Original Contribution

Person-to-Person Transmission of Hepatitis A Virus in an Urban Area of Intermediate Endemicity: Implications for Vaccination Strategies

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Developing countries with an increasing hepatitis A disease burden may target vaccination to specific groups, such as young children, as an initial control strategy. To better understand transmission of hepatitis A virus in such countries, the authors prospectively studied household and day-care/school contacts of cases in Almaty, Kazakhstan. Overall, by the time of identification of symptomatic index cases, half of transmission had already occurred, having been detected retrospectively. The odds of household contacts becoming infected were 35.4 times those for day-care/school contacts (95% confidence interval (CI): 17.5, 71.7). Within households, younger age of either index cases or susceptible contacts elevated the odds of secondary infection among susceptible contacts: The presence of a case under 6 years of age raised the odds 4.7 times (95% CI: 1.2, 18.7); and compared with contacts aged 14 years or older, the odds of infection were increased to 7.7 (95% CI: 1.5, 40.3) and 7.0 (95% CI: 1.4, 34.3) among contacts aged 0–6 years and 7–13 years, respectively. Young children are appropriate targets for sustainable hepatitis A vaccination programs in areas undergoing hepatitis A epidemiologic transition. If vaccine is determined to be highly effective postexposure and if it is feasible, vaccinating household contacts could be a useful additional control strategy.

Communicable disease control; disease transmission; hepatitis A; hepatitis A vaccines; immunization; vaccination

Abbreviations: anti-HAV, antibodies to hepatitis A virus; HAV, hepatitis A virus; IgM, immunoglobulin M; SEA, Sanitary Epidemiology Authority.

The vast majority of the world’s population is still at moderate-to-high risk of hepatitis A virus (HAV) infection (1). As countries around the world develop economically, the prevalence of HAV infection will probably fall, but paradoxically hepatitis A illness will become a greater public health problem. This is because the likelihood and severity of symptomatic illness with HAV infection are age-related (2–4). Under improved sanitation and living conditions, people escape infection in early childhood and are left susceptible in adolescence and adulthood, when risk of severe disease is higher. Because of the close nature of human contact, especially among young children, households and

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day-care centers are two of the settings where transmission is frequently identified (2, 5–7).

Inactivated hepatitis A vaccines are now available in much of the world (8). In many parts of the developed world, such as the United States, programs for preexposure vaccination against hepatitis A target young children (9, 10). This approach is taken because, in the absence of identified point-source outbreaks, unrecognized person-to-person transmission among young children has been shown to contribute substantially to community-wide epidemics (5, 6), and because vaccination of young children has been shown to dramatically reduce disease incidence, not only among vaccinated children but also among older children and adults, probably through a strong herd immunity effect (11, 12). Costs will probably prohibit implementation of universal preexposure vaccination against hepatitis A in most developing countries for the foreseeable future. However, limited vaccination against hepatitis A, especially where the epidemiologic shift is most pronounced, may be introduced first in areas undergoing epidemiologic transition.

Almaty, the largest city in Kazakhstan, has a population of approximately 1.14 million (13) and is rapidly developing. The reported annual incidence rate of hepatitis A in Almaty has varied widely, with substantial epidemics occurring between September and March each year. During those periods, incidence of disease is high, regularly peaking in children aged 5–9 years, with a substantial number of adult cases also being reported (Kazakhstan Ministry of Health, unpublished data). However, the true burden has remained unknown, since relatively few cases have been confirmed by serologic testing. In Almaty, clusters of hepatitis A cases are often identified in households, day-care centers, and schools, but the frequency of transmission in these groups is unknown because of a lack of resources for serologic testing and epidemiologic studies. In order to understand the frequency and nature of transmission in areas undergoing transition, we conducted a prospective study of HAV transmission among household and day-care/school contacts in Almaty. The findings broaden and strengthen our view that unrecognized person-to-person transmission among young children plays a primary role in sustaining hepatitis A epidemics, even in developing areas of intermediate endemicity.

