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Hepatitis A Vaccine versus Immune Globulin for Postexposure Prophylaxis

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ABSTRACT

BACKGROUND

Hepatitis A vaccine administered to persons after exposure to the hepatitis A virus has not been compared directly with immune globulin, which is known to be highly effective in preventing hepatitis A when given within 2 weeks after exposure to the virus.

METHODS

We randomly assigned household and day-care contacts, 2 to 40 years of age, in Almaty, Kazakhstan, to receive one standard age-appropriate dose of hepatitis A vaccine or immune globulin within 14 days after exposure to patients with hepatitis A. Instances of laboratory-confirmed, symptomatic hepatitis A infection occurring between 15 and 56 days after exposure were then assessed during active follow-up of all susceptible contacts.

RESULTS

Of 4524 contacts who underwent randomization, 1414 (31%) were susceptible to hepatitis A virus and 1090 were eligible for the per-protocol analysis. Among these contacts, 568 received hepatitis A vaccine and 522 received immune globulin. Most contacts were children (average age, 12 years), and most received prophylaxis during the second week after exposure (average interval after exposure, 10 days). The baseline characteristics of the contacts were similar in the two groups. Symptomatic infection with hepatitis A virus was confirmed in 25 contacts receiving vaccine (4.4%) and in 17 contacts receiving immune globulin (3.3%) (relative risk, 1.35; 95% confidence interval, 0.70 to 2.67).

CONCLUSIONS

Low rates of hepatitis A in both groups indicate that hepatitis A vaccine and immune globulin provided good protection after exposure. Although the study's prespecified criterion for noninferiority was met, the slightly higher rates of hepatitis A among vaccine recipients may indicate a true modest difference in efficacy and might be clinically meaningful in some settings. Vaccine has other advantages, including long-term protection, and it may be a reasonable alternative to immune globulin for postexposure prophylaxis in many situations. (ClinicalTrials.gov number, NCT00139139.)

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The hepatitis A virus causes an acute inflammatory disease of the liver. It is transmitted by the fecal–oral route and has an incubation period of 15 to 50 days (average period, 28 days).[1] The majority of the world's population is still at moderate-to-high risk for hepatitis A virus infection.[2] In the United States, the incidence of hepatitis A has decreased substantially with the introduction of childhood vaccination.[3]

Immune globulin has been the only product currently recommended for postexposure prophylaxis in the United States.[1] In some settings, the number of people with indications for immune globulin may be quite large. For example, in a 2003 foodborne outbreak in the United States, more than 9000 persons received immune globulin, either because of exposure to the hepatitis A virus at the involved restaurant or because of contact with persons who became ill with the virus.[4]

Data from immunogenicity studies,[5] studies in animals,[6,7] and phase 3 trials[8,9] indicate that hepatitis A vaccine may also be effective when given after exposure to the hepatitis A virus. Hepatitis A vaccine offers several advantages over immune globulin, including long-term protection, ease of administration, and widespread availability. Because no trial has directly compared hepatitis A vaccine with immune globulin for postexposure prophylaxis, we aimed to test the hypothesis that hepatitis A vaccine is not inferior to immune globulin in preventing clinical illness when given to contacts of patients with hepatitis A.

METHODS

STUDY POPULATION

Between October 2002 and February 2005, we enrolled index patients and their contacts in Almaty, Kazakhstan, where the hepatitis A virus is of intermediate endemicity. Index cases of hepatitis A were identified through surveillance.[10] An index case was defined as the first reported laboratory-confirmed symptomatic case of hepatitis A in a household or day-care center within the previous 60 days. Household and day-care contacts were ineligible to participate in the study if they were younger than 2 years or older than 40 years of age, reported a history of hepatitis A, had previously received hepatitis A vaccine, had liver disease of any kind, or had contraindications for study interventions.

