Schedules for hepatitis B vaccination of risk groups: balancing immunogenicity and compliance

K Van Herck, E Leuridan, P Van Damme

See end of article for authors' affiliations

Sex Transm Infect 2007;**83**:426–432. doi: 10.1136/sti.2006.022111

Correspondence to: Koen Van Herck, MD, PhD, Postdoctoral Fellow of the Research Fund Flanders (FWO), Centre for the Evaluation of Vaccination, Under the Patronage of Her Royal Highness Princess Mathilde, WHO Collaborating Centre for Prevention and Control of Viral Hepatitis, Department Epidemiology and Social Medicine, University of Antwerp, Campus Drie Eiken, Universiteitsplein 1, S5.25a, B-2610 Antwerp, Belgium; koen.vanherck@ua.ac.be

Accepted 1 August 2007

Introduction: Vaccination is an important tool in hepatitis B prevention. However, several vaccine doses are required to induce long-term protection. Several at-risk groups have difficulties in adhering to the standard vaccination schedule.

Objectives: This paper aims to review the use of accelerated hepatitis B vaccination schedules, in terms of immunogenicity and compliance.

Results: Accelerated schedules (0.1.2.12 months) or super-accelerated schedules (0.7.21.360 days) have been shown to result in higher proportions of healthy vaccinees reaching anti-HBs antibody levels ≥ 10 IU/l more rapidly. A fourth completing dose is required to lift antibody levels to an equal height, as does a standard (0.1.6 months) schedule.

Accelerated schedules do also increase the uptake of hepatitis B vaccine, that is the proportion of vaccinees who receive three doses. However, completing the schedule with a fourth dose is usually more difficult than completing a standard 0.1.6-month schedule. Several additional tools can help to increase the compliance (eg, reminder systems, outreach services and incentive schemes).

Conclusion: For rapid seroconversion and almost immediate protection in the short term, a (super)accelerated schedule could be used in at-risk groups. As long-term protection data with these (super) accelerated schedules have not been documented yet, a fourth dose at month 12 is still required. A shortened schedule (0.1.4 months) might be an alternative worth considering compared with the standard 0.1.6, as it convenes to internationally accepted minimum dose intervals and offers earlier protection. There is a clear need to study the long-term protection and effectiveness of the primary part of (super)accelerated schedules.

In 1992, the Global Advisory Group of the Expanded Programme on Immunisation (World Health Organization, WHO) set 1997 as the target for integrating hepatitis B virus (HBV) vaccination into national immunisation programmes worldwide.¹ Even if it was estimated that more than one-half of the world's infants were still not being immunised in 1999, substantial progress in implementing that WHO recommendation has been made since. By the end of 2005, 168 countries worldwide had implemented or were planning to implement a universal HBV immunisation programme for infants and/or adolescents.^{2,3}

Apart from the above-mentioned universal immunisation programmes, several risk groups are targeted by hepatitis B vaccination programmes. These groups are either at increased risk of HBV infection or at increased risk of complications in case an HBV infection were to occur.⁴ Unfortunately, despite the longstanding existence of recommendations, it often remains difficult to reach at-risk groups due to a combination of factors, including lack of perceived risk and the limited presence of specific healthcare programmes targeting certain risk groups (in particular sex workers, injecting drug users, and prisoners). Moreover, even if they can be reached, those who engage in high-risk behaviour often fail to complete the required vaccination regimen for hepatitis B.⁵

Whenever hepatitis B immunisation programmes targeting such at-risk groups are implemented or evaluated, the choice of the most efficient vaccination schedule is an important issue. After all, the standard hepatitis B vaccination schedule might need to be adapted, either to increase the probability of completing the vaccination in groups with limited compliance, to offer protection as soon as possible after starting the vaccination schedule, or to better fit this vaccination programme into existing vaccination or other preventive programmes in that

specific at-risk population. It is beyond doubt that any adaptations should aim to optimise the compliance to the immunisation programme, while maintaining the vaccine's immunogenicity and efficacy. Since people in these at-risk populations most often continue to be at risk, long-term protection against hepatitis B is highly important.

This paper aims to review the evidence on (accelerated) hepatitis B vaccination schedules for risk groups: those at increased risk of sexual HBV transmission (including men who have sex with men, sex workers, and attendees of STI clinics), injecting drug users, inmates and staff of correctional facilities and prisons, and travellers to areas of intermediate or high endemicity.

