



Hepatitis A vaccine in the last-minute traveler

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Current recommendations state that travelers should receive hepatitis A vaccine 2 to 4 weeks before departure. Such recommendations, however, may dissuade last-minute travelers from receiving the vaccine. A preponderance of evidence exists to support hepatitis A vaccination of the imminent-departure traveler and therefore suggests that these guidelines merit reconsideration. In examining this issue, one of the most important elements to determine is the amount of time required for seroconversion following vaccination. Clinical trials of hepatitis A vaccines measured antibody response at 2 and 4 weeks after vaccination. However, studies investigating early seroconversion found that the vast majority of vaccinees develop antibodies within 2 weeks of vaccination, some as early as 12 days after vaccination. This is relevant information, given that the hepatitis A virus has an average incubation period of 28 days. Seroconversion is predicated on achieving a "protective" antibody level. However, levels of antibody considered protective remain debatable. Evidence suggests that clinical disease does not occur at antibody levels lower than those currently accepted as protective. Furthermore, hepatitis A vaccine has been proved effective in controlling outbreaks worldwide. Research data show that a single dose of vaccine can halt outbreaks if an adequate number of susceptible individuals are vaccinated. Information from rapid-outbreak control studies and those assessing postexposure administration of hepatitis A vaccine suggest that late vaccination provides a significant degree of protection. For these reasons, hepatitis A vaccine may be administered at any time before departure because it will still provide travelers with protection.

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Despite the availability of effective vaccines, hepatitis A remains a major cause of morbidity in travelers. For this reason, most national and international authorities recommend hepatitis A vaccination for those individuals traveling to areas where they may be exposed to hepatitis A virus (HAV). Unfortunately, no consistent method exists to inform travelers of such recommendations; therefore, travelers are often unaware of the need for hepatitis A vaccine until shortly before their departure. To complicate this problem, current recommendations state that hepatitis A vaccine should be administered ≥ 2 to 4 weeks before travel to

countries with a moderate to high risk of infection.¹⁻⁴ Such recommendations imply that travelers presenting < 2 weeks before departure are not candidates for vaccination; thus, imminent-departure travelers may not receive hepatitis A vaccine. However, a preponderance of evidence suggests that these guidelines now merit reconsideration.

The prescribing information for the 2 hepatitis A vaccines licensed in the United States (Havrix, GlaxoSmith-Kline, Research Triangle Park, NC; Vaqta, Merck & Co., Inc., Whitehouse Station, NJ) recommends that primary immunization be given ≥ 2 weeks before expected exposure to HAV.^{1,2} The Centers for Disease Control and Prevention (CDC) recommend that "travelers who need optimal protection earlier than 4 weeks after the first dose of vaccine should also receive immune globulin with the first vaccine

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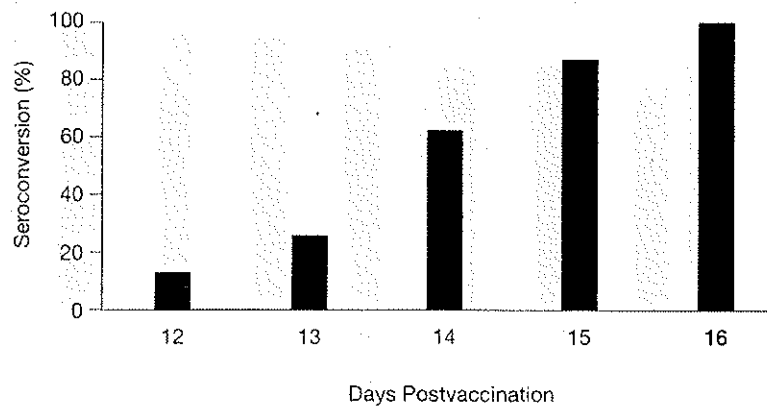


Figure 1 Rate of seroconversion following vaccination with 1 dose of hepatitis A vaccine. (Data from *Commun Dis Public Health*.¹¹)

dose.”³ Similarly, the World Health Organization (WHO) states that “travelers should be vaccinated 4 weeks before departure if possible.”⁴

A variety of reasons may explain why a significant proportion of travelers may not present for a pretravel medical visit until the last minute. Business travelers may be notified of travel on short notice. Leisure travelers may not be aware of the need for immunization or may delay their visit until shortly before departure. Special groups with short-notice deployment, such as the military, are often preimmunized, but others who may be called on to travel on short notice, such as journalists, aid and relief workers, and first responders, may not have adequate time to receive hepatitis A immunization on the basis of current official recommendations.