STUDY DESIGN

This randomized, double-blind, active-control, noninferiority trial was designed to compare the efficacy of hepatitis A vaccine with that of immune globulin in preventing laboratory-confirmed symptomatic hepatitis A when given to contacts within 14 days after exposure to a laboratory-confirmed index case of hepatitis A. For the purposes of this trial, the period of exposure was counted from the day of the onset of the first symptoms in the index patient. The study was approved by the institutional review boards of participating U.S. institutions and the National Medical University of Kazakhstan, and written informed consent was obtained from all index patients and contacts who were 14 years of age (the legal age of consent in Kazakhstan) or older, or from a parent or legal guardian of the index patient or contact. Assent was also obtained for children 7 to 13 years of age.

If no more than 14 days had passed since the onset of symptoms in the index patient, consenting contacts or their parents or guardians were interviewed by Almaty medical epidemiologists to collect baseline information and verify eligibility. Separately, a pediatrician then collected blood specimens for serologic, biochemical, and virologic analyses before randomly assigning participants and administering study interventions. Although the pediatricians were aware of the study interventions given, the medical epidemiologists remained unaware of the interventions given to the contacts.

Contacts who underwent randomization and subsequently were confirmed by means of serologic testing to have been susceptible to the hepatitis A virus at the time of enrollment were contacted weekly by medical epidemiologists to inquire about symptoms of hepatitis A. At weeks 4 and 8 after exposure, coinciding with the average incubation period and end of the incubation period of hepatitis A, respectively, special study visits were conducted to collect blood samples. If at any time during follow-up a contact reported hepatitis A–related symptoms, an illness visit was triggered during which the medical epidemiologist examined the contact in a blinded fashion and the pediatrician separately collected blood and stool samples. Alternatively, if a blood specimen from week 4 or 8 was positive for IgM antibodies to the hepatitis A virus (hereafter referred to as

IgM-positive), an illness visit was also triggered to assess potentially unreported mild illness.

STUDY INTERVENTIONS AND BLINDING

Contacts were randomly assigned in a 1:1 ratio within each household or day-care center to receive immune globulin (Massachusetts Biological Laboratories) at the standard postexposure dose of 0.02 ml per kilogram of body weight or hepatitis A vaccine (VAQTA, Merck) at the licensed, age-appropriate preexposure dose. All interventions were masked from participant view and administered in the deltoid muscle. For households and day-care centers, two separate randomization sequences were generated by a computer before the initiation of the study. Each sequence was divided into allocation lists for each household or day-care center. Pediatricians used labeled product vials to fill syringes that were labeled only with the study identification numbers.

LABORATORY TESTS

Serum specimens obtained at enrollment, week 4, week 8, and the illness visit were analyzed for the presence of IgM antibodies to the hepatitis A virus (ETI-HA-IgMK PLUS, DiaSorin) and for alanine aminotransferase levels (Reflotron Plus System, Roche Diagnostics) at the Virology Reference Laboratory of the Republic of Kazakhstan. Serum samples obtained at enrollment were also analyzed for total antibodies to the hepatitis A virus (ETI-AB-HAVK PLUS, DiaSorin). Serum and stool specimens obtained from persons with serum specimens that were IgM-positive were tested at the Centers for Disease Control and Prevention (CDC) by means of polymerase chain reaction for the presence of hepatitis A virus RNA.[11]

PRIMARY AND SECONDARY END POINTS

The primary study end point was laboratory-confirmed symptomatic hepatitis A, occurring between 15 and 56 days after exposure, defined by serum positive for IgM antibodies to the hepatitis A virus, a serum alanine aminotransferase level at least twice the upper limit of the normal range during an episode of illness with no other obvious cause, and one or more of the clinical signs or symptoms consistent with hepatitis A: dermal, scleral, or faucial icterus; light-colored stools; dark-colored urine; pain in the abdomen or upper right quadrant; nausea; vomiting; an axillary temperature of 37.5°C or higher; loss of appetite; or malaise. All cases were reviewed by an independent data monitoring committee in a blinded manner, and all primary end-point determinations were agreed on unanimously.