METHODOLOGY

The search strategy for this review consisted of the keywords ("hepatitis B" AND vaccine* AND schedule* AND accelerate*). Multiple databases were searched: BioMedCentral, the Cochrane Library, all Evidence Based Medicine reviews (Ovid), and Medline (National Library of Medicine's PubMed online search engine and Ovid Medline). The internet search engine Google was used with the same set of keywords AND "guideline" to additionally identify a number of guidelines regarding hepatitis B vaccination.

Searches were performed in February 2007, without any restrictions (eg, with regard to the year of publication or language). Related articles were assessed, and the reference lists of the retrieved articles were also used to identify related literature.

Retrieved papers were included in this review only if they described the immunogenicity and/or compliance for a stan-

Abbreviations: HBV, hepatitis B virus; WHO, World Health Organization

dard and/or altered hepatitis B vaccination regimen in healthy adolescents, healthy adults or one of the above-mentioned risk groups. Papers addressing hepatitis B vaccination in groups with specific medical conditions requiring additional efforts to improve the immunogenicity of routinely used hepatitis B vaccines (eg, haemodialysis patients, liver transplant candidates, immunosuppressed patients) were not included in this review. Alterations in hepatitis B vaccination schedules included modification of vaccine dosage and shortening of the interval between vaccine doses.

RESULTS

Existing vaccination schedules

Worldwide, the standard schedule for vaccination of healthy children, adolescents and adults against hepatitis B consists of three doses, given according to a 0.1.6-month vaccination schedule. However, the timing of the third dose allows substantial flexibility. The US Centers for Disease Control and Prevention recommend for adolescents and adults a minimal interval of 16 weeks between the first and the third dose of hepatitis B vaccine (and 8 weeks between dose 2 and dose 3), which allows the schedule to be shortened to 0.1.4 months. Conversely, in case the administration of the third dose were to be delayed, the complete schedule does not need to be restarted.⁶

Testing to determine antibody responses is not routinely recommended after routine vaccination of infants and adolescents. However, when feasible, knowledge of response to vaccination is important in the following groups: (1) all above-mentioned risk groups; (2) persons at risk of occupational HBV exposure; (3) infants born to HBsAg-positive mothers; (4) immunocompromised persons; and (5) sexual partners of HBsAg-positive persons. Testing for anti-HBs should be performed by a method that allows determination of whether the anti-HBs concentration is ≥ 10 IU/l. Adults should be tested 1–3 months after completion of the vaccination series. Persons found to be antibody-negative after the primary series should be referred for appropriate follow-up.⁷ Lifelong protection is assumed in healthy, fully vaccinated infants, children, adolescents or adults—the last, however, should be tested after the complete vaccination series, to demonstrate a seroprotective anti-HBs level.⁸ Seroprotection is defined as achieving an anti-HBs titre above or equal to 10 IU/l, measured 1–3 months after a completed immunisation schedule (ie, 0.1.6 or 0.1.2.12 months).

The need for accelerated vaccination schedules against hepatitis B is well recognised for specific at-risk groups. Several schedules have been investigated to enhance the compliance or to reach protective levels of antibodies earlier without cutting on the immunogenicity of hepatitis B vaccination. In high-risk situations, where one aims to offer protection against hepatitis B as rapidly as possible, the following alternative vaccination schedules may be considered: either 0.1.2.12 months or 0.7.21.360 days. It should be noted that both accelerated schedules require the administration of a fourth dose of vaccine, 1 year after starting the vaccination. The administration of this fourth dose of hepatitis B vaccine in case an accelerated schedule is used is consistently present in a number of recommendations and guidelines from both national and international Public Health Organisations, and organisations of clinicians, in several countries.^{6, 7, 9–16}

Immunogenicity and effectiveness/efficacy of the standard vaccination schedule

A complete vaccination course in healthy infants, children, and adolescents results in seroprotective anti-HBs levels in over 95% of vaccinees. In adults below the age of 40, this is slightly lower

(yet still more than 90%), to reach 65–75% by the age of 60 years. Decreased vaccine response is associated with smoking, obesity, genetic factors, chronic diseases and immune disorders.⁴

During the vaccination course, 30–55% of healthy adults below the age of 40 years reach the seroprotective anti-HBs level after the first dose, mounting to 75% after the second dose and over 90% after the third dose.⁴

