Epidemiol. Infect. (2006), **134**, 492–497. © 2005 Cambridge University Press
doi:10.1017/S0950268805005194 Printed in the United Kingdom

The increasing prominence of household transmission of hepatitis A in an area undergoing a shift in endemicity

J. C. VICTOR[1]*, T. Y. SURDINA[2], S. Z. SULEIMEOVA[3], M. O. FAVOROV[4], B. P. BELL[5] AND A. S. MONTO[1]

[1] *Department of Epidemiology, School of Public Health, The University of Michigan, Ann Arbor, MI, USA*
[2] *Department of Epidemiology, Republican Sanitary Epidemiology Station, Kazakhstan Ministry of Health, Almaty, Kazakhstan*
[3] *Virology Reference Laboratory, Republican Sanitary Epidemiology Station, Kazakhstan Ministry of Health, Almaty, Kazakhstan*
[4] *Division of International Health, Coordinating Office for Global Health, Centers for Disease Control and Prevention, Atlanta, GA, USA*
[5] *Division of Viral Hepatitis, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA*

(*Accepted 2 July 2005, first published online 30 September 2005*)

SUMMARY

In the rapidly developing city of Almaty, Kazakhstan, rates of hepatitis A have fallen, but no data on prevalence of antibody to hepatitis A virus (anti-HAV) exist with which to interpret incidence data. In the autumn of 2001, we determined the anti-HAV prevalence among household and school contacts of hepatitis A cases. For contacts aged 0–4 years, 5–9 years, 10–14 years, 15–19 years, or 20–30 years, immune prevalences were 9, 12, 33, 33 and 77% respectively, among immediate-family household contacts and 15, 28, 49, 52 and 77% respectively, among community contacts. Child community contacts were more likely to be immune than their immediate-family household counterparts (odds ratio 2·0, 95% confidence interval 1·3–3·2). Almaty is experiencing an epidemiological shift in hepatitis A incidence. Feasible and effective prevention strategies using hepatitis A vaccine should be explored.

INTRODUCTION

Hepatitis A virus (HAV), causes an acute inflammatory disease of the liver, and is acquired primarily by the faecal–oral route by either person-to-person contact or ingestion of contaminated food or water. The vast majority of the world's population is still at moderate to high risk of HAV infection [1]. As countries around the world develop, the prevalence of HAV infection is likely to fall, but hepatitis A will paradoxically become a greater public health problem. This is due to the fact that the likelihood and severity of symptomatic illness with HAV infection are related to the person's age [2–4]. Under improved sanitation and living conditions, individuals escape infection in early childhood and are left susceptible in adolescence and adulthood when the risk of severe disease is higher.

Age-specific prevalence of anti-HAV has been used to define several patterns of endemicity worldwide [5, 6]. Progressively developing nations typically exhibit a pattern of intermediate endemicity, where seroprevalence in adults may be 80–90% but only 20–30% in children <10 years [7–9]. Inactivated

* Author for correspondence: Dr J. C. Victor, Department of Epidemiology, 109 Observatory St, Ann Arbor, MI 48109, USA. (Email: jvictor@umich.edu)

hepatitis A vaccines are now available, but costs are likely to prohibit implementation of universal vaccination in most countries. Local officials may have to consider limited and targeted vaccination first. Designing such targeted vaccination programmes will require at least a basic understanding of the population susceptibility to hepatitis A.

Almaty, with a population in 2000 of ~1·14 million divided among six administrative districts, is the largest and most densely populated city in Kazakhstan. Following the collapse of the Soviet Union, Almaty is experiencing rapid development as the oil, gas and mineral wealth of Kazakhstan is increasingly tapped for the world market. The reported annual incidence rate of hepatitis A in Almaty has varied widely in the past, but substantial epidemics typically occur seasonally between September and March each year. Only 10 years ago, annual hepatitis A incidence was greater than 200 cases per 100 000; more recently incidence has fallen below 100 cases per 100 000 (T. Surdina, personal communication). Because no seroprevalence data are available for this population, we conducted a study of the anti-HAV prevalence in the Almaty population through testing of case contacts.