Three secondary end points were defined among contacts who became IgM-positive and who had confirmation of infection by means of either biochemical analysis (an alanine aminotransferase level that was two or more times the upper limit of the normal range) or detectable hepatitis A virus RNA on virologic analysis of any follow-up specimens. Two of these secondary end points were clinical (any reported symptom or jaundice), and one was subclinical (no symptoms).

STATISTICAL ANALYSIS

Differences between various group-specific rates were tested with the use of a two-sided Fisher's exact test. Differences between various group-specific means were tested with the use of two-sided independent-sample t-tests, assuming equal variances. The primary analysis was conducted on a per-protocol basis, whereas a supportive modified intention-to-treat analysis was conducted among all contacts found to have been susceptible at the time of enrollment.

To show the noninferiority of the hepatitis A vaccine, we required rejection of the null hypothesis that vaccine is substantially inferior to immune globulin. "Substantially inferior" was defined statistically in terms of a critical margin of the relative risk of the cumulative incidence of the primary end point among recipients of the vaccine as compared with the incidence among recipients of immune globulin,[12] set at the upper bound of a one-sided 95% confidence interval of the relative risk of no more than 3.0 (corresponding to an estimated relative risk of ≤1.59). During a pretrial meeting, experts in the clinical, epidemiologic, and laboratory aspects of hepatitis A virus infection and in statistics and vaccine field-trial design agreed on the critical margin of 3.0. This meeting was convened by University of Michigan and CDC investigators, and the critical margin was based on what was considered to be clinically relevant, statistically valid, and logistically and economically feasible.[13] The exact upper bound of the one-sided 95% confidence interval was calculated on the basis of the total number of cases observed in the study.[14,15] How-

ever, unless otherwise noted, all reported 95% confidence intervals are two-sided. Assuming an immune globulin efficacy of 90%, the critical margin of the study aimed to test whether the lower bound of the one-sided 95% confidence interval for vaccine efficacy would be at least 70%.

With the use of an end-point–driven design, 26 primary end points were originally planned to provide 80% statistical power. From this total, a sample size of 5778 subjects was calculated, assuming a 50% rate of susceptibility of contacts at the time of enrollment, an underlying secondary attack rate of 10%, and a 90% follow-up success rate. Only a few months after the beginning of the study, independent study results indicating 40% population susceptibility[16] and an underlying secondary attack rate of 30%[10] permitted an increase in power to 95% with another estimation of the sample size, based on 44 required end points, to 4074.

The study was initiated by the investigators and was supported by the CDC. Merck donated hepatitis A vaccine (VAQTA) and provided funds to the University of Michigan for the purchase of immune globulin. Merck scientists provided advice on the early trial design, but they were not involved in determining the final design, in collecting, analyzing, or interpreting the data, or in writing the article, and they did not have access to the data.

RESULTS

STUDY POPULATION

Of 4524 contacts (of 920 index patients with hepatitis A) randomly assigned to receive hepatitis A vaccine or immune globulin, 1414 contacts (of 609 index patients) were found to have been susceptible to the hepatitis A virus at the time of enrollment, and 1090 contacts (of 474 index patients) were fully eligible for the per-protocol analysis (Fig. 1). The most common reason susceptible contacts were excluded was that the corresponding index patient lacked the required result for the alanine aminotransferase level (12% of index patients).

In the per-protocol group, index patients ranged in age from 1 to 55 years (average age, 13 years; median, 11; interquartile range, 7 to 18) and had an average alanine aminotransferase level of 1133 U per liter; 450 (95%) had jaundice. Contacts ranged in age from 2 to 40 years (average age, 12 years) and included household contacts (83%) and day-care contacts (17%). A total of 586 (54%) contacts were girls or women. Baseline characteristics were similar between the two intervention groups (Table 1). There were no significant differences between the groups with regard to the proportion of contacts who withdrew from the study ($P=0.20$) or were lost during follow-up ($P=0.17$).

