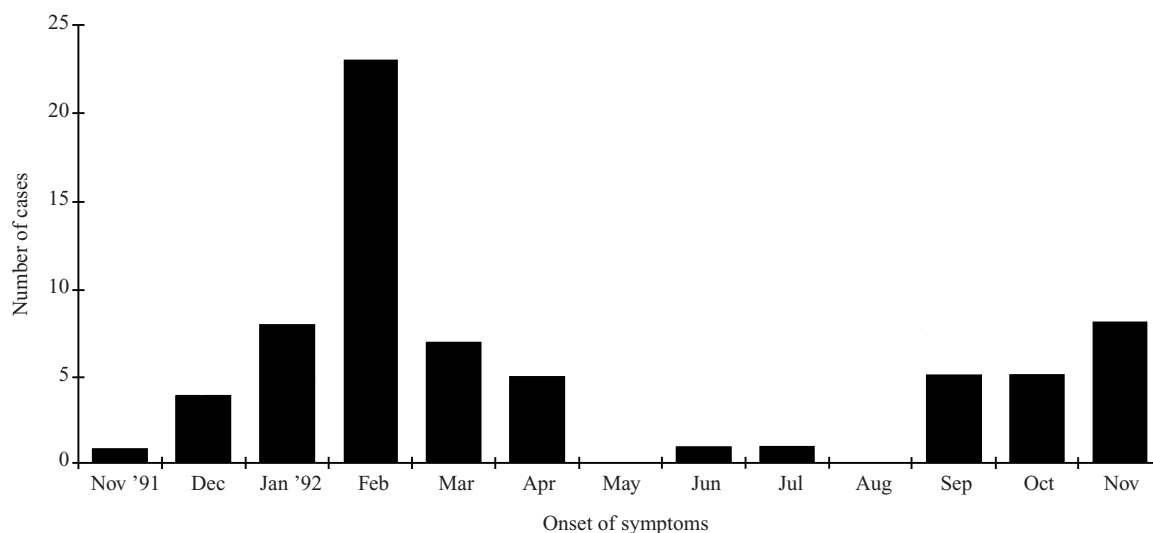
Fig. 1. Hepatitis A outbreak, Indiana, USA, November 1991–December 1992.

Table 1. *Age- and sex-specific attack rates of HAV infection per thousand of age group*

Age group	Female			Male			Both sexes	
	Popn	Cases	Rate	Popn	Cases	Rate	Cases	Rate
0–9	709	8	11·2	734	22	29·9*	31	20·7
10–19	507	10	19·7	574	6	10·4	16	14·8
20–39	617	8	12·9	633	8	12·6	16	12.8
40+	354	2	5·6	338	4	11·8	6	8·6
Total	2187	28	12·8	2279	40	17·5	68	15.4

* $P < 0·05$.

survey; one reminder was sent. Participating families were visited by staff from local and state health departments and informed consent obtained. Oral fluid samples were collected and a questionnaire administered. This elicited identifying information, symptomatology, administration of ISG and contact with persons who had symptomatic HAV infection. At the time of the visit health, promotion advice was given in verbal and written form regarding the prevention of HAV infection.

Oral fluid samples were collected using a standard kit supplied by Epitope Inc., and used as previously described [8]. The term 'oral fluid' rather than saliva is used here because it is likely that the sampling technique used in this survey collects gingival crevicular fluid as well as saliva [8]. Specimens were analysed with the Abbott HAVAB enzyme immuno-assay (EIA) kit to detect total anti-HAV antibody, using appropriate modifications required for oral fluid

assay [8]. If found to be reactive, samples were tested with the Abbott HAVAB-M EIA kit to detect anti-HAV IgM. Individuals were notified of their results.

