

# Rapid and Sustained Immune Response Against Hepatitis A and B Achieved With Combined Vaccine Using an Accelerated Administration Schedule

Bradley A. Connor, MD,\*† Mark M. Blatter, MD,‡ Jiri Beran, MD,§ Bin Zou, MD,|| and Andrew F. Trofa, MD||

\*Division of Gastroenterology and Hepatology, The Weill Medical College of Cornell University, New York, NY, USA; †The New York Center for Travel and Tropical Medicine, New York, NY, USA; ‡Primary Physicians Research, Pittsburgh, USA; §Department of Infectious Diseases, Vaccination and Travel Medicine Centre, Hradec Kralove, Czech Republic; ||GlaxoSmithKline Biologicals, King of Prussia, PA, USA

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**Background.** Combined hepatitis A and B vaccine administered on an accelerated schedule provides a rapid immune response against both hepatitis A and B viruses, which might be especially relevant for individuals who need protection quickly.

**Methods.** A prospective, open-label, randomized study to compare the immunogenicity and reactogenicity of the combined hepatitis A and B vaccine Twinrix (GlaxoSmithKline Biologicals, Rixensart, Belgium) ( $\geq 720$  EL.U/mL inactivated hepatitis A antigen and 20  $\mu\text{g}/\text{mL}$  recombinant hepatitis B surface antigen [HBsAg]) administered at 0, 7, 21 to 30 days, and 12 months compared with concurrent administration of Havrix [GlaxoSmithKline Biologicals, Rixensart, Belgium ( $\geq 1440$  EL.U/mL inactivated hepatitis A antigen)] at 0 and 12 months, and Engerix-B [GlaxoSmithKline Biologicals, Rixensart, Belgium (20  $\mu\text{g}/\text{mL}$  recombinant HBsAg)] at 0, 1, 2, and 12 months in seronegative healthy adults.

**Results.** At month 13, the anti-hepatitis B seroprotection rates ( $>10$  mIU/mL) for the combined vaccine compared to the monovalent hepatitis B vaccine were 96.4% (95% CI: 92.7–98.5) and 93.4% (95% CI: 89.0–96.4), respectively. The anti-hepatitis A seroconversion rates were 100% in both groups (95% CI: 98.1–100). At day 37, the anti-hepatitis A seroconversion rates were similar in both groups (98.5% for combined vaccine, 98.6% for the monovalent vaccine group), but the combined vaccine resulted in a statistically significantly ( $p < 0.001$ ) better anti-hepatitis B seroprotection compared to monovalent hepatitis B vaccine, 63.2% versus 43.5%, respectively. The reactogenicity profile was similar in both study groups.

**Conclusions.** The combined hepatitis A and B vaccine administered on an accelerated schedule was at least as immunogenic and as well tolerated as the corresponding monovalent vaccines.

Viral hepatitis is a worldwide health problem; hepatitis A and B viruses (HAV and HBV) account for the majority of cases. In 2003, the US national incidence of hepatitis A and hepatitis B was 2.6 cases per 100,000 people for each virus.<sup>1</sup> Worldwide, approximately 1.5 million cases of hepatitis A are reported every year,<sup>2,3</sup> and HBV has infected 2 billion people (one third of the world's population),

resulting in 350 to 450 million carriers worldwide and 500,000 to 1.2 million deaths per year caused by cirrhosis and primary hepatocellular carcinoma.<sup>4-6</sup> Extensive regions throughout the world are endemic for these viruses, and many international travelers may be at risk for contracting hepatitis A or hepatitis B.<sup>7</sup> In addition to travel, persons may be at risk for both diseases because of employment, institutionalization, or lifestyle factors.

Safe and effective monovalent vaccines against hepatitis A and hepatitis B are available.<sup>8-13</sup> Convenience may be enhanced by the use of a combined hepatitis A and B vaccine (Twinrix, GlaxoSmithKline Biologicals, Rixensart, Belgium), which has

**Corresponding Author:** Andrew Trofa, MD, GlaxoSmithKline Biologicals, 2301 Renaissance Boulevard RN 0220, King of Prussia, PA 19406. E-mail: andrew.f.trofa@gsk.com

been licensed in Europe since 1996 and in the United States since 2001.

