

Rapid Protection and Vaccination against Hepatitis A for Travellers

Bradley A. Connor,^{1,2} Koen Van Herck³ and Pierre Van Damme³

1 The New York Center for Travel and Tropical Medicine, New York, USA

2 Weill Medical College of Cornell University, New York, USA

3 Department of Epidemiology and Social Medicine, Centre for the Evaluation of Vaccination, University of Antwerp, Antwerp, Belgium

It is estimated that the majority of international travellers leaving Northern and Western Europe bound for developing countries are susceptible to hepatitis A infection. That is why many national and international authorities recommend hepatitis A vaccination. However, for various reasons a significant proportion of these travellers may not present for vaccination until the last minute. Some may need to travel urgently and/or unexpectedly, and others may not be aware of the manufacturers' recommendations that the vaccine be administered at least 2 weeks prior to travel.

Unfortunately, such recommendations imply that travellers presenting less than 2 weeks prior to departure are no longer considered as candidates for immunisation. Indeed, some agencies, such as the US Centers for Disease Control and Prevention (CDC), state that complete protection might not develop until 4 weeks after vaccine administration and that immune globulin should be given to persons travelling to high-risk areas before this time.^[1] Nevertheless, as there is now a preponderance of evidence to merit reconsideration of these guidelines, this review briefly looks at the information available and how it affects the options available to the last-minute traveller seeking protection from hepatitis A.

1. Seroconversion Rates

Surveys from Belgium and the US show a variation in the length of time travellers leave between visits to a medical clinic and departure. While the average time of visit in each of these surveys was 31 and 23 days prior to departure in Belgium and the US, respectively, 7.8% in Europe and 29% in the US consulted a physician ≤ 1 week prior to departure.^[2,3] Clearly, one of the most important things to determine for these late travellers is the time taken to seroconvert after vaccination.

The 2-week pre-travel vaccine recommendation advocated by authorities is based on studies that measured antibody

response at 2 and 4 weeks post-primer, rather than obtaining antibody levels prior to this time. However, in one of the few published studies to investigate early seroconversion prospectively, the earliest response was detected 12 days after a single dose of inactivated hepatitis A vaccine (Havrix 1440^{®1}, GlaxoSmithKline Biologicals, Rixensart, Belgium). The pilot trial included eight previously seronegative adults and found that all subjects were seropositive by day 16.^[4] A retrospective analysis of nine clinical trials of Havrix 1440[®] confirmed this result; of the 1694 seronegative adults included in the trials, 79% seroconverted by day 13 and all had seroconverted by day 19 (figure 1).^[5] Similar findings were also shown with other hepatitis A vaccines.^[6]

It is therefore apparent that the vast majority of vaccinees develop antibodies within 2 weeks of hepatitis A vaccination. This is very relevant information, given that the virus has a mean incubation period of 28 days;^[7] it virtually offers the opportunity to immunise travellers on their way to the airport.

2. Post-Exposure Protection

Natural immunity to hepatitis A is a long and complex process, and the use of immune globulin is proof that antibody alone is sufficient to provide a high level of protection against clinical disease. However, the levels of antibodies considered 'protective' remain debatable and concerns exist about the perceived safety of human-derived blood products.

There is increasing evidence to suggest that clinical disease does not occur even at antibody levels considered too low for protection. Studies in chimpanzees showed that low levels of passively transferred antibodies (<10 IU/L) do prevent clinical hepatitis and virus shedding.^[8] In addition, during a community-

1 Tradenames are used for product identification purposes only and do not imply endorsement.

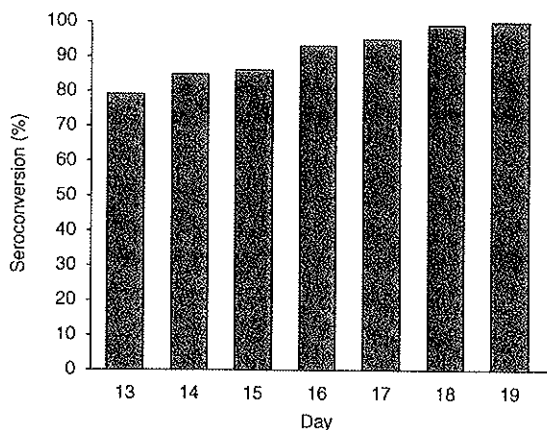


Fig. 1. Seroconversion rates in healthy adults ($n = 1694$) after vaccination with one dose of Havrix 1440[®] EL.U (ELISA Units).^[5]

wide hepatitis A outbreak in Alaska, the epidemic in one region was halted within 4–8 weeks after more than 80% of susceptible individuals were given a single dose of inactivated vaccine.^[9] During another community-wide outbreak, hepatitis A vaccination not only prevented new cases, but did so more rapidly and effectively than immune globulin.^[10] Furthermore, experimental studies in chimpanzees indicate that hepatitis A virus (HAV) vaccine prevented HAV infection when administered shortly after exposure.^[11]