SAFETY

No unexpected adverse reactions after immunization were reported. A total of 28 serious adverse events occurred among the study subjects. All subjects with serious adverse events were hospitalized: 25 for hepatitis A illness, 1 for appendicitis, 1 for rubella, and 1 for moderately severe bronchitis. Hospitalization for hepatitis A is the standard of care in Kazakhstan (>97% of index patients enrolled in this study had been hospitalized). All serious adverse events were determined, in a blinded fashion, to be unrelated to the receipt of study interventions, and all resolved without complications or sequelae.

PRIMARY END POINTS

Among contacts who provided at least one follow-up blood specimen, 188 of 666 contacts who received vaccine (28%) and 68 of 620 contacts who received immune globulin (11%) were IgM-positive at some point during follow-up. Among the 29 IgM-positive vaccine recipients who described an episode of illness confirmed by an elevated alanine aminotransferase level, the independent data monitoring committee determined that 26 (90%) reached valid primary end points. Among the 22 IgM-positive immune globulin recipients who described an episode of illness confirmed by an elevated alanine aminotransferase level, the independent data monitoring committee determined that 18 (82%) reached valid primary end points. Demographic and clinical characteristics of these contacts with hepatitis A in the vaccine and immune globulin groups were mostly similar (Table 2). However, the vaccine recipients were younger (11.2±8.7 years) and had higher average measured peak alanine aminotransferase levels (1001±397 U per liter) than recipients of immune globulin (16.8±11.5 years and 725±461 U per liter, respectively) (Table 2). This difference in alanine aminotransferase levels between recipients of vaccine and recipients of immune globulin was observed only among children 2 to 18 years of age (1006±399 U