Pre-exposure hepatitis B vaccine efficacy studies in several high-risk groups have demonstrated an overall efficacy of 80–100%, with nearly 100% efficacy in persons who developed a seroprotective anti-HBs response (≥ 10 IU/l).⁴

Immunogenicity and effectiveness/efficacy of accelerated vaccination schedules in different populations (table 1)

Healthy adolescents

Few studies have examined the use of accelerated hepatitis B vaccination schedules in adolescents. Nevertheless, since the immunogenicity of many vaccines, including hepatitis B vaccines, is higher in younger persons, the results of studies in healthy adults can safely be extrapolated to younger age groups.⁴

In a study by Chowdhury *et al*, 100% of vaccinated adolescents reached an anti-HBs level ≥ 10 IU/l, 1 month after the primary part of an accelerated vaccination schedule (0.1.2 months), with two different vaccines.¹⁷ Wilkinson *et al* described similar results in a small group of high-risk youth.¹⁸ In another study in healthy children, Bosnak and co-workers concluded that 1 month after administering the primary part of a super-accelerated schedule (0.7.21 days) similar rates of anti-HBs levels ≥ 10 IU/l were reached, when compared with the standard 0.1.6-month schedule. However, the proportion of vaccinees attaining 10 IU/l was higher within the first 2–3 months after dose 1. No data on the magnitude of anti-HBs levels were reported.¹⁹ Cassidy *et al* studied a shortened standard schedule (0.2.4 months), which resulted in a similar seroprotection rate as the standard schedule (0.1.6 months) 1 month after completion, but with remarkably lower antibody levels.²⁰

Healthy adults

Jilg *et al* clearly demonstrated in a study comparing a primary part of an accelerated (0.1.2 months) schedule with a standard (0.1.6 months) and a prolonged vaccination schedule (0.1.12 months) that a longer interval between the second and the last dose of hepatitis B vaccine resulted in higher anti-HBs levels.²¹ Scheierrmann *et al* reported similar seroprotection rates obtained by the standard (0.1.6 months) and the accelerated (0.1.2.12 months) vaccination schedule, even up to 4 years after the first dose. The accelerated schedule (including the fourth dose) yielded higher antibody levels.²² A study by Marchou *et al* comparing a super-accelerated 0.10.21.365 days to the accelerated 0.1.2.12-month schedule showed a more rapid immune response to the super-accelerated schedule (after 1 month), yet higher antibody levels after three doses when the intervals between doses were larger.²³

Other studies using the first three doses of an accelerated vaccination schedule concluded that seroprotection after the vaccination series was comparable with that obtained by the standard schedule. Accelerated schedules resulted in higher proportions reaching 10 IU/l between 3 and 6 months after the first dose; however, the antibody levels after three doses were markedly lower than with the standard schedule.^{24–28}

With the primary part of different super-accelerated vaccination schedules (three doses given within 3–4 weeks' time) the proportion reaching 10 IU/l after the vaccination series is comparable with that obtained after the standard schedule,

Table 1 Overview of immunogenicity results according to vaccination schedule, in different populations