Hepatitis A vaccines are administered as two doses given 6 to 18 months apart. For hepatitis B vaccines, the usual schedule is three doses over 6 months. Current dosing schedules mean that some people, such as those traveling to endemic areas at short notice, those facing imminent exposure because of behavioral risks or incarceration, or emergency responders to disaster areas, may receive only a single dose of hepatitis A or hepatitis B vaccine before exposure. Studies have demonstrated that the combined hepatitis A and B vaccine offers anti-hepatitis B surface antigen (HBs) seroprotection and anti-HAV seroconversion at least equivalent to the corresponding monovalent vaccines.<sup>14-16</sup> Although single doses of the hepatitis A vaccine may induce an immune response in most people, and accelerated schedules for hepatitis B exist, combination hepatitis A and B vaccines may offer benefit in persons needing rapid protection against both diseases.<sup>17,18</sup>

This study was designed to compare the immunogenicity and reactogenicity of an accelerated dosing schedule (0, 7, and 21-30 d, and 12 mo) using a combined hepatitis A and B vaccine (Twinrix) on an alternate schedule with the corresponding monovalent vaccines [Havrix (GlaxoSmithKline Biologicals, Rixensart, Belgium) at 0 and 12 mo, and Engerix-B (GlaxoSmithKline Biologicals, Rixensart, Belgium) at 0, 1, 2, and 12 mo].

## Methods

### Protocol

The protocol was approved by the Institutional Review Boards of the participating centers, and the study was conducted in accordance with good clinical practice and the Declaration of Helsinki (Somerset West, 1996 version). Written informed consent was obtained from each subject prior to the performance of any study-specific procedures.

### Study Design

This was a prospective, open-label, randomized, multicenter (12 centers), comparative study conducted in the United States, Norway, Belgium, and the Czech Republic between March 2003 and May 2005, which included a 6-month safety follow-up phase following the administration of the last dose. Subjects were randomized (1:1) to one of two groups: group 1 comprised subjects who received the combined hepatitis A and B vaccine, Twinrix ( $\geq 720$  EL.U/mL inactivated hepatitis A antigen and 20  $\mu\text{g}/\text{mL}$  recombinant hepatitis B surface antigen

[HBsAg]) at 0, 7, 21 to 30 days, and 12 months; and group 2 comprised subjects who received separate injections of the hepatitis A vaccine, Havrix ( $\geq 1,440$  EL.U/mL inactivated hepatitis A antigen) at 0 and 12 months, and the hepatitis B vaccine, Engerix-B (20  $\mu\text{g}/\text{mL}$  recombinant HBsAg) at 0, 1, 2, and 12 months, respectively. All vaccines were given intramuscularly in the deltoid muscle (right side for Havrix and left side for Engerix-B and Twinrix).

Subjects were screened for HBsAg and for antibodies to HAV, HBs, and hepatitis B core (HBc) antibodies before the first dose of vaccine. For group 1 subjects, additional blood samples for anti-HAV and anti-HBs antibodies were drawn at days 7, 14, 21 to 30, and 37, and months 3, 12, and 13. For group 2 subjects, blood samples were taken on days 14, 30, and 37, and months 3, 12, and 13. After study entry, all blood samples taken after vaccination were analyzed by the GlaxoSmithKline Biologicals laboratories in Rixensart, Belgium. Quantitative enzyme immunoassays were used to test for anti-HAV (anti-HAV Behring) and anti-HBs (AUSAB/Abbott).

### Study Population

Subjects were healthy adults (aged  $\geq 18$  years) who were seronegative for anti-HAV, anti-HBs, and anti-HBc antibodies, and for HBsAg. Pregnancy was an exclusion criterion and female subjects were required to be of non-childbearing potential or required to use adequate contraception. Other exclusion criteria included a history of hepatitis A or B, exposure to hepatitis A or B (confirmed by serology at screening), and previous hepatitis A or B vaccination.

### Immunogenicity Assessments

The primary study objective was to demonstrate that the immunogenicity of the combined hepatitis A and B vaccine was not inferior to that of the monovalent vaccines with respect to seroprotection rate against HBsAg, seroconversion rate for anti-HAV, and anti-HBs and anti-HAV geometric mean antibody concentrations (GMC) measured at month 13, 1 month after the last dose of vaccine. Secondary objectives included safety and assessment of anti-HBs seroprotection and seroconversion rates for anti-HAV antibodies at all other blood-sampling time points.

