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Pediatrics 2010;126;e1039; originally published online October 11, 2010;
DOI: 10.1542/peds.2010-0120

Hepatitis A in Internationally Adopted Children: Screening for Acute and Previous Infections

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KEY WORDS
hepatitis A, screening, international, adoption, immunization

ABBREVIATIONS
HAV—hepatitis A virus
IgM—immunoglobulin M
OR—odds ratio
CI—confidence interval

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www.pediatrics.org/cgi/doi/10.1542/peds.2010-0120

doi:10.1542/peds.2010-0120

Accepted for publication Jul 22, 2010

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: *The authors have indicated they have no financial relationships relevant to this article to disclose.*

WHAT'S KNOWN ON THIS SUBJECT: Transmission of hepatitis A virus infection to family members and close contacts of internationally adopted children has been reported. The birth countries of internationally adopted children have endemic HAV; however, the prevalence rates of infection and immunity are not known.

WHAT THIS STUDY ADDS: HAV immunity prevalence was 29%, increased with age, and varied according to birth country. Acute HAV infection prevalence was 1%. Screening children for HAV may be useful for infection prevention and immunization decisions.

abstract

OBJECTIVE: The goal was to determine the prevalence of acute hepatitis A virus (HAV) infection and immunity among internationally adopted children.

METHODS: Children seen at the International Adoption Center between September 25, 2006, and September 30, 2008, and were screened for HAV within 4 months after their arrival in the United States were eligible for the study. The age- and country-specific prevalence of acute HAV infection and immunity were determined.

RESULTS: Overall, 288 children underwent HAV serological testing. Of the 279 with total HAV serological results, 29% had positive findings. Immunity varied according to region and country. The prevalence was lowest among children born in Asia/Pacific Rim region (17%) and highest among children born in Africa (72%). Only 13% of children <2 years of age were immune, compared with 80% of children 12 to 17 years of age ($P = .002$). Increasing age and birth region were associated independently with immunity. Positive HAV immunoglobulin M test results were found for 3 (1%) of 270 children; all were without symptoms. Their ages were 18, 27, and 41 months, and they were born in Kazakhstan, Russia, and the Latin America/Caribbean region, respectively. The father of 1 child developed HAV infection after arriving home.

CONCLUSIONS: HAV immunity among internationally adopted children varied according to age and country of origin; 1% had acute infections. HAV screening is useful for determination of the need for HAV immunization and for prevention of transmission to family members and close contacts. *Pediatrics* 2010;126:e1039–e1044

Nearly 200 000 children, emigrating from >20 countries, were adopted internationally in the United States from 2000–2009.[1] The American Academy of Pediatrics recommends that all internationally adopted children be examined shortly after arrival with a comprehensive evaluation, including screening for infectious diseases and assessment of immunization status.[2] Although screening for acute hepatitis A virus (HAV) infection is not recommended, testing for immunity to HAV may be considered for children from HAV-endemic countries, to determine the need for HAV immunization.[2]

Most internationally adopted children come from HAV-endemic countries,[3] are young, and may have unrecognized infections with prolonged shedding,[4,5] which places their new families and other close contacts at risk for acquiring HAV infection. Although we know that transmission from internationally adopted children occurs,[6–9] information regarding the prevalence of acute HAV infection and immunity among internationally adopted children is lacking. To contribute data for evidence-based guidelines for HAV screening, we determined the prevalence of acute HAV infection and immunity in a large group of internationally adopted children.

METHODS

Children who were evaluated at the International Adoption Center at Cincinnati Children's Hospital Medical Center between September 25, 2006, and September 30, 2008, with HAV serological testing performed within 4 months after arrival in the United States, were eligible for the study. Data on age at adoption, gender, institutionalization (institutionalized for ≥6 months), and country of origin were abstracted from patient records. For country-specific analyses, if there were ≤10 children from a given country, the countries were grouped into 4 regions, that is, Africa (Ethiopia, Liberia, and Uganda), Asia and the Pacific Rim region (China, India, Kazakhstan, South Korea, Philippines, Taiwan, Thailand, and Vietnam), Eastern Europe (Latvia, Lithuania, Poland, Russia, Serbia, and Ukraine), and Latin America and the Caribbean region (Colombia, Dominican Republic, Guatemala, Haiti, and Honduras). Serological testing for total and immunoglobulin M (IgM) HAV-specific antibody levels was performed to detect immunity and current infection. Children with test results from any laboratory were included in the study; however, most children had total (96%) and IgM (93%) HAV-specific antibody testing performed at the Associated Regional and University Pathologists Laboratory (Salt Lake City, UT), with enzyme immunoassays manufactured by DiaSorin (Saluggio, Italy).