RESULTS

Between 1987 and October 1991 there had only been two patients with hepatitis A notified from a county in northern Indiana (equivalent to an annual rate of 1 per 100000 of the local population). On 29 November 1991 a notification was received by the Indiana State Department of Health (ISDH) from the local Health Department of an 11-month-old female infant who had developed jaundice and had serologically confirmed hepatitis A. Seven further cases were notified over the next 3 weeks, who had all been in social contact with the family of the index case. A total of 69 cases of HAV infection were reported to the ISDH between November 1991 and December 1992. The

Table 2. *Distribution of total anti-HAV antibody and anti-HAV IgM antibody by age group*

Age group	Number in age group	Number who had received ISG	Anti-HAV positive (%)	Anti-HAV IgM positive (%)	Percent of age group
0–9	130	51	12 (9·2)	3 (1)	2·3
10–19	94	41	8 (8·5)	1 (0·3)	1·1
20–39	78	28	5 (6·4)	1 (0·3)	1·3
40 +	42	17	18 (43)	0	0·0
Total	344	137	43 (12·5)	5 (1·4)	1·4

frequency of hepatitis increased gradually and peaked in February 1992. Figure 1 shows the outbreak curve, which is typical of case-to-case transmission. The median age of persons with hepatitis was 11·5 years, with a range from 5 months to 68 years. There were no hospital admissions or deaths. The age-specific attack rate was highest in boys aged 0–9 ($P < 0.05$, see Table 1). Geographical and surname analysis suggested that cases occurred only in the religious community.

In this outbreak a policy of offering ISG to school and household contacts of cases had been followed, according to the recommendations of the United States Immune Practices Advisory Committee (ACIP) [9]. There were many such contacts, and as a result a substantial proportion of the population had been given ISG 4 months after the beginning of the outbreak in November 1991. However, by October 1992 it was evident that the outbreak was continuing. The health department was now faced with the situation that many of those who had received passive immunization with ISG would by now have lost their protection [10].

The oral fluid and questionnaire survey proved acceptable and practical in the field situation. Seventy families (77%) responded positively to the request to participate, and 440 samples were obtained. Ninety-six samples (22%) were inadequate and had to be discarded. The remainder of the analysis refers to those 344 individuals who provided adequate samples. The mean age of the sample was 18·7 years, compared to 21·3 years for the population as a whole. The sex distribution was 1:1 for both the sample and the population. The median number of children in households in the sample was four, compared to a median of five for the population as a whole.

Table 2 shows the distribution of total HAV antibody and anti-HAV IgM antibody by age group, and the distribution of subjects who had received ISG.

The overall prevalence of anti-HAV in the community was 12·5% (95% confidence intervals (CI) 9–16%), and for anti-HAV IgM antibody was 1·4% (95% CI 0·5–3%). One of the individuals who was HAV IgM antibody positive recalled contact with a family member who had the symptoms of hepatitis A.

Of the 43 individuals who were anti-HAV antibody positive, one recalled jaundice (an adult). Five recalled malaise lasting several weeks but clearly it is not possible to definitely attribute this to HAV infection.

DISCUSSION

Saliva is a mixture of salivary-gland secretion and gingival crevicular fluid, a plasma transudate found between teeth and gums [11]. The salivary glands produce the greater part of its volume and IgA content, but its IgG and IgM content derives largely from the gingival fluid [12]. The development of salivary antibody assays has greatly facilitated the identification of individuals with current or recent infections, and persons who are immune and those susceptible. The reliability of the technique is influenced by the nature of the sample collection device used and the type of assay. Antibody capture tests, although sophisticated and time consuming have been found to be more reliable than conventional competitive assays.

When compared to serum assays, the salivary technique using the antibody capture assay has been found in various studies to be between 100% and 98% sensitive and specific for the detection of IgG and IgM anti-HAV antibody respectively [8, 11, 13, 14]. This is in comparison to the 'gold standard' of serological testing. Using a saliva collection technique which involves the subject spitting into a pot the competitive assay produced a specificity of 100% but a sensitivity of 10–15% [11, 13]. However, using a

technique which specifically samples gingival crevicular fluid Thieme and colleagues [8] have shown that the detection of anti-HAV using salivary samples can be reliably undertaken with conventional competitive ELISA kits used for serological samples. Use of the special sampling tool produced a sensitivity and specificity for anti-HAV of 100 % each [8]. No special laboratory equipment beyond that required for HAV antibody assay in serological samples is needed.

It is clear that the widespread use of ISG had little impact on the outbreak, although the outbreak curve does suggest that there may have been a transient decrease in the rate of notification of new cases. The overall effect of widespread administration of ISG appears to have been to slow the spread rather than prevent further cases. The oral fluid study revealed the low prevalence of anti-HAV antibody in the population. Despite the risk factors operating in the community, it appears that HAV had not been in the community for a number of years. This is reinforced by the fact that only one of the adults who was HAV antibody-positive remembered jaundice, suggesting the majority may have had their infections as children. This may be related to the relative social isolation which members of this religious group maintain with respect to other communities.