METHODS

Participants

Subject identification

Participating subjects were contacts of acute hepatitis A cases. Hepatitis A cases were identified through laboratory-based surveillance [10] and required IgM anti-HAV seropositivity and signs or symptoms consistent with hepatitis A disease. Contacts were considered for enrolment only if the identifying case resided within the city of Almaty, had household and/or school or day-care contacts, had no other reported cases of hepatitis A in the household or classroom during the previous 60 days and had self-reported illness onset within 14 days of interview.

Contact enrolment

Household contacts were defined as individuals who resided with the case during the 2-week period prior to case illness onset, or neighbours who shared toilet facilities with the case in a dormitory-type living situation during that same period. School/day-care contacts were defined as any child or teacher who attended school/day-care with the case during the 2-week period prior to illness onset in the case. Participation was limited to those aged $\leqslant 30$ years. Biographical information (date of birth, gender, ethnicity, occupation and relationship to the case) was collected on a standard questionnaire. Self-reported immunization history and past diagnosis with hepatitis A were also recorded.

The study protocol was approved by institutional review boards at the University of Michigan, the US Centers for Disease Control and Prevention and the National Medical University of Kazakhstan. For all contacts, written informed consent was obtained from the subject or his/her parent or guardian.

Laboratory assays

Blood specimens were collected from participating contacts, and sera were tested by ELISA for reactivity to IgM anti-HAV using ETI-HA-IGMK PLUS (DiaSorin Inc., Stillwater, MN, USA) and total anti-HAV using ETI-AB-HAVK PLUS (DiaSorin Inc.) according to standard operating procedures at the Republic of Kazakhstan Sanitary Epidemiology Station Virology Reference Laboratory.

Data categorization

Contacts were divided into two exposure groups that plausibly represent similar exposure histories. These were defined as either immediate family, which consisted of only parents, spouses, children or siblings of cases, or community contacts, which consisted of school/day-care contacts, neighbour contacts and all other household contacts, including extended family members, not defined as immediate family. A contact was defined as immune if the subject was total anti-HAV positive *and* anti-HAV IgM negative; a contact was defined as susceptible if the subject was total anti-HAV negative *or* anti-HAV IgM positive. Because IgM positivity lasts a minimum of ~3 months [11], anti-HAV IgM-positive contacts were considered susceptible prior to the outbreak under study.

Statistical analyses

Factors associated with immunity were analysed using multivariate logistic regression modelling techniques that accounted for correlation within clusters of contacts, using SAS, version 9.1 (SAS Institute Inc., Cary, NC, USA). Clusters were defined as each group of immediate-family members from within a household or all community contacts taken together as one group.

All bivariate analyses were conducted using an appropriate χ^2 test.

RESULTS

Demographics

Enrolment was conducted from 1 October to 31 December 2001. During this period, 539 cases of acute hepatitis A were identified through positive IgM anti-HAV test results at the Virology Reference Laboratory. Of these 162 (30%) cases were located, eligible according to the four specified criteria and agreed to participate. Through the 162 total cases, 2608 contacts were identified – 1987 school contacts, 593 household contacts, and 28 neighbour contacts. Of the school contacts, 1334 (67%) agreed to participate, although nine gave specimens unsuitable for serological tests. Age data were not available for individual school contacts who did not participate in the study, but based on median classroom age, 64% of school contacts from classrooms of median age of <15 years agreed to participate, while 83% of school contacts from classrooms of median age of $\geqslant 15$ years agreed to participate. Of the household contacts, 341 (58%) were $\leqslant 30$ years and eligible to participate. Among those household contacts aged 0–19 years or 20–30 years, 153 (76%) and 119 (46%), respectively, attended the household meeting and agreed to participate. Participating household contacts consisted of 213 immediate-family members and 59 extended family members.