Univariate analyses were performed and differences of proportions were tested by using χ^2 tests; P values of .05 were considered statistically significant. The Cochran-Armitage test was used to assess trends. Multivariate analyses were performed by using multivariate logistic regression to determine whether gender, age, institutionalization, and region were associated independently with HAV immunity. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. The Cincinnati Children's Hospital Medical Center institutional review board approved the study.

RESULTS

Overall, HAV serological testing was completed for 288 children. These children came from 22 countries, and 70% emigrated from just 3 countries, namely, China, Guatemala, and Russia (Table 1). Most children (85%) were ≥1 year of age, and 56% were female. Children from China were significantly more likely to be female, compared with children from other individual countries, and children from Guatemala were significantly more likely to be younger, compared with children from all areas except Ethiopia and other Asian/Pacific Rim countries. The majority of children (70%) had been institutionalized; however, children from Guatemala were significantly less likely to have been institutionalized, compared with children from other countries ($P < .0001$). The timing of the antibody screening ranged from <1 week to 17 weeks after arrival respectively. More than one-half (52%) of the children were screened within 2 weeks after arrival in the United States, 79% within 4 weeks, and 93% within 8 weeks.

Nearly all children (91%) underwent complete HAV serological testing. Of the 27 children with incomplete testing, 18 had only total HAV-specific antibody testing performed and 9 had only HAV IgM testing performed. Of the 279 children with total HAV-specific antibody serological test results, 29% had positive findings (Table 2). In the univariate analyses, the proportion of children with HAV immunity varied according to birth region and country. Only 9% of Chinese children were immune, compared with 67% of Ethiopian children. Similarly, the proportion of children from the Asia/Pacific Rim region with HAV immunity was 17%, whereas 72% of African children were immune. The proportion of children with HAV immunity increased with age; 13% of children <2 years of age were immune, compared with 80% of children ≥12 years of age ($P < .0001$). Children <12 months, 12 to 17 months, and 18 to 23 months of age had similar rates of immunity (15%, 11%, and 16%, respectively). The age-specific prevalence also varied according to country. Among children ≥2 years of age, Chinese and Russian children were less

TABLE 1 Demographic Characteristics of Study Population According to Birth Region and Country

	Total, *n* (%)	Female, *n* (%)	Age, Median (Range), mo	Institutionalized, *n* (%)
Regions				
Africa	29 (10)	14 (48)[a]	44 (5–184)[b]	19 (66)
Asia/Pacific Rim	112 (39)	77 (69)	19 (5–127)	79 (71)
Eastern Europe	78 (27)	33 (42)[c]	23 (12–189)[d]	78 (100)
Latin American/Caribbean	69 (24)	36 (52)[a]	14 (6–141)	25 (36)
Countries				
Africa				
Ethiopia	24 (8)	11 (46)[e]	41 (5–163)	16 (67)
Other African countries	5 (2)	3 (60)	123 (42–184)[f]	3 (60)
Asia/Pacific Rim				
China	80 (28)	64 (80)	18 (9–102)[f]	57 (71)
Kazakhstan	12 (4)	5 (42)[e]	34 (18–100)[f]	12 (100)
Other Asian/Pacific Rim countries	20 (7)	8 (40)[g]	20 (5–127)	10 (50)
Eastern Europe				
Russia	63 (22)	25 (40)[h]	20 (12–115)[i]	63 (100)
Other Eastern European countries	15 (5)	8 (53)[j]	92 (18–189)[k]	15 (100)
Latin American/Caribbean				
Guatemala	60 (21)	31 (52)[g]	13 (6–141)	18 (30)
Other Latin American countries	9 (3)	5 (56)	79 (41–141)[k]	7 (78)
Total	288 (100)	160 (56)[g]	21 (5–189)[k]	201 (70)

[a] Gender with Asia as reference, $P < .05$.
[b] Age with Latin American/Caribbean as reference, $P < .05$.
[c] Gender with Asia as reference, $P < .001$.
[d] Age with Latin American/Caribbean as reference, $P < .01$.
[e] Gender with China as reference, $P < .01$.
[f] Age with Guatemala as reference, $P < .01$.
[g] Gender with China as reference, $P < .001$.
[h] Gender with China as reference, $P < .0001$.
[i] Age with Guatemala as reference, $P < .001$.
[j] Gender with China as reference, $P \leq .05$.
[k] Age with Guatemala as reference, $P < .0001$.