Surveys from Belgium and the United States show a variation in the length of time between travelers’ visits to a medical clinic and their departure. In each of these surveys, Belgian and American travelers visited a medical clinic an average of 31 and 23 days before departure, respectively; however, 8% in Europe and 29% in the United States consulted a physician ≤ 7 days before departure.^{5–7} Clearly, among the most important items to determine in these late travelers is the amount of time needed for seroconversion to occur after hepatitis A vaccination.

Early seroconversion rates after vaccination

Hepatitis A vaccines provide high immunogenicity. Antibodies to HAV (anti-HAV), including neutralizing antibody, rapidly develop within 2 weeks after 1 dose of vaccine. Protection due to vaccination relates to the presence of antibody; postvaccination protection has been associated with the onset of seroconversion and an anamnestic antibody response after a booster dose.^{8–10}

The 2-week pretravel vaccination recommendation advocated by authorities is based on results of clinical trials that measured antibody response 2 and 4 weeks after 1 dose of vaccine was administered. In these trials, antibody levels

were not measured before vaccine administration.^{1,2} Furthermore, these studies used a somewhat arbitrary “protective” antibody level, which may be higher than the true level of protection. Data suggest that protection may actually occur with antibody levels lower than this so-called protective level.

In 1 of the published studies that investigated early seroconversion prospectively, 8 previously seronegative adults received a single dose of inactivated hepatitis A vaccine.¹¹ All subjects were seropositive by day 16, with the earliest seroconversion detected at day 12 (**Figure 1**). Early seroconversion also was seen in a retrospective analysis of 9 clinical trials in which Havrix 1,440 enzyme-linked immunosorbent assay (ELISA) units (ELU) was administered. Of the 1,694 seronegative adults included in the analysis, 79% seroconverted by day 13 and all had seroconverted by day 19 (**Figure 2**,⁷ **Table 1**).¹² In a series of 114 healthy young adults, 77% to 85% seroconverted within 2 weeks after a single dose of Havrix 720 ELU.¹³ In another study using Havrix 1,440 ELU, 88% of 450 enrolled adults seroconverted by day 14 with high serum levels of neutralizing antibodies.¹⁴ Similar findings also have been shown with other hepatitis A vaccines.¹⁵ Thus, it is apparent that the vast majority of vaccinees develop antibodies within 2 weeks of hepatitis A vaccination.

“Protective” antibody levels reexamined

Natural immunity to HAV is a complex process; several distinct arms of the immune system are operative, including natural killer cells, human leukocyte antigen-restricted cytotoxic T cells, and B-cell antibody.¹⁶ On the basis of vast experience with immunoglobulin in protecting against HAV infection, antibody alone is known to provide high-level protection against clinical disease. However, the precise levels of antibody considered protective remain debatable.

Seroconversion is predicated on achieving a so-called protective antibody level. These levels have been variably defined in clinical trials with Vaqta as 10 mIU/mL

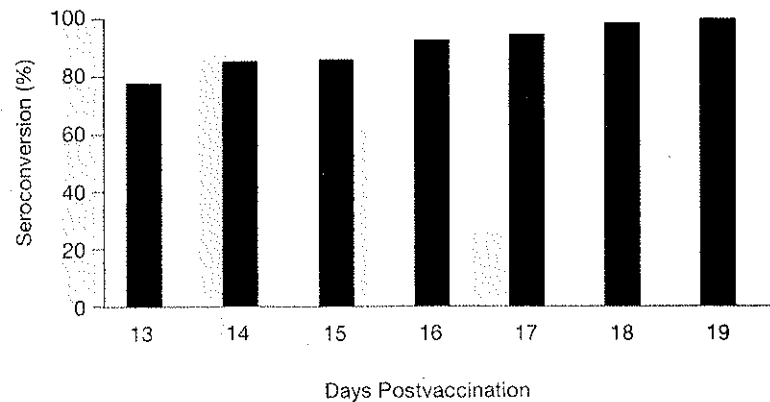


Figure 2 Seroconversion rates after vaccination with 1 dose of hepatitis A vaccine (Havrix 1,440 ELISA units). ELISA = enzyme-linked immunosorbent assay. (Reproduced with permission from *Biodrugs*.⁷)