MATERIALS AND METHODS

Identification of hepatitis A cases

To identify cases and settings in which to study person-to-person transmission, we implemented laboratory-based surveillance in cooperation with the Almaty Sanitary Epidemiology Authority (SEA) and the Virology Reference Laboratory of Kazakhstan (Almaty, Kazakhstan). On September 25, 2001, a public health directive was issued, requiring serologic confirmation of all suspected acute clinical cases of hepatitis A. No case definition was specified for submission of specimens; physicians were requested to use their best clinical judgment in submitting specimens for testing. All testing was conducted free of charge at the Virology Reference Laboratory between October 1, 2001, and February 28, 2002, during the typical period of high incidence of hepatitis A.

Transmission study population

Index cases. A patient was considered an index case if he/she had had the first reported and confirmed hepatitis A illness in either a household or a day-care center/school classroom during the previous 60 days. This definition did not exclude enrollment of index cases in other classrooms in the same school at a later time. Contacts of index cases were then identified for enrollment in the prospective transmission study.

Contacts. Household and day-care/school classroom contacts were entered into the prospective transmission study sequentially as index cases were identified. Only households and classrooms identified within 14 days after illness onset in the index case were considered for enrollment. Household contacts were defined as persons who had resided with the case during the 2-week period prior to case illness onset. Day-care/school contacts were defined as any child or teacher who was regularly present in the index case’s day-care/school classroom during this same period. Participation was limited to persons aged 30 years or younger, because relatively few reported cases of hepatitis A occur among older persons in Almaty.

Transmission study design

Contacts were enrolled and interviewed by SEA epidemiologists. Biographic information and information on the occurrence of hepatitis A-like symptoms during the previous 2 months was recorded on a standard questionnaire. After providing enrollment blood specimens for serologic testing, contacts found to be susceptible were followed prospectively for 8 weeks postexposure (starting from the day of symptom onset in the index case). Household contacts were followed using weekly telephone calls or visits to inquire about the occurrence of symptoms among household contacts during the previous 7 days. For day-care/school contacts, a SEA epidemiologist visited the school weekly and consulted with the school physician, who was already mandated to follow up student contacts of hepatitis A cases. Finally, on day 56 (week 8) postexposure, SEA epidemiologists interviewed all followed contacts regarding symptoms and requested a second blood specimen to test for serologic evidence of infection. Because 2 months of follow-up for contacts was to be completed by the end of the laboratory testing period, only contacts of index cases whose illnesses were ascertained between October 1, 2001, and December 31, 2001, were enrolled in the transmission study. 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 participants, written informed consent was obtained from each subject or his/her parent or guardian.

Laboratory assays

Blood serum specimens were analyzed for the presence of immunoglobulin M (IgM) and total antibodies to HAV
TABLE 1. Age-group-specific frequencies and incidence rates of reported hepatitis A virus (HAV) infection and estimated age-group-specific HAV infection rates, Almaty, Kazakhstan, October 2001–February 2002

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Reported cases</th>
<th>Incidence rate*</th>
<th>Estimated infection rate †</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>756</td>
<td>100</td>
<td>161</td>
</tr>
<tr>
<td>0–4</td>
<td>126</td>
<td>17</td>
<td>489</td>
</tr>
<tr>
<td>5–9</td>
<td>222</td>
<td>29</td>
<td>724</td>
</tr>
<tr>
<td>10–14</td>
<td>150</td>
<td>20</td>
<td>390</td>
</tr>
<tr>
<td>15–19</td>
<td>85</td>
<td>11</td>
<td>212</td>
</tr>
<tr>
<td>20–29</td>
<td>108</td>
<td>14</td>
<td>124</td>
</tr>
<tr>
<td>≥30</td>
<td>64</td>
<td>8</td>
<td>26</td>
</tr>
</tbody>
</table>

* Annualized, per 100,000 persons; based on the 2000 Almaty Population Census. † Annualized, per 100,000 susceptible persons. ‡ Insufficient data to estimate incidence rate.

(anti-HAV) using standard assays (ETI-HA-IGMK PLUS and ETI-AB-HAVK PLUS; DiaSorin, Inc., Stillwater, Minnesota) at the Virology Reference Laboratory.