Seropositivity rate for anti-HAV antibodies was defined as the percentage of subjects with antibody concentrations of  $\geq 15$  mIU/mL and for anti-HBs  $\geq 3.3$  mIU/mL. Seropositivity rate for anti-HAV antibodies was considered equivalent to seroconversion rate as all enrolled subjects were seronegative at study entry. Seroprotection rate for anti-HBs

antibodies was defined as the percentage of subjects with antibody concentrations of  $\geq 10$  mIU/mL.

#### Reactogenicity and Safety Assessments

Adverse events (AEs) were recorded throughout the study. Subjects recorded solicited AEs on diary cards during a 4-day post-vaccination follow-up. Solicited AEs were graded 1 to 3, with grade 3 representing a severe AE. Redness and swelling were scored by measuring the longest diameter (in mm) and classified as severe at a diameter  $> 50$  mm. Fever  $> 39^\circ\text{C}$  was classified as severe, as were other solicited AEs that prevented normal daily activities. During the 6-month safety follow-up, serious adverse events (SAEs) were recorded.

#### Statistical Analysis

Safety was analyzed on the total vaccinated population, which included all subjects with at least one vaccine administration. Immunogenicity was analyzed on the according-to-protocol (ATP) cohort, which included all evaluable subjects (ie, those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria assigned to them, and who had data available for immunogenicity end-point measures).

Determination of statistical power was based on the primary end points. A total of 204 evaluable subjects per group was needed to achieve an overall power of 90% to reach all primary objectives simultaneously. A total of 240 subjects per group were planned to allow for 15% dropout rate. For the primary objectives at month 13, noninferiority of the combined hepatitis A and B vaccine compared to the monovalent vaccines with respect to anti-HBs seroprotection rates and anti-HAV seroconversion rates would be concluded if the upper limit of the two-sided standardized asymptotic 95% confidence intervals (CIs) for the difference between groups Havrix + Engerix-B group minus the Twinrix group was lower than the predefined noninferiority limit of 7%. For anti-HBs antibody GMC and anti-HAV antibody GMC, combined hepatitis A and B vaccine was considered noninferior to monovalent vaccines if the upper limit of 95% CI for the ratios of GMCs (the Havrix + Engerix-B group divided by the Twinrix group) at month 13 was lower than the predefined noninferiority limit of 2.

## Results

#### Study Population and Disposition

A total of 496 subjects (group 1,  $n = 250$ ; group 2,  $n = 246$ ) were enrolled in the study: 253 enrolled

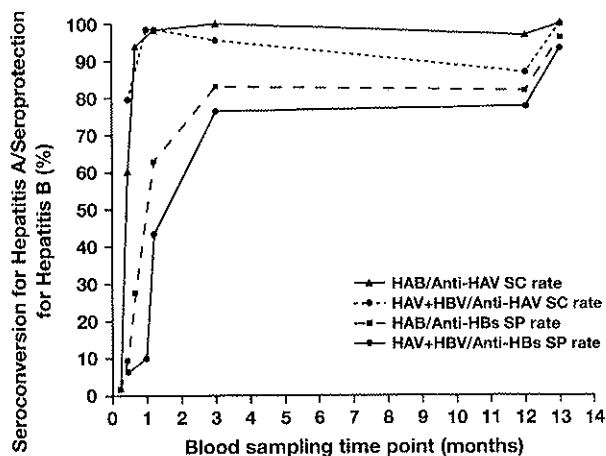
in the United States and 243 in the European Union. Baseline demographic characteristics were similar in the two groups.

#### Immunogenicity

Anti-HBs and anti-HAV immunoresponse data at all time points are summarized in Figure 1 and Table 1. There were no major differences in immunoresponse between the total vaccinated cohort and the ATP population at any time point for any of the vaccines.

#### Anti-HBs Response

At month 13, seroprotection rates in both groups were over 93%. Because the upper limit of the standardized asymptotic two-sided 95% CI on the difference between the groups, 1.49%, was less than the predefined limit of 7%, noninferiority could be concluded. Rates were comparable between groups at all other matched time points except for day 37, where the combined vaccine demonstrated a significantly ( $p < 0.001$ ) better response (Table 1). At this time point, seroprotection was achieved in 129 subjects (63.2%) in the combined vaccine group compared with 90 subjects (43.5%) in the monovalent vaccine group. At month 13, noninferiority of the anti-HBs GMC ratio was demonstrated (Table 2).