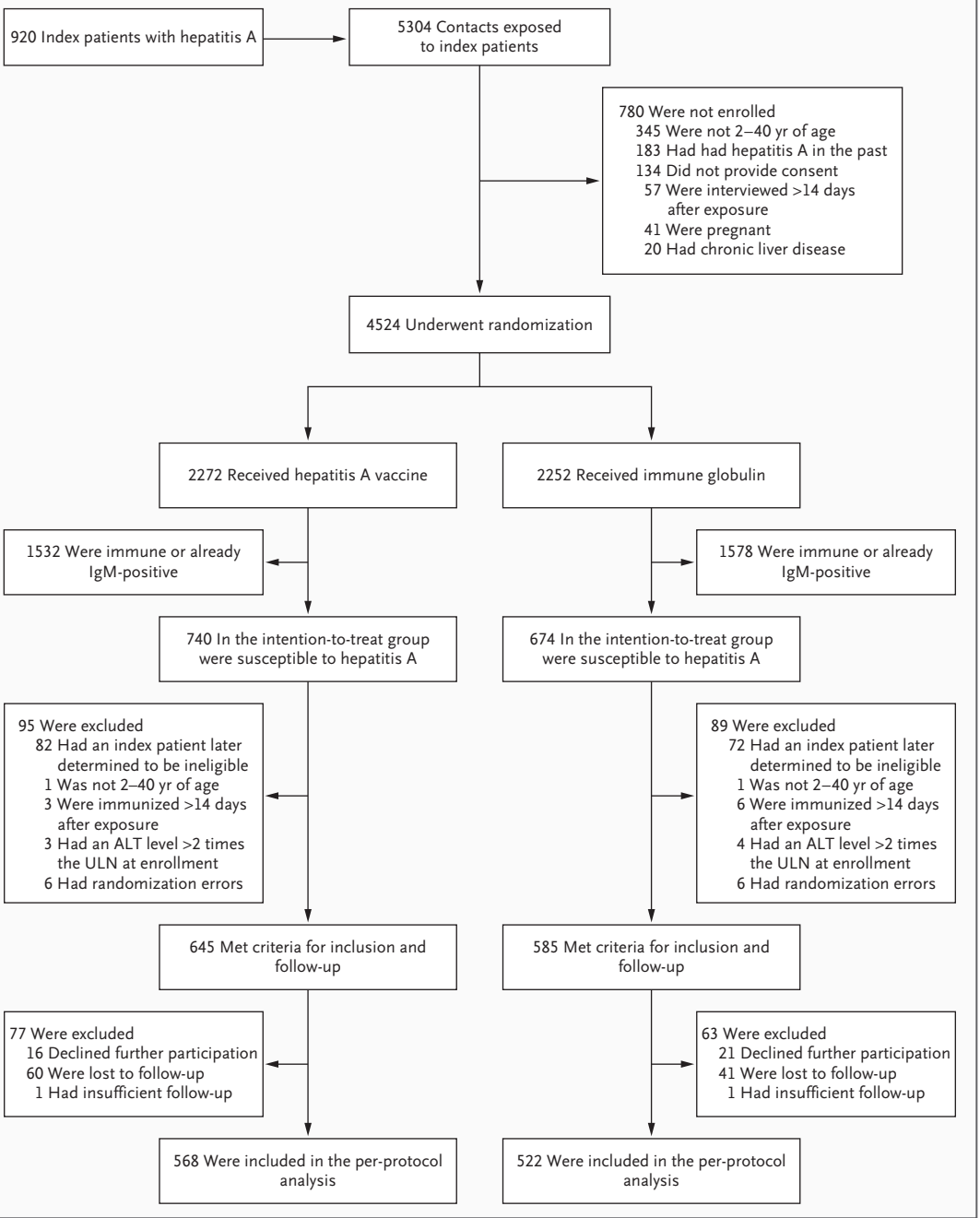

Figure 1. Trial Enrollment, Treatment Assignments, and Follow-up.

ALT denotes alanine aminotransferase, and ULN upper limit of the normal range.

per liter vs. 623±431 U per liter, P=0.01), but not among people older than 18 years of age (977±437 U per liter vs. 991±475 U per liter, P=0.96). The remaining participants with serologic tests that were IgM-positive were asymptomatic or did not have infection confirmed by an elevated alanine aminotransferase level. Transient vaccine-induced IgM positivity was common. Among the 102 asymptomatic vaccine recipients with normal alanine aminotransferase levels with specimens that at week 4 were IgM-positive, 73 (72%) were no longer IgM-positive at week 8.

Table 1. Baseline Characteristics of the Contacts and Rates of Study Completion.*

Variable	Per-Protocol Population		Modified Intention-to-Treat Population†	
	Vaccine Group (N=568)	Immune Globulin Group (N=522)	Vaccine Group (N=740)	Immune Globulin Group (N=674)
Sex — no. (%)				
Male	271 (48)	233 (45)	345 (47)	298 (44)
Female	297 (52)	289 (55)	395 (53)	376 (56)
Ethnic group — no. (%)‡				
Kazakh	306 (54)	280 (54)	410 (55)	374 (55)
Slavic	147 (26)	148 (28)	182 (25)	189 (28)
Uighur	53 (9)	56 (11)	66 (9)	64 (9)
Other	58 (10)	36 (7)	77 (10)	45 (7)
Unspecified	4 (<1)	2 (<1)	5 (<1)	2 (<1)
Type of contact — no. (%)				
Household	470 (83)	437 (84)	629 (85)	575 (85)
Day-care	98 (17)	85 (16)	111 (15)	99 (15)
Age — yr	11.4±8.1	13.1±9.4	11.8±8.4	13.4±9.7
Time from exposure to immunization — days	10.1±2.4	10.0±2.4	10.1±2.5	10.1±2.6
Study completion — no. (%)				
Sufficient follow-up			654 (88)	601 (89)
Lost to follow-up			67 (9)	47 (7)
Declined further participation			17 (2)	24 (4)
Missed required questionnaires			2 (<1)	2 (<1)

* Plus–minus values are means ±SD.
† The modified intention-to-treat population included all subjects in the intention-to-treat population who were determined to have been susceptible to the hepatitis A virus at the time of enrollment.
‡ Ethnic group was reported by the subject or by the parent or guardian.