Statistical analyses

Age-group-specific population infection rates were estimated by dividing annualized age-group-specific surveillance case rates by 1 minus the corresponding seroprevalence estimates for the Almaty population (14), dividing the result by age-group midpoint estimates for the probability of jaundice given infection (15), and finally multiplying this result by the age-group-specific proportion of reported cases with jaundice in Almaty. Factors associated with IgM anti-HAV seropositivity among contacts 8 weeks postexposure were analyzed by backward elimination in multivariate logistic regression models that accounted for correlation between contacts within exposure groups. Analyses were carried out using SAS, version 9.1 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Cases identified and enrolled in prospective study

During the surveillance period, 756 specimens tested positive for IgM anti-HAV, for an annualized incidence rate of 161 cases per 100,000 persons. The age distribution of hepatitis A cases displayed a pattern typical for a region of intermediate endemicity: Incidence of reported cases peaked in the age group 5–9 years at an annualized rate of 2,303 cases per 100,000 persons. The age distribution of hepatitis A cases ranged in size from one room to eight rooms (mean = 3.1 rooms; median, three rooms), and the total number of persons living in a household ranged from two to 12 (mean = 5.2 persons; median, five persons).

Investigation of household contacts

Sero status of household contacts at enrollment. Of 341 eligible contacts in 118 households, 272 agreed to participate (80 percent). Household contacts were enrolled 1–23 days after illness onset in the index case (median, 11 days). Thirty-four household contacts were IgM anti-HAV-positive at enrollment (13 percent), indicating recent infection with HAV; 101 were total anti-HAV-negative (37 percent), indicating that they were still susceptible; and 136 were IgM anti-HAV-negative and total anti-HAV-positive (50 percent), indicating that they were immune from past exposure.

The highest proportion of IgM anti-HAV-positive household contacts at enrollment was among children under 7 years of age (the ages prior to regular school entry in Kazakhstan) (33 percent), followed by children aged 7–13 years (27 percent) (figure 1). Fifteen percent of those aged 14 years or older were IgM anti-HAV-positive. Five of the 34 IgM anti-HAV-positive contacts (15 percent) reported having had hepatitis A-like symptoms within the 2 months prior to enrollment, but none had undergone serologic testing at the time of illness or had been reported as cases of hepatitis A.

Secondary transmission within households. Only the 101 seronegative contacts were followed 8 weeks postexposure, and of these, 95 contacts from 63 households had complete follow-up data. Week 8 blood specimens were collected 56–109 days postexposure (median, 57 days). Twenty-six contacts from 22 households became IgM anti-HAV-positive (27 percent), including 42 percent of those aged 0–6 years, 32 percent of those aged 7–13 years, and 10 percent of those aged 14 years or older (figure 1). Twenty-four of these contacts (92 percent) had an episode of symptomatic illness. One contact (4 percent) became ill within 14 days of illness in the index case; among the other 23 IgM

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anti-HAV-seropositive household contacts, illness occurred 17–51 days postexposure (mean = 29.7 days; median, 28 days). Of the 24 household contacts with symptoms, 16 had icteric illness (jaundice, dark urine, and/or pale stool) (67 percent); among the remaining eight persons with nonicteric symptomatic infections, three had gastrointestinal symptoms of abdominal pain, nausea, and/or vomiting (38 percent), eight had constitutional symptoms of fever and/or malaise (100 percent), and five had loss of appetite (63 percent). Six of 11 persons aged 1–7 years (55 percent), five of 11 persons aged 8–18 years (46 percent), and two of two persons aged 19 years or older (100 percent) had icteric illness.

Age was the only demographic variable that was significantly predictive of infection postexposure among household contacts. In multivariate logistic regression analyses, the odds ratios for becoming infected for persons aged 0–6 years or 7–13 years versus those aged 14 years or older were nearly equal at 7.7 and 7.0, respectively (table 2). Other variables identified as significant predictors of infection postexposure in multivariate logistic regression analyses were “being the contact of an index case less than 6 years of age” and “the presence of other IgM anti-HAV-positive contacts at the time of study enrollment” (coprevalent with index case) (table 2). No other variables, such as gender, ethnicity, district of residence, number or density of persons in the household, or number of rooms in the household, were associated with infection postexposure.