**Figure 1** Seroprotection rates for anti-hepatitis B surface antigen antibodies and seroconversion rates for anti-hepatitis A virus after vaccination with combined hepatitis A and B vaccine (Twinrix) or separately administered monovalent vaccines (Havrix + Engerix-B) over time (according-to-protocol immunogenicity cohort). Seroconversion for anti-HAV antibodies was defined as an antibody concentration  $\geq 15$  mIU/mL; seroprotection for anti-HBs antibodies was defined as an antibody concentration  $\geq 10$  mIU/mL. SC = seroconversion; SP = seroprotection.

**Table 1** Anti-HAV seroconversion rate and anti-HBs seroprotection rate after vaccination with combined hepatitis A and B vaccine (Twinrix) or separately administered monovalent vaccines (Havrix + Engerix-B) (according-to-protocol immunogenicity cohort)

	Group 1: Twinrix, N(%)	Group 2: Havrix + Engerix-B, N(%)	p Value	Difference: group 2–group 1, % (95% confidence interval)
SC for anti-HAV				
Day 37	204 (98.5)	207 (98.6)	1.000	0.02 (–2.88 to 2.95)
Month 3	203 (100.0)	206 (95.60)	0.004	–4.37 (–8.09 to –2.32)
Month 12	195 (96.9)	198 (86.9)	<0.001	–10.05 (–15.82 to –4.93)
Month 13	194 (100.0)	197 (100.0)	1.000	0.00 (–1.91 to 1.94)
SP for anti-HBs				
Day 37	204 (63.2)	207 (43.5)	<0.001	–19.76 (–28.99 to –10.16)
Month 3	202 (83.2)	206 (76.7)	0.110	–6.47 (–14.25 to 1.32)
Month 12	195 (82.1)	198 (77.8)	0.315	–4.27 (–12.22 to 3.69)
Month 13	194 (96.4)	197 (93.4)	0.251	–2.99 (–7.80 to 1.49)

Seroconversion for anti-HAV antibodies was defined as an antibody concentration  $\geq 15$  mIU/mL; seroprotection for anti-HBs antibodies was defined as an antibody concentration  $\geq 10$  mIU/mL. Twinrix: 0, 7, 21 to 30 d, and 12 mo; Havrix: 0 and 12 mo; Engerix-B: 0, 1, 2, and 12 mo. Anti-HAV = anti-hepatitis A virus; anti-HBs = anti-hepatitis B surface antigen; SC = seroconversion; SP = seroprotection.

The upper limit of the 95% CI for the anti-HBs GMC ratio (the Havrix + Engerix-B vaccine group divided by the Twinrix vaccine group) was 0.98, which was lower than the predefined clinical limit for noninferiority of 2.

#### Anti-HAV Response

Rates were comparable between groups at all other matched time points except for months 3 and 12, when the combined vaccine demonstrated a significantly ( $p < 0.05$  and  $p < 0.001$ ) better response (Table 1). Noninferiority of the Twinrix vaccine administered on an alternate schedule compared to the Havrix + Engerix-B vaccine group with respect to the anti-HAV seropositivity rates at month 13 was demonstrated: the upper limit of the standardized asymptotic two-sided 95% CI for the difference between the Havrix + Engerix-B vaccine group and (minus) the Twinrix vaccine group was 1.94%,

which was less than the predefined clinical limit for noninferiority of 7%. Noninferiority was also demonstrated with respect to the anti-HAV GMCs. The upper limit of the 95% CI for the anti-HAV GMC ratio (Havrix + Engerix-B vaccine group divided by the Twinrix vaccine group) was 0.56, which was lower than the predefined clinical limit for noninferiority of 2.

#### Reactogenicity

Reactogenicity data for the 4-day postvaccination period (days 0–3) were obtained from subject symptom diary cards, with 2,001 doses of vaccines administered in 496 subjects. Overall, 65.6% of the subjects in the Twinrix group and 67.9% in the Havrix + Engerix-B vaccine group reported at least one local symptom. General symptoms were also reported with similar frequency in the Twinrix (58.0%) and the Havrix + Engerix-B vaccine groups

**Table 2** Antibodies to anti-HAV and anti-HBs GMC after vaccination with combined hepatitis A and B vaccine (Twinrix) or separately administered monovalent vaccines (Havrix + Engerix-B) (according-to-protocol immunogenicity cohort)