RELATIVE EFFICACY OF PROPHYLACTIC MEASURES

In the per-protocol analyses, 25 primary end points were reached among vaccine recipients (4.4%) and 17 were reached among immune globulin recipients (3.3%), yielding a relative risk among vaccine recipients as compared with immune globulin recipients of 1.35 (95% confidence interval [CI], 0.70 to 2.67) (Table 3). The upper bound of the one-sided 95% confidence interval was 2.40, and it met our prespecified criterion for noninferiority based on a one-sided test of a relative risk of less than 3.0. In the modified intention-to-treat analysis, 26 primary end points were reached among vaccine recipients (3.5%) and 18 primary end points were reached among immune globulin recipients (2.7%), yielding a relative risk among vaccine recipients as compared with immune globulin recipients of 1.32 (95% CI, 0.69 to 2.55) (Table 3). Among subgroups, the modified intention-to-treat estimates of the relative risk were generally similar when stratified according to age group (children 2 to 18 years of age: relative risk, 1.38; adults 19 to 40 years of age: relative risk, 1.23; Breslow–Day test, P=0.72) or week of receipt of prophylaxis after exposure (first week after exposure: relative risk, 1.16; second week after exposure: relative risk, 1.34; Breslow–Day test, P=0.76). For secondary end points, estimates of relative risk ranged from 1.15 to 1.44 and were largest for icteric illness (Table 3).

DISCUSSION

In this comparative trial, rates of hepatitis A among contacts who received hepatitis A vaccine or immune globulin were less than 5%. Although the

Table 2. Characteristics of Contacts with Hepatitis A.*

Variable	Vaccine Group (N=26)	Immune Globulin Group (N=18)	P Value
Time from exposure to immunization (days)			0.403
Mean	10.1±2.2	9.5±2.2	
Range	6–14	6–12	
Time from exposure to onset of illness (days)			0.560
Mean	24.9±3.8	24.2±4.2	
Range	17–33	16–33	
Age (yr)			0.075
Mean	11.2±8.7	16.8±11.5	
Range	2–34	5–40	
Average peak ALT level measured at time of illness (U/liter)			0.040
Mean	1001±397	725±461	
Range	156–1610	65.8–1500	
Positive for HAV RNA in serum, stool, or both (%)	62	56	0.761
Jaundice (%)	73	61	0.515
Nausea, vomiting, or abdominal pain (%)	85	83	1.000

* Plus–minus values are means ±SD. ALT denotes alanine aminotransferase, and HAV hepatitis A virus.

study's prespecified criterion for noninferiority was met, rates were higher in the vaccine group as compared with the immune globulin group for all study end points examined, a finding that suggests that immune globulin performed modestly better than vaccine. However, the risk of hepatitis A in the vaccine group was never more than 1.5% greater than that in the immune globulin group.

We could not directly measure absolute vaccine efficacy because it was not ethical to include a placebo-control group. Nonetheless, vaccine efficacy may be estimated on the basis of an assumed efficacy of immune globulin after exposure, which has been considered for many years to be more than 80%.[1,17-24] If immune globulin was truly 90% efficacious in our study, the efficacy of hepatitis A vaccine may be estimated to be 86% (95% CI, 73 to 93%), and if immune globulin was truly 80% efficacious, the vaccine efficacy may be estimated to be 73% (95% CI, 47 to 86%) (see the Supplementary Appendix, available with the full text of this article at www.nejm.org). These estimates are consistent with that from a previously reported study of hepatitis A vaccine used after exposure in which vaccine was reported to be 79% effective in preventing hepatitis A virus infection as compared with an observation-only control group.[9]

The finding that hepatitis A vaccine may be modestly less efficacious after exposure than immune globulin may be clinically meaningful for persons who are likely to have severe illness if infected with the hepatitis A virus, such as older persons or those with chronic liver disease.[1] However, hepatitis A vaccine offers a number of advantages over immune globulin. Protection conferred by immune globulin is temporary, whereas vaccination against hepatitis A results in active immunity and long-term protection. The volume of immune globulin required can be large, resulting in a painful injection. The supply of immune globulin has been limited, and currently there is only one producer of immune globulin in the United States. Also, there is a perceived concern by the public about the safety and purity of a blood-derived product. The use of immune globulin in children complicates adherence to childhood immunization schedules for live, attenuated vaccines.[1] The cost of immune globulin has increased substantially and approaches that of vaccine.[25] Hence, the risk of infection, the likelihood of severe illness, the possible difference in efficacy between vaccine and immune globulin,