Investigation of day-care/school contacts

Serologic status of school contacts at enrollment. Of 1,955 day-care/school contacts in 81 classrooms, 1,335

agreed to participate (68 percent). School contacts were enrolled 0–17 days postexposure (median, 11 days). Ten school contacts (1 percent) were IgM anti-HAV-positive at enrollment, 730 were total anti-HAV-negative (55 percent), and 584 were IgM anti-HAV-negative and total anti-HAV-positive (44 percent). Eleven school contacts had indeterminate results or blood specimens deemed of insufficient quality for serologic testing. Overall, the 740 contacts who were recently infected or susceptible at enrollment were from 79 classrooms, and the 10 recently infected contacts (1 percent) were from eight of these classrooms (10 percent). None of the 10 IgM anti-HAV-positive contacts reported having had hepatitis A-like symptoms within the 2 months prior to enrollment. The highest proportion of IgM anti-HAV-positive school contacts at enrollment was among children under 7 years of age (4 percent) (figure 1). One percent of children aged 7–13 years were IgM anti-HAV-positive, and 1 percent of those aged 14 years or older were IgM anti-HAV-positive.

Secondary transmission within classrooms. Follow-up data obtained 8 weeks postexposure were available for 711 contacts from 79 classrooms. Week 8 blood specimens were collected from school participants 54–126 days postexposure (median, 57 days). Ten contacts from eight classrooms became IgM anti-HAV-positive (1 percent). Only three of these 10 school contacts reported symptoms. No contact aged 14 years or older became IgM anti-HAV-positive, and only a small proportion of children under age 14 years had serologic evidence of infection (4 percent of those aged 0–6 years and 1 percent of those aged 7–13 years) (figure 1). In contrast to the finding for households, neither “being a school contact of an index case less than 6 years of age”
nor “the presence of other IgM anti-HAV-positive contacts in the classroom at study enrollment” was a significant predictor of infection in school contacts followed 8 weeks postexposure (results from multivariate model not shown).

Comparison of exposure groups

Overall, there was evidence of transmission in 45 of 84 (54 percent) households with susceptible contacts, while transmission occurred in 14 of 79 (18 percent) school classrooms. For persons within these exposure groups, the odds of household contacts’ having been or becoming infected (IgM anti-HAV-positive) were 35.4 times those for school contacts (95 percent confidence interval: 17.5, 71.7; \( \chi^2 \) test: \( p < 0.001 \)).

**DISCUSSION**

Because of the rapidity with which hepatitis A outbreaks have developed in Almaty, many local officials have speculated that common sources, such as contaminated food or water, are solely to blame. However, estimates of infection rates among susceptible persons indicated that young children supported a disproportionately large burden of infection, a result not consistent with the general population’s being exposed to a common source of infection. Additionally, households were identified as intense foci of transmission, with age being identified as the strongest predictor of infection and transmission. These findings support the hypothesis that transmission of HAV in Almaty is driven substantially by interactions between young children, at least once virus is introduced into the community.

This study also demonstrated the relative importance of household contact as a risk factor for transmission, as compared with the preschool/school classroom, in an area undergoing an epidemiologic shift. Classroom attack rates were quite low, even among children under 7 years of age in day care or preschool, supporting previous findings that schools do not play a substantial role in sustaining transmission and probably only reflect transmission in the community (10). Households provide the close contact required for person-to-person transmission, and households with young children, in particular, have been shown to be important foci of infection in many parts of the world (5, 14, 16–24).

In a recent study from Salt Lake County, Utah, the presence of young children in the household was associated with increased risk of household transmission of HAV (5). However, because of the cross-sectional nature of that study, the authors acknowledged that, in many circumstances, they were unable to determine who transmitted the virus to whom. In the current study, with prospective follow-up, we were able to determine that the risk of transmission was increased among susceptible contacts living with an index case under 6 years of age as compared with an index case who was older. This was true even after controlling for the susceptible contact’s age. This demonstrates that the risk of transmission between an infected person and a susceptible person is elevated independently when either person in the transmission pair is a young child.