(10 IU/L) and with Havrix as 20 mIU/mL (20 IU/L).^{1,2} However, these levels are arbitrary: the results of in vitro studies using cell-culture-derived HAV indicate that antibody concentrations <10 to 20 mIU/mL can be neutralizing.¹⁶ When interpreting results of immunogenicity studies, the clinician must remain aware that the absolute lowest count of antibody needed for protection has not been determined. The protective antibody level is derived from the knowledge that 1 to 2 months after a dose of hepatitis A immunoglobulin, antibody levels are 10 to 20 mIU/mL. These levels are known to be protective. However, over time, antibody levels decrease to <10 mIU/mL yet continue to provide protection from HAV infection for ≤ 5 months. This finding suggests that antibody levels <10 mIU/mL may be protective.¹⁶

Postexposure protection in outbreak studies and controlled trials

Although clinical disease with HAV has been seen as early as 15 days and as late as 50 days after exposure, the average incubation period for natural or experimental infec-

tion is 28 days.^{17,18} An efficacy trial of a hepatitis A vaccine (Vaqta 25 U) was conducted in a high-risk closed religious community in upstate New York that had experienced annual outbreaks of hepatitis A.¹⁹ At the beginning of an outbreak, 519 children received the vaccine and 518 received placebo. Before day 21, 3 cases of hepatitis A occurred in the placebo group and 7 cases occurred in vaccine recipients. However, after that time, no case of hepatitis A was seen in the vaccine group compared with 34 cases seen in placebo recipients. This suggests that vaccine recipients who contracted hepatitis A within the first 3 weeks had already been incubating virus at the time of enrollment in the trial and that vaccination provided some postexposure prophylaxis.

Historically, outbreaks of hepatitis A have been difficult to control.²⁰ Widespread postexposure prophylaxis with immune globulin may decrease transmission but does not appear to stop outbreaks. Hepatitis A vaccine, however, has been proved effective in controlling outbreaks worldwide.²¹⁻²⁷ Evidence from the use of vaccine in outbreak situations shows that a single dose of hepatitis A vaccine can halt community outbreaks if an adequate number of susceptible individuals are vaccinated (**Table 2**). Vaccination also may prevent an epidemic from becoming established in communities in which only a few cases of HAV infection have occurred. Vaccination of school or family contacts of individuals with hepatitis A within a few days of identification appears to shorten the duration of an outbreak.²⁷

During community-wide hepatitis A outbreaks in Alaska, a single dose of vaccine was given to 4,930 susceptible persons in 25 rural communities where 529 cases of hepatitis A were noted during the preceding 12 months.²¹ In 1 community in which <50% of susceptible individuals received vaccine, the outbreak continued for >50 months. In another community in which >80% of susceptible persons were vaccinated, the outbreak ceased within 4 to 8 weeks.²¹ During a community-wide outbreak in Slovakia, hepatitis A vaccination prevented new cases and did so more rapidly

Table 1 Seroconversion rates and geometric mean titers after the first dose of hepatitis A vaccine

Time	N	Seroconversion (%)	Geometric Mean Titer (mIU/mL)*
Day 13	157	79.0	139.5
Day 14	150	85.3	227.8
Day 15	716	86.3	265.4
Day 16	407	93.4	325.6
Day 17	125	95.2	444.6
Day 18	67	98.5	594.8
Day 19	72	100.0	731.8

Reproduced with permission from Van Damme et al.¹²

*To convert conventional units to SI units, use the same numeral with "IU/L."