	Group 1: Twinrix		Group 2: Havrix + Engerix-B		p Value	GMC ratio: group 2/group 1, ratio (95% confidence interval)
	N	Value	N	Value		
GMC for anti-HAV						
Day 37	204	454.6	207	241.7	<0.001	0.53 (0.43–0.66)
Month 3	203	480.6	206	120.7	<0.001	0.25 (0.21–0.31)
Month 13	194	7110.5	197	3235.7	<0.001	0.46 (0.37–0.56)
GMC for anti-HBs						
Day 37	204	15.7	207	7.5	<0.001	0.48 (0.33–0.69)
Month 3	202	53.4	206	52.2	0.908	0.98 (0.65–1.46)
Month 13	194	7648.1	197	4380.9	0.044	0.57 (0.33–0.98)

Twinrix: 0, 7, 21 to 30 d, and 12 mo; Havrix: 0 and 12 mo; Engerix-B: 0, 1, 2, and 12 mo. Anti-HAV = anti-hepatitis A virus; anti-HBs = anti-hepatitis B surface antigen; GMC = geometric mean concentration.

(60.6%). Furthermore, no trends were seen in the proportion of doses followed by general solicited symptoms (fatigue, gastrointestinal, headache, fever) (Table 3). Fatigue was the most common of these general solicited symptoms, and fever was reported in only a small number of subjects. In both groups, grade 3 general solicited symptoms were rarely reported (0.2%–1.2% of doses).

Overall, similar numbers of doses in each group were followed by at least one unsolicited AE in the 30-day postvaccination period: combined vaccine group, 12.5% (95% CI: 10.5–14.7) and Havrix + Engerix-B, 14.5% (95% CI: 12.3–16.9). Unsolicited symptoms were rarely assigned by the investigators to be causally related to vaccination: 2.2% (95% CI 1.3–3.3) for Twinrix and 3.3% (95% CI: 2.2–4.6) for Havrix + Engerix-B.

During the active phase of the study, 22 SAEs were reported in 12 subjects: three subjects in the Twinrix group reported 1 SAE each and nine subjects in the Havrix + Engerix-B group reported a total of 19 SAEs. In the 6-month safety follow-up phase, 16 SAEs in 14 subjects (eight subjects in the Twinrix group and six in the Havrix + Engerix-B group) were collected. No SAEs were considered causally related to vaccination.

## Discussion

Vaccination with the combined hepatitis A and B vaccine (Twinrix) administered on a 0, 7, and 21 to 30 days schedule plus booster at 12 months was at least as immunogenic as equivalent monovalent vaccines 1 month after completion of the respective schedules (Havrix: 0 and 12 months; Engerix-B: 0, 1, 2, and 12 mo). At day 37, after the first doses of vaccines, seroprotection for anti-HBs antibodies was significantly ( $p < 0.001$ ) better with combined hepatitis A and B vaccine than with monovalent vac-

cines. This improvement is likely attributable to the accelerated schedule, consistent with published results from studies with monovalent hepatitis B vaccines,<sup>19,20</sup> but could also relate to the higher rates of seroprotection against hepatitis B seen with combined versus monovalent vaccines.<sup>15,21</sup> Seroconversion for anti-HAV antibodies approached 100% for combined and monovalent vaccines at this time point. Both schedules were similarly well tolerated. Excellent immunogenicity and tolerability with the combined vaccine have been shown in previous studies,<sup>15,22,23</sup> with similar immunogenicity and reactogenicity profiles observed between conventional and accelerated schedules with the combined hepatitis A and B vaccine.<sup>17,18,24</sup> In particular, local and general symptoms reported in the current study were consistent with those reported previously for both the combined vaccine (Twinrix) and for the monovalent vaccines (Havrix and Engerix-B) administered concurrently.<sup>15,21,25</sup>

Both hepatitis A and hepatitis B should be considered travelers' diseases because risk factors (eg, sexual exposure) and endemicity may overlap.<sup>26</sup> For international travelers to areas endemic for both hepatitis A and hepatitis B, the risk for hepatitis A and B infection may not be solely dependent on length of stay as short-term travelers can also be at risk.<sup>27,28</sup> Transmission of HAV can readily occur via contaminated food and water,<sup>2</sup> whereas HBV can be transmitted by sexual contact<sup>29</sup> or by exposure to invasive medical procedures, and skin-perforating cosmetic procedures.<sup>30,31</sup> Studies have shown 10% to 15% of persons are voluntarily or involuntarily exposed to blood and bodily fluids when traveling abroad.<sup>30,32</sup>