As is illustrated in figure 1, only about half of total household transmission occurred during follow-up, with the other half of susceptible persons having been infected sometime within the 3 months prior to index case identification; rates of IgM anti-HAV positivity were 25 percent at enrollment and 27 percent after 8 weeks postexposure. Most recent infections were asymptomatic, or at least not severe enough to be recognized; thus, no control measures would have been triggered at the time of their occurrence. Analyses indicated that transmission subsequent to the index case was highly dependent on the presence of these recent or coprevalent infections in the household at the time of index case identification. We could not determine whether we found

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of contacts</th>
<th>%</th>
<th>Odds ratio estimate</th>
<th>95% confidence interval</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–6</td>
<td>26</td>
<td>27.4</td>
<td>7.7</td>
<td>1.5, 40.3</td>
<td>0.016</td>
</tr>
<tr>
<td>7–13</td>
<td>38</td>
<td>40.0</td>
<td>7.0</td>
<td>1.4, 34.3</td>
<td>0.016</td>
</tr>
<tr>
<td>14–30</td>
<td>31</td>
<td>32.6</td>
<td>1.0*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Index case &lt;6 years of age?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9</td>
<td>9.5</td>
<td>4.7</td>
<td>1.2, 18.7</td>
<td>0.028</td>
</tr>
<tr>
<td>No</td>
<td>86</td>
<td>90.5</td>
<td>1.0*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At enrollment, had coprevalent contacts with immunoglobulin M antibodies to hepatitis A virus?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8</td>
<td>8.4</td>
<td>17.9</td>
<td>3.1, 102.9</td>
<td>0.001</td>
</tr>
<tr>
<td>No</td>
<td>87</td>
<td>91.6</td>
<td>1.0*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Referent.
this because there were more infectious persons to effectively increase the transmission probability (by increasing the number of opportunities for a susceptible contact to become infected) or because the presence of coprevalent seropositive contacts was related to other risk factors (such as poorer household hygiene or a common infection source for all household members). We also could not determine when those contacts who were IgM anti-HAV-positive and coprevalent with the index case had been infected or had become infectious, nor could we determine whether they had contributed to secondary transmission among susceptible contacts observed during follow-up. Although many identified households had coprevalent cases, secondary transmission in these households did not appear to have been complicated by the presence of these cases, because secondary case timing occurred within the expected incubation period. Among household contacts, postexposure prophylaxis would probably have been successful in preventing these cases.

Although the strength of this study was that it was prospective, it was limited in several other ways. First, lack of a specific case definition for laboratory surveillance might have affected calculation of disease incidence if physicians believed that most adults are immune to hepatitis A, resulting in underascertainment of adult cases. However, nonicteric cases were reported among adults, and infection rate estimation methods attempted to account for at least some of this underreporting. Second, only a relatively small number of enrolled household contacts turned out to be susceptible. Although attack rates were high, only 26 infections were detected; thus, estimates may have been less precise. Although participation among children under 2 years of age was low, this was often because mothers were more hesitant to subject small children to needle sticks, and it probably did not affect the validity of the results among young children. Third, it has been suggested that play contacts are more important than school contacts (25), but no play contacts from either classrooms or neighborhoods were specifically identified and enrolled. Fourth, contacts were not asked about other potential HAV exposures and vigorous investigation of chains of transmission was not undertaken, because the focus of the study was primarily identifying the locations of the highest rates of secondary transmission. However, index cases were asked about potential sources of infection, and contacts were not enrolled if the index case was able to identify a source of infection in that contact group. Fifth, the study began some time after the beginning of the autumn outbreak. Because incidence had peaked in the first month of the study, it was more difficult to interpret the presence of coprevalent IgM anti-HAV-positive persons among household contacts.

Although the explosive nature of hepatitis A outbreaks in the rapidly developing city of Almaty might suggest a common source introduction, the primary mode of transmission is probably person-to-person. As such, young children especially play a pivotal role in the dynamics of transmission. Because of their importance, vaccination targeted to these children would probably provide strong herd immunity and have a major impact in reducing hepatitis A incidence within the population. Since universal vaccination may not yet be practical in most populations undergoing transition, targeted prophylaxis, if shown to be feasible, may offer an alternative strategy for control of hepatitis A in regions where the disease burden is high.

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Conflict of interest: none declared.

REFERENCES