Ref.	Vaccine brand (antigen dosage*)	Schedule (months†)	Type‡	Population	Age range (years)	Mean age (years)	N	M/F§	Anti-HBs testing (month)	Tested n	≥ 10 IU/l n (%)¶	Anti-HBs geometric mean concentration (IU/l)
18	Engerix-B (20 mcg)	0;1/2;3/2	(A)	High-risk youth	13–20		42	0.56	4.5	14	14 (100)	630
20	Recombivax-HB (5 mcg)	0;1;6	S	Healthy adolescents	11–19	14.2–14.5			1.02–1.22	7	179	177 (99)
20	Recombivax-HB (5 mcg)	0;6	2D	Healthy adolescents	11–19	14.2–14.5			1.02–1.22	7	162	154 (95)
20	Recombivax-HB (10 mcg)	0;4	2D	Healthy adolescents	11–19	14.2–14.5			1.02–1.22	5	187	183 (98)
20	Recombivax-HB (10 mcg)	0;6	2D	Healthy adolescents	11–19	14.2–14.5			1.02–1.22	7	185	180 (97)
20	Recombivax-HB (5 mcg)	0;2;4	SS	Healthy adolescents	11–19	14.2–14.5			1.02–1.22	5	184	178 (97)
19	Engerix-B (10 mcg)	0;1;6	S	Healthy children		5	20	1	6	20	16 (80)	
19	Engerix-B (10 mcg)	0;1/3;3/4	(SA)	Healthy children		5	20	1	6	20	19 (95)	
21	Merck recombinant hepB (10 mcg)	0;1;6	S	Healthy adults		24.4	30	1.14	7	30	30 (100)	5846
21	Merck recombinant hepB (10 mcg)	0;1;2	(A)	Healthy adults		24.7	29	1.42	7	18	17 (94)	207
21	Merck recombinant hepB (10 mcg)	0;1;12	P	Healthy adults		24.6	30	1.14	13	24	23 (96)	19 912
22	Engerix B (20 mcg)	0;1;6	S	Healthy adults		24.3			48	55	54 (98)	204
22	Heptavax (20 mcg)	0;1;6	S	Healthy adults		24.3			48	52	49 (94)	244
22	Engerix B (20 mcg)	0;1;2;12	A	Healthy adults		24.3			48	17	16 (94)	435
22	Heptavax (20 mcg)	0;1;2;12	A	Healthy adults		24.3			48	20	20 (100)	640
29	Engerix-B (20 mcg)	0;1;2	(A)	Healthy adults	18–40	26.6	101	0.66				
29	Engerix-B (20 mcg)	0;1/2;1	(SA)	Healthy adults	18–40	28.3	109	0.45				
29	Engerix-B (20 mcg)	0;1/4;3/4	(SA)	Healthy adults	18–40	26	96	0.60				
23	Gen-Hevac B (20 mcg)	0;1;2;12	A	Healthy adults	18–40	23.5	133	0.48	3	133	122 (92)	175
23	Gen-Hevac B (20 mcg)	0;1/3;3/4;12	SA	Healthy adults	18–40	23.9	137	0.62	1.75	137	96 (70)	22
24	Engerix-B (20 mcg)	0;1;6	S	Healthy adults	>18	27.5	117	0.83	7	107	106 (99)	4264
24	Engerix-B (20 mcg)	0;1;2	(A)	Healthy adults	>18	27	113	0.38	7	98	95 (97)	347
25	Engerix-B (20 mcg)	0;1;2	(A)	Healthy adults			13	1.17	2.5	13	9 (69)	27
25	Engerix-B (20 mcg)	0;1/2;3/2	(A)	Healthy adults			17	1.83	2	17	14 (82)	43
26	Gen-Hevac B (20 mcg)	0;1;2	(A)	Healthy subjects		22.5	30	0.88	2			
26	Gen-Hevac B (20 mcg)	0;1/3;3/4	(SA)	Healthy subjects		25.9	90	0.80	2			