Only a minority of American adults has acquired immunity to hepatitis A or B, and many travelers may be unaware of, or unwilling to discuss, high-risk behaviors. Vaccination can help protect

**Table 3** Incidence of solicited symptoms reported during 4-day post-vaccination period by dose overall

	Symptoms overall/dose % (95% CI)		
	Group 1	Group 2	
	Twinrix (N = 962)	Havrix (N = 467)	Engerix-B (N = 939)
Pain	33.0 (30.0–36.0)	36.2 (31.8–40.7)	26.8 (24.0–29.8)
Redness	11.3 (9.4–13.5)	11.6 (8.8–14.8)	8.9 (7.2–11.0)
Swelling	5.1 (3.8–6.7)	3.9 (2.3–6.0)	3.4 (2.3–4.8)
	Twinrix (N = 962)	Havrix + Engerix-B (N = 940)	
Fatigue	18.6 (16.2–21.2)	21.0 (18.4–23.7)	
Gastrointestinal	7.5 (5.9–9.3)	6.7 (5.2–8.5)	
Headache	14.4 (12.3–16.8)	15.1 (12.9–17.6)	
Fever (oral temperature >37.5°C)	0.9 (0.4–1.8)	1.6 (0.9–2.6)	

CI = confidence interval; N = number of doses for which a symptom sheet was available.

against the risks of both hepatitis A and B.<sup>26</sup> Furthermore, an accelerated schedule with combination vaccines may enhance adherence to, and completion of, vaccination schedules.<sup>18</sup> An accelerated schedule with combined hepatitis A and B vaccine, which has been used in the European Union for almost a decade, may benefit the last minute traveler who cannot adhere to the schedules for the currently available monovalent vaccines.

Previous studies of combined hepatitis A and B vaccine have shown good levels of HBV seroprotection and HAV seroconversion on completion of the full schedule.<sup>14,15,17,22,24</sup> On an accelerated schedule, three doses of the combined hepatitis A and B vaccine will have been received by 1 month, rather than only two doses by the currently licensed US schedule for the combined vaccine. The accelerated schedule has the advantage of requiring less time between doses and may reduce the likelihood of nonadherence to the vaccine schedule. In addition, the accelerated schedule provides a favorable option for those at imminent risk for hepatitis A and B, such as the last minute traveler, prison inmates, military personnel, and first responders in disaster situations. Furthermore, the benefits of the accelerated schedule are most apparent by 37 days in the current study, when 20% more subjects achieved seroprotection for anti-HBs antibodies with combined hepatitis A and B vaccine than with monovalent vaccines, and seroconversion for anti-HAV antibodies approached 100%. Previous investigators have highlighted the benefits of the accelerated schedule with combined hepatitis A and B vaccine at 1 month.<sup>33</sup> It is important that the fourth (booster) dose of combined vaccine is offered at 12 months to provide long-term protection against hepatitis A and hepatitis B, although doing so may be more of a challenge with respect to prison inmates or intravenous drug users than for either travelers or healthcare workers.

The results of this study demonstrate that combined hepatitis A and B vaccine on a 0, 7, and 21 to 30-day schedule with booster injection at 12 months provides equivalent levels of seroconversion/seroprotection for hepatitis A and B, with a reactogenicity profile similar to monovalent vaccines. Furthermore, at day 37, seroprotection and GMCs for anti-HBs were significantly ( $p < 0.001$ ) better for combined hepatitis A and B vaccine than monovalent vaccines. Therefore, a combined hepatitis A and B vaccine administered according to an accelerated vaccination schedule may represent the preferred option for individuals at imminent risk

for hepatitis A and hepatitis B. These include travelers to countries endemic for hepatitis A and hepatitis B, prison inmates, military personnel, emergency care first responders to disaster areas, persons with high-risk sexual behavior, and intravenous drug users.

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### Declaration of Interests

M. M. B. received speakers fees from Sanofi and GlaxoSmithKline Biologicals. B. Z. is an employee of GlaxoSmithKline Biologicals. A. F. T. is an employee of GlaxoSmithKline Biologicals. The other authors state that they have no conflicts of interest.

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