Overall, 213 immediate-family contacts and 1412 community contacts participated and provided specimens for testing. Contacts ranged in age from 1 year to 30 years (mean 13·7, median 12·5 years); no participating contact was <12 months old, and 906 were female (56%). Ethnicity was only collected for household contacts; among immediate-family contacts 117 (55%) were of Kazakh ancestry, 90 (42%) were of Slavic ancestry, and six (3%) were of other ethnicities.

Seroprevalence

A total of 738 (45%) of 1625 contacts, including 137 (50%) household and 601 (44%) community contacts, were immune. Age was the most important descriptor of immune status (Fig.). For contacts aged

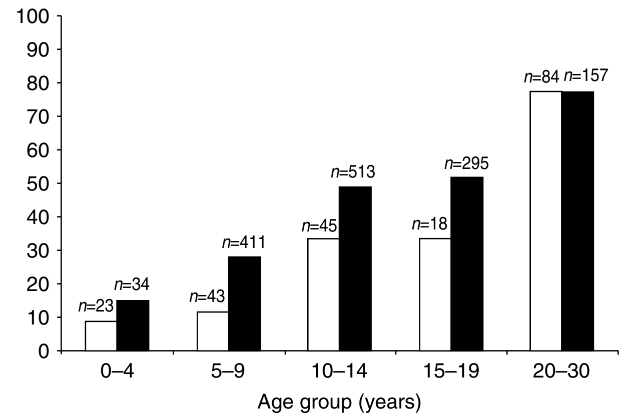

Fig. Age group-specific prevalence of immunity to hepatitis A among immediate-family (□) and community (■) contacts of hepatitis A cases prior to the seasonal outbreak beginning in autumn 2001, Almaty, Kazakhstan.

0–4 years, 5–9 years, 10–14 years, 15–19 years, or 20–30 years, crude immune prevalences were 9, 12, 33, 33 and 77% respectively among immediate-family household contacts and 15, 28, 49, 52 and 77% respectively among community contacts. Among immediate-family contacts aged <20 years, those of Kazakh ethnicity had an immune prevalence of 30% while those of Slavic ethnicity had an immune prevalence of only 11%. For adults aged 20–30 years, the crude immune prevalence was 88% for Kazakh ethnicity and 64% for Slavic ethnicity.

Multivariate analyses confirmed significant differences in immune prevalence by age, but also revealed significant differences in immune prevalence between immediate-family and community contacts. Comparing older children and adolescents to young children aged 0–4 years, the odds ratio of being immune at the start of the outbreak ranged from 2·2 to 6·3 for both immediate-family and community contacts (Table 1). However, comparing adults aged 20–30 years to young children aged 0–4 years, among immediate-family contacts the odds ratio of being immune at the start of the outbreak was 39·6, but among community contacts it was only 18·8. Comparing community contacts to immediate-family contacts, among children and adolescents in all age groups <20 years, the odds ratio of being immune at the start of the outbreak was 2·0. Among adults aged 20–30 years this odds ratio was 1·0.

Also in the multivariate model including all contacts, females did not have an increased probability of being immune from past HAV infection compared to males [odds ratio (OR) 1·1, 95% confidence interval (CI) 1·0–1·2, $P=0{\cdot}110$].

Table 1. *Multivariate logistic regression summary of age-exposure groups associated with immunity to hepatitis A among all contacts of hepatitis A cases prior to the seasonal outbreak beginning in autumn 2001, Almaty, Kazakhstan*

Age group	Exposure group	n	OR	95% CI
20–30 years				
	Community	157	1·0	0·3–2·8
	Immediate family	84	Referent	
All <20 years				
	Community	1253	2·0	1·3–3·2
	Immediate family	129	Referent	
Exposure group	**Age group**	n	**OR**	**95% CI**
Community				
	20–30 years	157	18·8	5·1–69·4
	15–19 years	295	6·3	3·3–11·9
	10–14 years	513	5·8	3·2–10·4
	5–9 years	411	2·2	1·2–4·0
	0–4 years	34	Referent	
Immediate family				
	20–30 years	84	39·6	18·3–85·7
	15–19 years	18	6·3	3·3–11·9
	10–14 years	45	5·8	3·2–10·4
	5–9 years	43	2·2	1·2–4·0
	0–4 years	23	Referent	

OR, Odds ratio; CI, confidence interval.