17	Bevac (10 mcg <10 years old; 20 mcg >10 years old)	0;1;2	(A)	General population	5–35			1.05	3		(100)	2628
17	Engerix-B (10 mcg <10 years old; 20 mcg >10 years old)	0;1;2	(A)	General population	5–35			1.47	3		(100)	2273
27	Enivac HB (20 mcg)	0;1;2	(A)	Healthy adults	18–29	110			3			3025
27	Enivac HB (20 mcg)	0;1;2	(A)	Healthy adults	30–39	105			3			2096
27	Enivac HB (20 mcg)	0;1;2	(A)	Healthy adults	40–49	92			3	92	72 (97)	1592
28	Revac B (20 mcg)	0;1;6	S	Students	17–30	23.5	32	0.68	7	32	32 (100)	1237
28	Revac B (20 mcg)	0;1;2	(A)	Students	17–30	23.5	31	1.38	7	31	31 (100)	533
28	Revac B (20 mcg)	0;1	2D	Students	17–30	23.5	26	1.45	7	16	16 (100)	858
38	Engerix-B (20 mcg)	0;1;6	S	Heroin users		25.7	486		7	340	313 (92)	
38	Engerix-B (20 mcg)	0;1;2	(A)	Heroin users		25.7	689		3	474	317 (67)	
50	Engerix-B (20 mcg)	0;1;6	S	Prisoners IVDU			15		7			
50	Engerix-B (20 mcg)	0;1/4;3/4;7	SA	Prisoners IVDU			19		7			
50	Engerix-B (20 mcg)	0;1/4;3/4;7	SA	Prisoners IVDU			566		7	145	97 (67)	27
37	Twinrix	0;1;6	S	Drug users		25.8	34	3.85	8	34	33 (97)	1726
32	Recombivax-HB (10 mcg)	0;1;6	S	Healthy older adults	40+	48.2	58	0.53	7		(90)	536
32	Recombivax-HB (20+10 mcg)	0;6	2D	Healthy older adults	40+	50.9	20	0.67	7		(80)	126
32	Recombivax-HB (20+20 mcg)	0;6	2D	Healthy older adults	40+	48	35	0.59	7		(83)	174
32	Recombivax-HB (40+10 mcg)	0;6	2D	Healthy older adults	40+	50.4	36	0.57	7		(81)	241
32	Recombivax-HB (40+20 mcg)	0;6	2D	Healthy older adults	40+	50.8	26	0.30	7		(96)	369
33	Engerix-B (20 mcg)	0;1;6	S	Alcoholic patients		51.7	52	NA	12	52	24 (46)	39
33	Engerix-B (40 mcg)	0;1;2;6	A	Alcoholic patients		50.4	48	NA	12	48	36 (75)	76
39		0;1;6	S	STI clinic								
39		0;1;2	(A)	STI clinic								
40	Engerix-B (20 mcg)	0;1;6	S	STI clinic		30.1	104	33.67	7.5	40	35 (88)	
40	Engerix-B (20 mcg)	0;1;2	(A)	STI clinic		30	110	35.67	3.5	59	49 (83)	
46	Engerix-B (20 mcg)	0;1;6	S	MSM, GUM clinic	16–72	32.4	42			22	21 (96)	
43	Engerix-B (20 mcg)	0;1/4;3/4	(SA)	GUM clinic			116		3		(69)	
43	Engerix-B (20 mcg)	0;1;6	S	GUM clinic			171		3			
44	Engerix-B (20 mcg)	0;1;6	S	MSM, GUM clinic		27				118		
44	Twinrix	0;1/4;3/4	(SA)	MSM, GUM clinic		25				220		
45	Engerix-B (20 mcg)	0;1;2	(A)	Male sex workers			489					
34	Engerix-B (20 mcg)	0;1/4;3/4;12	SA	Healthy adult travellers	18–48	27	240	1.16	3	184	167 (91)	131
34	Twinrix (20 mcg)	0;1/4;3/4;12	SA	Healthy adult travellers	18–45	24.9	239	0.81	3	206	196 (95)	183