Table 3. Outcomes among Recipients of Hepatitis A Vaccine and Recipients of Immune Globulin.*

End Points	Per-Protocol Population		Modified Intention-to-Treat Population†		Relative Risk (95% CI)	
	Vaccine Group (N=568)	Immune Globulin Group (N=522)	Vaccine Group (N=740)	Immune Globulin Group (N=674)	Per-Protocol Population	Modified Intention-to-Treat Population
	number (percent)					
Clinical						
Primary						
Any symptom plus IgM-positive and ALT ≥ twice ULN	25 (4.4)	17 (3.3)	26 (3.5)	18 (2.7)	1.35 (0.70–2.67)	1.32 (0.69–2.55)
Secondary						
Any symptom plus IgM-positive and ALT ≥ twice ULN or HAV RNA–positive on PCR‡	29 (5.1)	19 (3.6)	30 (4.1)	20 (3.0)	1.40 (0.76–2.64)	1.37 (0.75–2.54)
Jaundice plus IgM-positive and ALT ≥ twice ULN or HAV RNA–positive on PCR	18 (3.2)	12 (2.3)	19 (2.6)	12 (1.8)	1.38 (0.63–3.14)	1.44 (0.66–3.25)
Subclinical						
Asymptomatic IgM-positive and ALT ≥ twice ULN or HAV RNA–positive on PCR	20 (3.5)	16 (3.1)	26 (3.5)	18 (2.7)	1.15 (0.57–2.37)	1.32 (0.69–2.55)
Clinical plus subclinical	49 (8.6)	35 (6.7)	56 (7.6)	38 (5.6)	1.29 (0.82–2.05)	1.34 (0.87–2.08)

* CI denotes confidence interval, HAV hepatitis A virus, ALT alanine aminotransferase, ULN upper limit of the normal range, and PCR polymerase chain reaction.
† The modified intention-to-treat population included all persons in the intention-to-treat population who were determined to have been susceptible to HAV at the time of enrollment.
‡ This end point includes all primary end points and six cases of clinical illness that did not reach the primary-end-point criteria.

and the vaccine's advantages may all be relevant considerations in each decision regarding whether to use vaccine or immune globulin.

Public health authorities in many countries in the developed world, including much of Europe and Canada, recommend hepatitis A vaccine after exposure.[26-28] In some countries, immune globulin was never routinely used, whereas in other countries, recommendations were changed because vaccine was considered to be preferable to immune globulin.[29] Since studies comparing the postexposure efficacy of vaccine with that of immune globulin were lacking, the Advisory Committee on Immunization Practices continued to recommend immune globulin for postexposure prophylaxis.[1] The results of our study informed a recent decision of the committee to update U.S. recommendations for prophylaxis after exposure to the hepatitis A virus.[30]

In some previous studies, immune globulin appeared to attenuate the clinical expression of hepatitis A.[17,31] In our trial, we found some evidence that hepatitis A illnesses occurring among immune globulin recipients were milder than those occurring among vaccine recipients. For example, jaundice and observed elevations in alanine aminotransferase levels among patients with clinical illness occurred less frequently among immune globulin recipients than among vaccine recipients. Because our study did not aim to measure the severity of illness, and because too few of the contacts in the nonpediatric study population, where disease is typically more severe, had jaundice, firm conclusions cannot be drawn. However, we found no evidence of an effect of immune globulin on the duration of viremia or viral shedding; the proportion of patients with detectable hepatitis A virus RNA in at least one specimen was similar between the two intervention groups.