Table 2 Effectiveness of hepatitis A vaccine in the control of outbreaks of hepatitis A virus (HAV) infection

Country	Setting	Number of vaccinees	Vaccine dose (ELISA units)	Outbreak measures	Results
United States (Alaska) ²¹	25 rural communities	4,930	1,440 (≥ 20 yr) 720 (< 20 yr)	Development of symptomatic illness compatible with HAV infection	Regions with $> 80\%$ coverage: outbreak ceased in 4–8 wk Regions with $< 50\%$ coverage: outbreak continued for > 50 wk
Slovakia ²²	2 village schools	404 138 Not vaccinated 19 Received anti-HAV globulin	360	Development of clinical hepatitis A	Vaccinated group: 1 case; attack rate 0.25% Nonvaccinated group: 5 cases; attack rate 3.6%
United States (Tennessee) ²³	Urban (Memphis)	35,054 Children	360	Hepatitis A	Number of cases declined by 64%
Croatia ²⁴	Refugee camp	34 Children	720	Development of clinical hepatitis A	1 case 5 days postvaccination
United Kingdom ²⁵	Village primary school	250	1,440 adults 720 children	Serologic or salivary evidence of HAV infection	78% coverage achieved; only 2 cases in subsequent 7 days
Italy (Tuscany) ²⁶	Nursery school	60	1,440 adults 360 children	Development of clinical hepatitis A	7 of 60 (11.7%) cases of HAV infection postvaccination; all contracted prior to vaccination

anti-HAV = antibodies to hepatitis A virus; ELISA = enzyme-linked immunosorbent assay.

and effectively than did immunoglobulin.²² In an urban community in Tennessee, the number of cases of hepatitis A decreased by 64% when children were given 1 dose of hepatitis A vaccine.²³ This success of hepatitis A vaccine in stopping community-wide outbreaks, much more effectively and rapidly than immunoglobulin, implies postexposure benefits.²⁸

Increasing evidence suggests that clinical disease may not occur even at antibody levels considered too low for protection. Experimental studies in chimpanzees showed that low levels of passively transmitted antibodies (< 10 mIU/mL [< 10 IU/L]) prevented clinical hepatitis and viral shedding.²⁹ Furthermore, studies in chimpanzees and marmoset monkeys demonstrated efficacy of hepatitis A vaccine in providing postexposure prophylaxis.^{29,30} Vaccine administered shortly after exposure protected chimpanzees and marmosets from HAV infection. In the latter study, 8 marmosets were challenged with HAV; group A received hepatitis A vaccine 360 ELU (Havrix) 48 hours after infec-

tion and group B received hepatitis A vaccine 1,440 ELU (Havrix) 48 hours after infection. In group A, 50% of subjects developed modified or mild disease and 50% were completely protected. In the higher-dose group B, 100% were completely protected when the vaccine was given 48 hours after exposure to HAV.

Additional evidence of postexposure prophylaxis comes from a randomized controlled trial in Italy.³¹ A single dose of hepatitis A vaccine provided 79% (95% confidence interval [CI], 7%–95%) effective protection when given to household contacts of subjects with hepatitis A infection. Of 197 household contacts who were vaccinated, 2 developed secondary infections; however, both cases were asymptomatic with normal plasma levels of liver enzymes and silent immunoglobulin M anti-HAV seroconversions. In contrast, 10 of the 12 secondary infections that occurred in the control group showed symptoms or elevated values for liver enzymes. This suggestion of postexposure prophylaxis in the household setting is intriguing.

Summary

On the basis of current knowledge of hepatitis A antibody kinetics in response to vaccine, the natural incubation period of HAV infection, and postexposure prophylaxis data from outbreak control and animal studies, the current recommendations on timing of hepatitis A vaccine administration clearly require reconsideration.

Theoretically, if an individual were immunized on the way to the airport, arrived at the destination, and were then exposed to HAV during the first meal of the ensuing trip, that individual should be spared from developing clinical hepatitis A. Additional research is needed to determine an accurate postexposure window; however, given that the average incubation period of hepatitis A is 28 days with a minimum incubation period of 15 days, antibody levels attained 15 days after vaccination should be fully protective for the vast majority of individuals. Further support for this theory is provided by data showing postexposure protection due to vaccination, both in outbreak situations and in stopping household transmission, as well as in animal challenge studies.

Despite current recommendations that hepatitis A vaccine be administered between 2 and 4 weeks before expected exposure, a preponderance of evidence now supports the efficacy of the vaccine administered to the imminent-departure traveler.

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