*Bold values refer to a higher antigen dosage; † schedule expressed in months; 1/4;1/3;1/2;3/4;3/4 therefore correspond to 7, 10, 14, 21 days, and 1.5 months (6 weeks), respectively; ‡ type of vaccination schedule: coded as S (standard), SS (shortened standard), A (accelerated), SA (super-accelerated) or P (prolonged); parentheses indicate schedules without the final dose; § M/F: male/female ratio; NA: not applicable (all males); ¶ numbers and percentages either reported in the paper or calculated from the reported values.

while this proportion is higher within the first 2–3 months after the first dose. Yet again, super-accelerated schedules result in lower anti-HBs levels after three vaccine doses.^{25 26 29–31}

The immune response to hepatitis B vaccination is known to decrease with increasing age. Both Rosman and Gellin reported

a beneficial effect of increasing the vaccine's antigen dosage in adults over 40 years of age.³² The use of an accelerated schedule with a high-dose vaccine was shown to induce higher seroprotection levels compared with the standard schedule in a population of alcoholic older subjects.³³

Table 2 Overview of hepatitis B vaccine uptake according to vaccination schedule, in different at-risk populations

Ref.	Population	Schedule (months*)	Type†	N	Uptake dose 2 n (%)‡	Uptake dose 3 n (%)‡	Uptake dose 4 n (%)‡	Anti-HBs testing (month)	Anti-HBs testing n (%)‡	Additional interventions
38	Heroin users	0;1;2	(A)	689				3	474 (69)	
38	Heroin users	0;1;6	S	486				3	350 (72)	
49	Homeless drug users	0;1;6	S	54	23 (43)	3 (6)				
49	Homeless drug users	0;1/4;3/4	(SA)	90	64 (71)	35 (39)				
50	Prisoners with intravenous drug use	0;1;6;7	S	15	8 (53)	3 (20)	1 (7)	7	1 (7)	
50	Prisoners with intravenous drug use	0;1/4;3/4;7	SA	19	13 (68)	12 (63)	3 (16)	7	3 (16)	
50	Prisoners with intravenous drug use	0;1/4;3/4;7	SA	566	516 (91)	457 (81)	236 (42)	7	236 (42)	
37	Drug users	0;1;6	S	34		31 (91)		8	34 (100)	
48	Drug users	0;1/4;3/4	(SA)	90	74 (82)	64 (71)				Outreach programme with active reminding Vaccination at the STI clinic vs referral to a vaccination centre
39	STI clinic	0;1;6	S	161	64 (40)	45 (28)				
39	STI clinic	0;1;2;12	A	170	66 (39)	58 (34)	23 (14)			
58	STI clinic	0;1;6	S	233	113 (49)	68 (29)				Reminder by mail and telephone
58	STI clinic	0;1;2;12	A	197	97 (49)	67 (34)	35 (18)			
40	STI clinic	0;1;6	S	104	84 (81)	64 (62)		7–8	40 (38)	Mail and telephone
40	STI clinic	0;1;2	(A)	110	88 (80)	83 (75)		3–4	59 (54)	
62	STI clinic			319		179 (56)				
43	STI clinic	0;1/4;3/4	(SA)	116	105 (91)	84 (72)		3		
43	STI clinic	0;1;6	S	171	134 (78)	105 (61)		3		
41	MSM, IDU, CSW and STI	0;1;6	S	13184	(77)	(59)				Pilot vaccination group with programmes for high-risk populations Outreach programme Outreach programme
57	CSW	0;1;6	S	148		100 (68)				
42	CSW	0;1;2;12	A	414	314 (76)	281 (68)	184 (44)			
42	CSW	0;1;6	S	474	321 (68)	227 (48)				
63	CSW	0;1;6	S	79	69 (87)	57 (72)				
56	CSW	0;1;6	S	369		221 (60)		7	161 (44)	Outreach programme with active reminding Outreach programme with active reminding Outreach programme with active reminding
55	CSW	0;1;6	S	59		32 (54)				
45	CSW	0;1;2	(A)	489		292 (60)				Specialist and holistic nature of the services; reminder by telephone
47	CSW	0;1;4	SS	322		190 (59)		Anytime	121 (38)	Outreach programme with active reminding
47	CSW	0;1;6	S	293		158 (54)		Anytime	117 (40)	
64	HCW male	0;1;6	S	101		101 (100)		8–12	96 (95)	
64	HCW female	0;1;6	S	131		131 (100)		8–12	129 (98)	
64	MSM	0;1;6	S	104		89 (86)		8–12	76 (73)	
46	MSM	0;1;6	S	42		30 (71)		7	22 (52)	Reminder letters
44	MSM	0;1;6	S	146	135 (92)	118 (81)			118 (81)	
44	MSM	0;1/4;3/4;12	SA	302	264 (87)	220 (73)			220 (73)	
65	MSM in STI clinics			5669		2588 (46)				

*Schedule expressed in months; 0;1/4;3/4 therefore corresponds to 0.7.21 days; † type of vaccination schedule: coded as S (standard), SS (shortened standard), A (accelerated) or SA (super-accelerated); parentheses indicate schedules without the final dose; ‡ numbers and percentages either reported in the paper, or calculated from the reported values

Travellers to areas of intermediate or high endemicity

Travellers form a very specific at-risk group; they often have a very limited time to start a vaccination schedule. Moreover, completing a hepatitis B vaccination regimen, being at 6 or 12 months after the first dose, is often neglected. Nevertheless, most travellers are healthy persons. The above-mentioned results thus also hold for travellers.³⁴ This has been confirmed in two recent reviews.^{35 36}

Drug users

Lugoboni *et al* found a similar immunogenicity as compared with the general population, using the combined vaccine according to a standard (0.1.6-month) vaccination schedule against hepatitis A and B in a population of drug users.³⁷

Quaglio *et al* compared a 0.1.2 to a standard 0.1.6-month schedule in heroin users; they found a significantly lower proportion reaching the 10 IU/l antibody level after three doses with the accelerated schedule (67 vs 92%).³⁸

Compliance with accelerated vs standard vaccination schedules in different populations (table 2)

SW/MSM/Multiple partners/STI clinic attendants

Several studies have reported being able to administer three doses of hepatitis B vaccine to a higher proportion of the population targeted, when an accelerated or a super-accelerated schedule was used, at least the primary part of it. Unfortunately, few of these studies report immunogenicity data; this is mainly due to the difficulties to administer three

vaccine doses, and thus the low proportion that can actually be tested afterwards.^{39–46}