For the primary end point, we required only general symptoms rather than those that are highly specific for viral hepatitis. As such, there was a risk of nondifferential misclassification, which is especially threatening in noninferiority studies such as this one. However, because the clinical

expression of hepatitis A virus infection varies among persons of different age groups,[32,33] and infected children can transmit the hepatitis A virus to others even though jaundice does not develop in most of them,[34,35] we thought it was important to include these cases to more accurately reflect the spectrum of illness among persons with hepatitis A virus infection.

The endemicity of hepatitis A in Kazakhstan is higher than that in the United States; however, it is unlikely that the level of endemicity in Kazakhstan influenced the study's findings, because our analysis included only susceptible persons. Furthermore, transmission studies conducted in the population before the trial showed that hepatitis A transmission patterns in Almaty were similar to those seen in the United States, with hepatitis A virus transmission occurring predominantly in households.[10,36]

Other factors might have affected generalizability or our ability to detect valid differences between the two interventions. The hospitalization of nearly all index patients ended further exposure for contacts. However, this factor is unlikely to have had an appreciable effect on transmission, because the period of greatest communicability is at or just before the time of illness onset.[10,34,37,38] Keeping participants unaware of the intervention they received was somewhat difficult because injections of immune globulin are generally more painful than vaccination. Finally, if illnesses occurred differentially and were missed among the 13% of subjects lost to follow-up, a bias could have been introduced.

In conclusion, hepatitis A occurred infrequently among susceptible contacts who received either hepatitis A vaccine or immune globulin. Although the vaccine efficacy after exposure appeared to be high, as compared with immune globulin, modest and potentially clinically relevant differences were measured. Given the logistical difficulties in conducting such a trial, it is unlikely that another study will be undertaken to replicate these findings. By providing a scientific context in which to reevaluate the relative benefits of immune globulin and vaccine, our study informed policy decisions regarding hepatitis A vaccine.

Supported by the CDC through an Association of Schools of Public Health cooperative agreement to the University of Michigan. Merck donated hepatitis A vaccine, VAQTA, and provided funds to the University of Michigan for purchase of immune globulin.

For the purposes of this trial, there were no contractual arrangements or confidentiality agreements between any author and the vaccine manufacturer, Merck. Dr. Monto reports receiving fees from GlaxoSmithKline. No other potential conflict of interest relevant to this article was reported.

APPENDIX

The following persons contributed to the trial: *Independent Data Monitoring Committee* — K. Gensheimer, M. Glode, B. McMahon, R. Little; *Pretrial Consultants* — M. Green, P. Van Damme, M. Foulkes, I. Longini, J. Koopman, B. Robertson, D. Shouval, Y. Ashur; *Merck Advisors* — B. Kuter, H. Cohen, J. Gress, E. Jensen, J. Heyses, H. Lakkis, H. Matthews; *Kazakhstan Ministry of Health Consultants* — V. Merker, G. Kembabanova, L. Belanog, K. Ospanov, A. Sheyanov; *Medical Epidemiologists* — O. Asaeva, A. Bekmukhamedova, M. Bektemirova, Y. Bumburidi, A. Kuatbaeva, S. Nurgalieva, Z. Nurgozhina, N. Tursunova; *Pediatricians* — R. Idrissova, E. Gabatashvili, M. Golovenko, E. Karpova, A. Kumbaeva, N. Mikhaleva, E. Soboleva; *Database Design and Construction* — A. Izmukhambetov; *Study Center Management* — D. Nabirova, M. Disenova, O. Vetoshkina, B. Bochugulov, L. Markovenko; *Laboratory Testing* — N. Baranova, A. Utegenova, A. Nurkaskaeva, Z. Arzueva, L. Kodukova, Z. Vostryikova, Y. Khudyakov, L. Ganova-Raeva, J. Li, J. Drobeniuc; *Logistics* — D. Mulcahy, M. Fouks, L. Noll; *Administrative Support* — T. Canales Maricle, S. Imanbayeva, Y. Khvan, G. Omarbekova, L. Vakhmistrova, M. Aitmagambetov, J. Anischenko, Y. Neudakhina, B. Abma.

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