TABLE 2 Proportions of Children With HAV Immunity According to Age, Birth Region, and Country

	Children With HAV Immunity, *n* (%)				
	<2 y	2–5 y	6–11 y	12–17 y	Overall
Regions					
Africa[a]	9 (22)	10 (90)	7 (100)	3 (100)	29 (72)
Asia/Pacific Rim[b]	70 (10)	29 (24)	11 (45)	0 (0)	110 (17)
Eastern Europe	40 (13)	26 (35)	5 (20)	2 (50)	73 (22)
Latin American/Caribbean[c]	45 (18)	9 (78)	13 (85)	0 (0)	67 (39)
Countries					
Africa					
Ethiopia[b]	9 (22)	9 (89)	5 (100)	1 (100)	24 (67)
Other African countries	0 (0)	1 (100)	2 (100)	2 (100)	5 (100)
Asia/Pacific Rim					
China	56 (9)	21 (10)	2 (0)	0 (0)	79 (9)
Kazakhstan	4 (25)	6 (67)	2 (50)	0 (0)	12 (50)
Other Asian/Pacific Rim countries	10 (10)	2 (50)	7 (57)	0 (0)	19 (32)
Eastern Europe					
Russia	40 (13)	19 (32)	2 (0)	0 (0)	61 (18)
Other Eastern European countries	0 (0)	7 (43)	3 (33)	2 (50)	12 (42)
Latin American/Caribbean					
Guatemala[c]	45 (18)	7 (71)	7 (86)	0 (0)	59 (32)
Other Latin American countries	0 (0)	2 (100)	6 (83)	0 (0)	8 (88)
Total[c]	164 (13)	74 (43)	36 (67)	5 (80)	279 (29)

[a] Trend for increasing HAV immunity with age, $P < .001$.
[b] Trend for increasing HAV immunity with age, $P < .01$.
[c] Trend for increasing HAV immunity with age, $P < .0001$.

likely to be immune (9% and 29%, respectively), compared with children from Guatemala and Ethiopia (79% and 93%, respectively), where the prevalence was highest. When findings were examined according to region, children from Africa had the highest prevalence, compared with other regions. In the multivariate analysis, increasing age and region were independently associated with HAV immunity. For each increased year of age, there was a 33% increase in the odds of immunity (OR: 1.33 [95% CI: 1.19–1.48]; $P < .0001$). With Asia as the reference group, children from Africa were 11.21 (OR) times (95% CI: 3.93–32.01 times) more likely to be immune ($P < .0001$), whereas children from Latin America and the Caribbean region were 4.16 (OR) times (95% CI: 1.81–9.57 times) more likely to be immune ($P < .001$). There was no significant difference in immunity between children from Eastern Europe and those from Asia (OR: 0.98 [95% CI: 0.44–2.22]; $P = .97$). Although children who had been institutionalized were more likely to exhibit HAV immunity, compared with children who had not been institutionalized, this result was not statistically significant (OR: 2.19 [95% CI: 1.00–4.81]; $P = .05$).

Acute infection was assessed for 270 children. Three children (1%) had IgM antibody to HAV. These children were 18, 27, and 41 months of age, were born in Kazakhstan, Russia, and Latin American/Caribbean region, and had testing performed 7, 16, and 24 days after arrival in the United States, respectively. All 3 children were without symptoms; their families were notified of the results, and all members of 2 of the families had received HAV vaccine before travel. A report of the second family's experience is described below.

CASE STUDY

A 27-month-old girl was evaluated at the International Adoption Center 13

days after arriving in the United States (day 13) from Russia with her twin sister and adoptive parents. Her parents had no medical concerns and reported her to have a good appetite, normal activity, and no fever or gastrointestinal symptoms. Her physical examination results were normal, without hepatosplenomegaly or icterus. Her immunization record from Russia was current for diphtheria-tetanus toxoids-pertussis virus, polio virus, hepatitis B virus, measles, mumps, and rubella. There was no documentation of previous HAV infection or immunization. On day 17, the child's HAV serological test results revealed reactive IgM and total HAV-specific antibodies; on day 20, those results were reported to the health department. Because the child had no symptoms, the case definition for acute HAV was not met and a contact investigation was not initiated. The child's father developed fever, chills, and malaise on day 39 and later developed jaundice. Twelve days later, HAV serological testing was performed for the father, which yielded positive results for both total and IgM HAV-specific antibodies. A contact investigation was initiated. The child's twin sister had no history of HAV infection or immunity in her Russian records, and the results of HAV serological testing at her initial evaluation were negative. Although both parents were aware of the recommendation for HAV immunization before travel to Russia, they did not think they were at high risk and therefore were not immunized. The child's mother, sister, and grandparents, who did not have symptoms, were given immunoglobulin and HAV vaccine by the health department. None of them subsequently developed symptoms. The father did not return to his normally good state of health for 2.5 months.