Although salivary antibody testing has been used in outbreak investigations in the United Kingdom [15, 16], this is the first description of the use of an oral-fluid survey in this situation in the United States. The population surveyed has traditionally been relatively inaccessible. However, participation was excellent and initial reports from community leaders suggest the survey was well received. The non-invasive nature of specimen collection, and the personal usefulness of the result of the test to individuals sampled may have been contributory factors.

As with other diseases transmitted via the faecal–oral route such as polio, environmental and socio-economic factors are important [17]. Populations in both non-industrialized and industrialized countries show a striking age-related prevalence of HAV antibody [18–20]. As sanitary conditions have improved in certain countries, a birth cohort trend in the prevalence of immunity has been discerned [21], with many workers reporting a decline in the prevalence of anti-HAV antibody in the younger age-groups [22–24]. The decline in prevalence is likely to be due to reduced exposure in the early years of life [21]. Family size has been found to be an independent predictor of HAV antibody prevalence [25].

Since this outbreak occurred, a recommendation has been made, which these findings support, that systematic screening should not routinely be undertaken since a high proportion of individuals are likely to be susceptible and screening would only delay immunization (personal communication, Dr Norman Begg). The main aim of this is to reduce the frequency of symptomatic cases; however, giving ISG to contacts of cases in an outbreak may reduce the number of new symptomatic cases but does not shorten outbreaks [26, 27]. Its administration to young children, an important vector in community outbreaks [28], is controversial.

As ISG does not affect transmission of the virus and the frequency of symptomatic cases in children is low, active vaccination may be preferable in outbreak situations where a well-defined target population exists [29, 30], although it had not been licensed in the USA at the time of the outbreak.

In June 1995, the United States Public Health Service Advisory Committee on Immunization Practices (ACIP) issued recommendations about the use of hepatitis A vaccine for the prevention and control of hepatitis A. In communities with high rates of hepatitis A and periodic outbreaks, the ACIP recommended vaccination of young children and catch-up vaccination of previously unvaccinated older children. A preliminary report suggested that the magnitude and duration of a predicted outbreak may have been lessened by this policy [31]. Traditionally, ISG has been seen as having a role in the prevention of secondary symptomatic cases by reducing the clinical expression of the disease rather than prevention of spread; however, there is now evidence that hepatitis A vaccine is also effective in the prevention of secondary infection [32].

ACKNOWLEDGEMENTS

REFERENCES

1. Shaw FE Jr, Sudman JH, Smith SM, et al. A community-wide epidemic of hepatitis A in Ohio. J Am Epidemiol 1986; **12**: 1057–65.

2. Hadler SC, Webster HM, Erben JE. Hepatitis A in day care centers: a community-wide assessment. N Engl J Med 1980; **320**: 1222–7.

3. McIntyre N. Clinical manifestations of acute viral hepatitis. Br Med Bull 1990; **46**: 533–47.

4. Benenson MW, Takafuji Et, Bancroft WH, Lemon SM, Calahan MC, Leach DA. A military outbreak of hepatitis A related to transmission in a child care facility. Am J Epidemiol 1980; **112**: 471–81.

5. Lednar WM, Lemon SM, Kirkpatrick JW, Redfield RR, Fields ML, Kelley PW. Frequency of illness associated with hepatitis A infection in adults. Am J Epidemiol 1985; **122**: 226–33.

6. Yang NY, Yu PH, Mao ZX, Chen NL, Chai SA, Mao JS. Inapparent infection of hepatitis A virus. Am J Epidemiol 1988; **127**: 599–604.

7. Pavia AT, Nielsen L, Armington L, Thruman 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**: 1085–93.

8. Thieme T, Yoshihara P, Piacentini S, Beller M. Clinical evaluation of oral fluid samples for diagnosis of viral hepatitis. J Clin Microbiol 1992; **30**: 1076–9.

9. Centers for Disease Control. Protection against viral hepatitis. Recommendations of the Immunisation Practices Advisory Committee. MMWR 1990; **39**: (RR-2): 2.