However, contacts from the Zhetysusky district had a significantly increased probability of being immune to hepatitis A compared to contacts from the Bostandisky district (OR 1·9, 95% CI 1·4–2·7, $P<0·001$).

Results from the multivariate model with only immediate-family contacts suggested that females had an increased probability of past HAV infection (OR 1·9), although not significant ($P=0·110$) (Table 2). This was probably because among immediate-family contacts, females comprised a larger proportion of participants in the 20–30 years group (71%) than in the age groups <20 years (49%) ($P=0·010$). However, ethnicity was found to be significantly associated with immune status. Immediate-family contacts of Kazakh ethnicity had an odds of being immune that was 4·1 times greater ($P<0·001$) than that of persons of Slavic ethnicity, after controlling for age, gender and district of residence. Finally, among immediate-family contacts, being a resident of either Turksibsky or Zhetysusky districts was a determinant of an increased probability of being immune, compared to the Bostandisky district. The odds ratios for contacts from the Turksibsky or Zhetysusky districts compared to contacts from the Bostandisky district were 3·7 and 9·0 respectively, with $P=0·048$ and $P=0·001$ (Table 2). A general association was found between district of residence and ethnicity for immediate-family contacts ($P=0·015$), but the proportion of contacts of Slavic ethnicity was highest in the Turksibsky and Zhetysusky districts at nearly 50% of immediate-family contacts. In the Almalinsky and Bostandisky districts, persons of Slavic ethnicity accounted for only ~30% of immediate-family contacts.

DISCUSSION

The results of this serological study show that hepatitis A endemicity in Almaty is intermediate, since relatively few children <10 years old were immune. Although the majority of adult contacts aged 20–30 years were immune, nearly 25% of these adults remained susceptible. While this study did not measure the immune status of any person older than 30 years, persons aged 20–30 years are often the parents of young children who are typically at highest risk of HAV infection [6, 10, 12, 13]. Because adults are at highest risk of severe disease if they are infected [4], these data indicate the potential for a substantial burden of hepatitis A disease among adults in this population exists. With a large proportion of young children still susceptible, sufficient introduction of HAV into the community could result in such an outbreak.

Supporting the hypothesis that households are important foci of transmission in Almaty, lower immune prevalence was found among child household contacts compared to child community contacts. This finding was a result of how contacts were identified for the study, i.e. through identification of acute cases. Before cases were infected and identified they had been susceptible persons. Thus, under the condition that transmission does, in fact, occur more frequently in households than in the community in Almaty, household child contacts of previously susceptible cases were more likely to have been susceptible than children from the community. Also supporting this view was that many contacts were

https://doi.org/10.1017/S0950268805005194 Published online by Cambridge University Press

Table 2. *Multivariate logistic regression analysis of factors associated with immunity to hepatitis A among only immediate-family contacts of hepatitis A cases prior to the seasonal outbreak beginning in autumn 2001, Almaty, Kazakhstan*

	n (%)	OR	95% CI
Age group (yr)			
30	18 (8·5)	357·1	40·9–3117·9
20–29	66 (31·0)	45·4	8·4–245·0
15–19	18 (8·5)	6·8	0·9–53·4
10–14	45 (21·1)	8·2	1·3–50·6
5–9	43 (20·2)	1·8	0·3–12·0
0–4	23 (10·8)	Referent	
Gender			
Female	123 (57·7)	1·9	0·9–4·0
Male	90 (42·3)	Referent	
Ethnicity			
Kazakh	117 (54·9)	4·1	1·9–8·8
Other	6 (2·8)	3·1	0·4–21·0
Slavic	90 (42·3)	Referent	
District			
Zhetysusky	45 (21·1)	9·0	2·4–33·7
Turksibsky	43 (20·2)	3·7	1·0–13·3
Auezovsky	60 (28·2)	2·2	0·6–8·3
Medeusky	11 (5·2)	2·4	0·4–14·7
Almalinsky	23 (10·8)	3·6	0·6–21·0
Bostandisky	31 (14·6)	Referent	