A randomised controlled trial in Italy reported that post-exposure vaccination with a single dose of inactivated hepatitis A vaccine had a 79% (95% CI 7–95%) protective efficacy when given to the household contacts of subjects with sporadic hepatitis A infection.^[12]

3. Schedule Flexibility

The recommended schedule for hepatitis A immunisation is two doses given between 6 or 12–18 months apart, depending on which product is used. However, studies have shown that the timing of the second dose is not critical. Efficient boosting still occurs when the second dose is given up to 6 years after the first. Geometric mean titres (GMTs) at 1-month post-booster of 2993 and 3342 IU/L were obtained in travellers given boosters 24–66 months after the primary dose in two separate trials,^[13,14] compared with, respectively, 4383 and 4775 IU/L if the second dose was offered at month 6 or 12.^[15]

4. Coadministration

Another problem often faced by the last-minute traveller is the need for multiple, rather than single vaccinations. This is

especially true for travellers to developing countries in which several infectious diseases may be endemic. Fortunately, the hepatitis A vaccine can be safely coadministered with a number of other vaccines. It does not affect the immunogenicity or tolerability of vaccines against tetanus, diphtheria, rabies, yellow fever, typhoid fever, Japanese encephalitis or hepatitis B.^[16–18] For those countries in which both hepatitis A and B are endemic, travellers have the option of a combined vaccine, Twinrix[®] (GlaxoSmithKline Biologicals, Rixensart, Belgium), which has immunogenicity and safety equivalent to those of each vaccine administered separately.^[19–21] There is also a dual hepatitis A/typhoid vaccine (Hepatyrix[®]; GlaxoSmithKline Biologicals, Rixensart, Belgium), which was developed for the convenience of the traveller because of the similar geographic distribution of the two diseases. Again, this is a vaccine with a good safety profile that offers consistent and rapid immunogenicity.

5. Duration of Protection

For those persons who travel frequently, the duration of protection offered by hepatitis A vaccination is important. According to a study in 115 healthy adults, the vaccine remained effective 10 years after its administration. All 33 subjects available for testing had protective antibody titres and a GMT of 501 IU/L at this time (figure 2).^[22] Furthermore, a GMT of 242 IU/L was observed in 31 subjects 12 years after vaccine administration.^[23] Although these studies looked specifically at Havrix 720[®], assessments of other hepatitis A vaccines have demonstrated similar results.^[24–27] All these findings appear to substantiate a mathematical model for anti-HAV antibody kinetics developed by Van Herck et al. that estimated antibody persistence for 20–25 years.^[28]

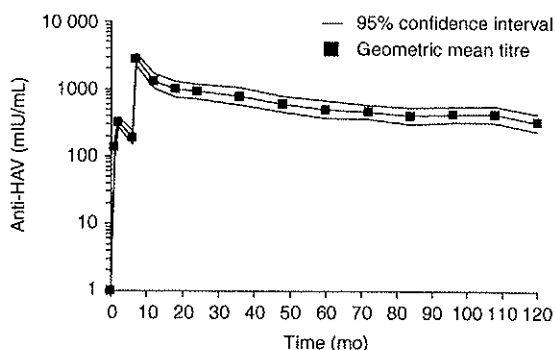


Fig. 2. Long-term persistence of anti-hepatitis A virus (HAV) antibodies after vaccination with Havrix 720[®] EL.U (ELISA Units); schedule 0–1–6 months (geometric mean titres in IU/L).^[22]

6. Conclusions

There is now substantial evidence that the official recommendations for immunisation against hepatitis A in the last-minute traveller should be rewritten. Indications from rapid outbreak control studies and those dealing with post-exposure administration suggest that late vaccination still provides a significant degree of protection. In particular, the 2-week seroconversion experienced by most vaccinees is within the incubation period of the virus, but more research is needed to determine an accurate post-exposure window. For these reasons, if travellers cannot be vaccinated in a timely manner, then the first dose of hepatitis A vaccine should still be given at any possible time before departure, even up to their day of travel, as this will still provide travellers with protection.

In terms of flexibility, the timing of the second dose is not critical, meaning that last-minute travellers do not need to try and obtain a booster during their travels, but can wait some time without having to start a new schedule. Travel physicians should also emphasise that the protection acquired for such a short time investment is substantial, generating at least 20–25 years or more of shielding against hepatitis A. Furthermore, the safety and efficacy of the vaccine means that several convenient coadministration options are available. Hepatitis A vaccination provides rapid protection, flexible administration and long-term benefits, and should be considered the prophylaxis of choice for the last-minute traveller over immune globulins.

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K. Van Herck and P. Van Damme are employees of the University of Antwerp and have been principal investigators of many vaccine trials for several vaccine manufacturers.

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Correspondence and offprints: Dr Bradley A. Connor, The New York Center for Travel and Tropical Medicine, 50 East 69th Street, New York, NY 10021, USA.
E-mail: bconnor@travelhealth.net