DISCUSSION

HAV infection is a common infection throughout the world, with a high prevalence in resource-poor countries. We found a high prevalence of HAV in our patient population, even among young children. Although we did not find other studies describing the prevalence of HAV in internationally adopted children, we did find that our prevalence was consistent with the overall risk reported for the birth countries of such children.[3]

The American Academy of Pediatrics states that clinicians should consider screening children whose childhood was spent in a country with high endemicity, to determine their need for the HAV vaccine.[2,4,5] With the high levels of immunity in our study, we found testing to be a useful tool for determining which children needed to be immunized. Several studies showed screening to be cost-effective when the expected prevalence was high.[10–14] The study populations in those studies included travelers,[10–11] health care workers,[12] and general populations.[13,14] In the study performed in Bangladesh, which was more comparable to our study, the authors found that the cost of vaccination with screening was 3 times less than the cost of vaccination without screening, and they suggested that a policy of vaccination against HAV on the basis of screening before vaccination was cost-effective, safe, and more rational.[14]

According to the recommendations of the American Academy of Pediatrics, children ≥12 months of age with positive total HAV-specific antibody results should be considered immune and do not need HAV vaccine. For children 12 to 23 months of age with negative total HAV-specific antibody results, HAV vaccine should be given; for nonimmune children ≥24 months of age, vaccine should be given if the children live in areas that are at high risk for HAV.[5]

In our study, 1% of children had positive HAV IgM test results, which likely represented acute HAV infections. Although false-positive results for HAV serological tests have been described,[15,16] those findings were noted for adults who did not have a history of risk factors for acquiring HAV. To our knowledge, false-positive results have not been described for young, internationally adopted children from HAV-endemic countries. Because our case did not meet the Centers for Disease Control and Prevention definition of an acute HAV infection (positive serological test results and clinical hepatitis),[17] a contact investigation was not initiated. The child's parent subsequently became infected. Although the father might have acquired HAV through exposure in Russia, it is more likely that he acquired HAV from his daughter, because the child had evidence of a recently acquired infection, came from an intermediate- to high-risk country for HAV, and was in a high-risk setting for acquisition (orphanage), and the father had close contact, with daily care of the child. In addition, the interval from US arrival to first symptoms was 39 days, which is at the far end of the range of the incubation period (15–50 days) for exposure in Russia.[4,5] In addition, it is unlikely that the father acquired HAV from other sources in the United States, because the father's case was not epidemiologically linked to other cases in his county of residence (V.A. Brendemuehl, BSN, oral, personal communication, 2009).

The Centers for Disease Control and Prevention recommends limiting HAV testing to individuals with clinical findings typical of HAV or persons with recent exposure to settings where HAV transmission is suspected.[17,18] Internationally adopted children residing in orphanages in disease-endemic countries meet these criteria, because they have been exposed recently to settings where there is increased risk for HAV

transmission. Screening of children shortly after arrival in the United States provides an opportunity to identify children with acute HAV infection, so that secondary prophylaxis can be provided to close contacts. In the case we describe, HAV infection might have been prevented if the IgM test results had been considered true-positive results and if the case definition included positive IgM test results for children without symptoms from disease-endemic countries. We found that screening internationally adopted children for acute HAV infection provides an opportunity to identify children with positive HAV IgM results, so that the immunization status of family members and other close contacts can be assessed. If the child has positive HAV IgM results, then family members without a history of HAV immunization can be vaccinated. Most families would have been with their children for 2 to 4 weeks before arrival in the United States. However, a small proportion of children with acute HAV infections might have had less time with their families in country and might have been infected shortly before arrival in the United States. Such children might be missed with IgM testing performed shortly after arrival in the United States if they are in the incubation period, when IgM testing does not yet yield positive results.[4,5,7] Conversely, the longer children are in the United States, the less likely it is that testing performed several months after arrival would identify children infected acutely in their birth countries, although HAV excretion in the stool may continue for as long as 5 to 6 months.[4,5,19] With high transmission rates of 20%[20] and prolonged shedding of the virus, pretravel immunization and immunization of other family members who are not traveling is critically important.

Although we agree with the new recommendation of the Centers for Disease Control and Prevention for immunizing traveling and nontraveling close contacts of internationally adopted children before the children join the family,[18] we cannot be assured that all families will be aware of this recommendation. Increased efforts should be made to educate adoption agencies and professionals, as well as adoptive families, regarding this new recommendation.

CONCLUSIONS

On the basis of the experience of our first 2 years of HAV screening, our current practice to screen all internationally adopted children for acute and previous HAV infections will continue. HAV screening provided useful information for assessing the need for HAV immunization and has the potential to identify acute infections. Given the high HAV prevalence among internationally adopted children in most countries, especially among those >2 years of age, screening is likely to be cost-effective for internationally adopted children. Policymakers should revisit guidelines for the screening of internationally adopted children, to determine the best approach for screening in the changing environment of international adoption and HAV epidemiological features. In addition, as HAV vaccine becomes adopted abroad, the prevalence of HAV will need to be monitored over time, to revisit HAV screening practices for international adoptees in the future.[3]

ACKNOWLEDGMENTS

We thank the Columbus Department of Health for assistance and for care of the case subject's family. We are indebted to all of the wonderful children and their families who participated in this study and who, through this work, will help to improve the health of internationally adopted children and their families in the future.

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