OR, Odds ratio; CI, confidence interval.

identified as IgM anti-HAV positive at enrolment, both within and outside of households; however, most of these already IgM anti-HAV-positive contacts were immediate-family members within households (data not shown). The importance of household contact as a risk factor for HAV infection has been shown in other countries [4, 13–18]. Although outbreaks have been known to occur in day-care centres [2, 19], school contact has not been shown to impart substantial risk for HAV infection [14, 20]. Therefore, the seroprevalence of sampled school contacts probably more generally reflected that of the whole community.

Although it is possible that a finding of lower immune prevalence among household child and adolescent contacts compared to their school and neighbour counterparts arose because parents in households excluded their child from participation because they believed that the child had had hepatitis A in the past, it is unlikely that this would totally explain the consistent difference across age groups <20 years, for several reasons. First, past hepatitis A disease was not a study exclusionary criterion. Study field staff discussed with parents how, even though their child may have received a past diagnosis of hepatitis A from a physician, only a small percentage of such diagnoses were confirmed by serological tests in the past, and it would be in the best interest of the child to know for sure if he/she was still at risk for disease. Parental interest for their child's participation in the study was high, because hepatitis A is generally viewed as an important childhood disease in Almaty. Finally, if parents excluded their children because of past disease, this probably would have occurred equally for household and school contacts, as parental consent for child participation was sought for all participants.

Among immediate-family households, ethnicity was a predictor of an increased probability of being immune regardless of age. In Kazakhstan, data on ethnicity has not regularly been used to analyse health data, except among immigrants (T. Surdina, personal communication). Ethnicity may be acting as a proxy for socio-economic status, but no other data related to socio-economic status were collected to test this idea. Alternatively, persons of Kazakh ethnicity in the study may be more likely to have recently migrated to Almaty from rural villages or other regions of the country where hepatitis A rates are known to be substantially higher (T. Surdina, personal communication). There was an association between district of residence and ethnicity for immediate-family contacts. However, this association was the opposite of what might have been expected based on the immune prevalence results by ethnicity alone, since immediate contacts from the high-immune-prevalence Turksibsky and Zhetysusky districts were more likely to be of Slavic ancestry. As ethnicity was a consistent predictor in models with or without district (model not shown), it was unlikely that results by ethnicity were confounded by differences in district of residence for different ethnicities.

Hepatitis A endemicity in Almaty appears to be decreasing as the region develops. Yet the city remains surrounded by large rural areas which are poorer and likely have higher endemicity and pose a continual risk for introduction of infection and large outbreaks. Use of hepatitis A vaccine ultimately may be the best way to protect the population and prevent the increasing number of severe cases which will probably result as Almaty undergoes an epidemiological shift in hepatitis A incidence. A number of policy options could be considered, including universal vaccination of young children or vaccination programmes targeted to high-incidence areas or population groups. Consideration of the relative effectiveness and cost effectiveness of these strategies in the context of hepatitis A epidemiology in the area can help inform these policy decisions.

ACKNOWLEDGEMENTS

The authors thank the medical epidemiologists of the Almaty Sanitary Epidemiology Stations for data collection and the virologists and technicians of the Virology Reference Laboratory at the Republic of Kazakhstan Sanitary Epidemiology Station for serological testing. They also thank the staff of the US CDC/Central Asia Region office for logistical support. This project was funded by a CDC/US Association of Schools of Public Health Cooperative Agreement to the University of Michigan.