10. Krugman S. The clinical use of gamma globulin. N Engl J Med 1963; **269**: 198–201.

11. Parry JV, Perry KR, Mortimor PP. Sensitive assays for viral antibodies in saliva. An alternative to tests on serum. Lancet 1987; **ii**: 72–5.

12. Roitt I, Lehner T. Oral immunity. Immunology of oral diseases, 2nd ed. Oxford: Blackwell Scientific Publications, 1983; 279–304.

13. Parry JV. Detection of viral antibodies in saliva specimens as an alternative to serum. J Clin Chem 1989; **27**: 245–6.

14. Parry JV, Perry KR, Panday S, Mortimer PP. Diagnosis of hepatitis A and B by testing saliva. J Med Virol 1989; **28**: 255–60.

15. Bull AR, Kimmance KJ, Parry JV, Perry KR. Investigation of an outbreak of hepatitis A simplified by salivary antibody testing. Epidemiol Infect 1989; **103**: 371–6.

16. Stuart JM, Majeed FA, Cartwright KAV, et al. Salivary antibody testing in a school outbreak of hepatitis A. Epidemiol Infect 1992; **109**: 161–6.

17. Szmuness W, Dienstag R, Stevens C, et al. The prevalence of antibody to hepatitis A antigen in various parts of the world: a pilot study. Am J Epidemiol 1977; **106**: 392–8.

18. Stroffolini T, Chiaramonte M, Franco E, et al. Baseline seroepidemiology of hepatitis A virus infection among children and teenagers in Italy. Infection 1991; **19**: 97–100.

19. Chin KP, Lok AS, Wong LS, Lai CL, Wu PC. Current seroepidemiology of hepatitis A in Hong Kong. J Med Virol 1991; **34**: 191–3.

20. Stroffolini T, Franco E, Mura I, Uccheddu P, Cauletti M, Azara A, Scarpa B. Age-specific prevalence of hepatitis A virus infection among teenagers in Sardinia. Microbiologica 1991; **14**: 21–4.

21. Gust ID, Lehman NI, Lucas CR. Relationship between prevalence of anitbody to hepatitis A antigen and age: a cohort effect? J Infect Dis 1978; **138**: 425–6.

22. Vranckx R, Muylle L. Hepatitis A virus antibodies in Belgium: relationship between prevalence and age. Infection, 1990; **18**: 364–6.

23. Green MS, Tsur S, Slepon R. Sociodemographic factors and the declining prevalence of anti-hepatitis A antibodies in young adults in Israel: implications for the new hepatitis A vaccines. Int J Epidemiol 1992; **21**: 136–41.

24. Chiaramonte M, Moschen ME, Stroffolini T, et al. Changing epidemiology of hepatitis A virus (HAV) infection: a comparative seroepidemiological study (1979 vs 1989) in north-east Italy. Ital J Gastroenterol 1991 **23**: 344–6.

25. Green MS, Zaaide Y. Sibship size as a risk factor for hepatitis A infection. Am J Epidemiol 1989; **129**: 800–5.

26. Majeed FA, Stuart JM, Cartwright KA, et al. An outbreak of hepatitis A in Gloucester, UK. Epidemiol Infect 1992; **109**: 167–73.

27. Pavia AT, Nielson L, Armington L, et al. A community-wide outbreak of hepatitis A in a religious community: impact of mass administration of immune globulin. Am J Epidemiol 1990; **131**: 1085–92.

28. Smith PF, Grabau JC, Werzberger A, et al. The role of young children in a community-wide outbreak of hepatitis A. Epidemiol Infect 1997; **118**: 243–52.

29. Werzberger A, Mensch B, Kuter B, et al. A controlled trial of a formalin-inactivated hepatitis A vaccine in healthy children. N Engl J Med 1992; **327**: 453–7.

30. Hepatitis A outbreak in a socially-contained religious community in rural southern Ontario. Can CDR 1997; **23**: 161–5.

31. Anonymous. Hepatitis A vaccination programs in communities with high rates of hepatitis A. MMWR. 1997; **46**: 600–3.

32. Sagliocca L, Amoroso P, Tommaso S, et al. Efficacy of hepatitis A vaccine in prevention of secondary cases: a randomised trial. Lancet 1999; **353**: 1136–9.