DECLARATION OF INTEREST

None.

REFERENCES

1. **WHO.** Global distribution of hepatitis A, B and C, 2001. Weekly Epidemiol Rec 2002; **77**: 45.
2. **Hadler SC, Webster HM, Erben JJ, et al.** Hepatitis A in day-care centers: a communitywide assessment. N Engl J Med 1980; **302**: 1222–1227.
3. **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**: 453–457.
4. **Lednar WM, Lemon SM, Kirkpatrick JW, et al.** Frequency of illness associated with epidemic hepatitis A virus infection in adults. Am J Epidemiol 1985; **122**: 226–233.
5. **Hadler SC.** Global impact of hepatitis A infection: changing patterns. In: Hollinger FB, Lemon SM, Margolis HS, eds. Viral hepatitis and liver disease. Baltimore: Williams & Wilkins, 1991; 14–20.
6. **Margolis HS, Alter MJ, Hadler SC.** Viral hepatitis. In: Evans A, Kaslow R, eds. Viral infections of humans, 4th edn. New York: Plenum Publishing Corp, 1997; 363–375.
7. **Hsu HY, Chang MH, Chen DS, et al.** Changing seroepidemiology of hepatitis A virus infection in Taiwan. J Med Virol. 1985; **17**: 297–301.
8. **Kremastinou J, Kalapothaki V, Trichopoulos D.** The changing epidemiologic pattern of hepatitis A infection in urban Greece. Am J Epidemiol 1984; **120**: 703–706.
9. **Stroffolini T, Biagini W, Lorenzoni L, et al.** An outbreak of hepatitis A in young adults in central Italy. Eur J Epidemiol 1990; **6**: 156–159.
10. **Victor JC.** The epidemiology of hepatitis A in Almaty, Kazakhstan: background for a comparative trial of hepatitis A vaccine versus immune globulin for postexposure prophylaxis [Dissertation]. Ann Arbor, Michigan: University of Michigan, 2004.
11. **Liaw YF, Yang CY, Chu CM, et al.** Appearance and persistence of hepatitis A IgM antibody in acute clinical hepatitis A observed in an outbreak. Infection 1986; **14**: 156–158.
12. **Armstrong GL, Bell BP.** Hepatitis A virus infections in the United States: model-based estimates and implications for childhood immunization. Pediatrics 2002; **109**: 839–845.
13. **Staes CJ, Schlenker TL, Risk I, et al.** Sources of infection among persons with acute hepatitis A and no identified risk factors during a sustained community-wide outbreak. Pediatrics 2000; **106** (http://www.pediatrics.org/cgi/content/full/106/4/e54).
14. **Knight V, Drake ME, Belden EA, et al.** Characteristics of spread of infectious hepatitis in schools and households in an epidemic in a rural area. Am J Hyg 1954; **59**: 1–16.
15. **Strom J.** A comparison between family infections during epidemics of poliomyelitis and hepatitis in Stockholm. Acta Med Scand 1949; **165**: 49.
16. **Roumeliotou A, Papachristopoulos A, Alexiou D, et al.** Intrafamilial spread of hepatitis A. Lancet 1992; **339**: 125.
17. **Minuk GY, Ding LX, Hannon C, et al.** The risks of transmission of acute hepatitis A and B virus infection in an urban centre. J Hepatol 1994; **21**: 118–121.
18. **Bell BP, Shapiro CN, Alter MJ, et al.** The diverse patterns of hepatitis A epidemiology in the United States – implications for vaccination strategies. J Infect Dis 1998; **178**: 1579–1584.
19. **Gingrich GA, Hadler SC, Elder HA, et al.** Serologic investigation of an outbreak of hepatitis A in a rural day-care center. Am J Pub Health 1983; **73**: 1190–1193.
20. **Anon.** Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). Morb Mortal Wkly Report. Recommendations and Reports 1999; **48**: 1–37.