A recent paper that did report immunogenicity data studied a shortened standard schedule (0.1.4 months) as an alternative option, in a setting (sex workers) where other strategies are used to improve the compliance. Even if the 0.1.4 months schedule failed to significantly improve the compliance, it offered equal protection within a shorter interval.⁴⁷

Drug users

Rogers and Lubman reported that the use of a super-accelerated schedule in an outreach programme had a positive impact on the compliance of a population of young drug users.⁴⁸

Wright *et al* described the vaccine uptake in a population of homeless drug users in a single primary care centre. The standard schedule (0.1.6 months) that was offered in 1999 changed to the primary part of a super-accelerated 0.7.21-day vaccination schedule in 2000. As a result, the uptake of hepatitis B vaccination increased once the vaccination regimen was introduced, and completion rates were even seven times higher with the super-accelerated schedule.⁴⁹

Christensen *et al* showed that a super-accelerated schedule resulted in a significantly higher proportion of vaccinated prisoners with intravenous drug use, and a higher efficacy. Vaccination with a 3-week schedule in prison reached a higher proportion with anti-HBs ≥ 10 IU/l (measured at day 210) than what could have been obtained with a standard 0.1.6-month schedule.⁵⁰

DISCUSSION AND CONCLUSIONS

This review aimed to discuss the preferred vaccination schedules for vaccinating risk groups against hepatitis B, trying to balance the immunogenicity of the vaccine and the compliance of the vaccinees.

Indeed, there is substantial evidence that accelerated and super-accelerated hepatitis B immunisation regimens offer a clear benefit: a larger proportion of vaccinees will reach an anti-HBs level ≥ 10 IU/l within the first months after the first vaccine dose. However, this favourable effect is rather short-lived; the standard (0.1.6 months) vaccination schedule induces comparable seroprotection from month 6 after the first dose onwards. Moreover, the standard schedule results in higher antibody levels; this effect is even stronger when the administration of the final dose is scheduled at month 12.²¹ Therefore, with regards to *immunogenicity*, the (super)accelerated schedule should strictly be reserved for those persons for whom protection as early as possible is desirable (including postexposure prophylaxis), or for travellers leaving within a month.^{9 36 51} Offering the fourth dose would guarantee a long-term protection equal to what is known for the traditional schedules (0.1.6 or 0.1.2.12 months).

Another benefit of the (super)accelerated schedules is the improved uptake of hepatitis B vaccine in a number of at-risk groups who are difficult to stay in touch with over a longer period of time. Studies in drug users, STI clinic attendees, sex workers and so on have demonstrated that there is a larger proportion of vaccinees who receive three doses of hepatitis B vaccine when a (super)accelerated schedule is offered. As shown in table 2, this is especially the case in settings where the coverage of the third dose of the standard 0.1.6-month schedule is very low (eg, homeless drug users, etc). This defines another situation where a (super)accelerated schedule could be chosen for reasons of *compliance*.

However, offering only the primary part of the accelerated schedules also has a downside: the final anti-HBs levels are markedly lower, compared with schedules with a larger interval between the first and the last dose of hepatitis B vaccine. On

top of that, the groups who would benefit from the more rapid protection or improved compliance offered by the accelerated schedules most often are at continuous risk or—in the case of travellers—are likely to repeat their risk over the years to come. Therefore, these groups would also benefit from long-term protection.

Even if the current consensus regarding the need for hepatitis B booster vaccinations recommends relying on underlying cellular immunity induced by hepatitis B vaccines, rather than on persistence of antibodies alone, the consensus statement on long-term (lifetime) protection against hepatitis B is based on data from healthy, fully vaccinated persons. When adults are concerned—which most often is the case in these at-risk groups—the confirmation of an adequate internationally accepted seroprotective immune response (anti-HBs ≥ 10 IU/l) after a complete series of hepatitis B vaccine is recommended.⁸ As of today, the terms “fully vaccinated persons” and “complete vaccination series” still refer to either the standard schedule (0.1.6 months) or the accelerated (0.1.2.12 months) or super-accelerated schedule (0.7.21.360 days) including the fourth dose after 12 months.^{6 7 9–15} Even if an adequate immune response after the first three doses of a (super)accelerated hepatitis B vaccination schedule might be sufficient to also offer long-term protection (there is as yet insufficient scientific evidence to support this), this could become subject to further research. Based on the presently available data, we cannot conclude that long-term protection against hepatitis B is warranted in persons who only received the first three doses of an accelerated schedule, either 0.1,2 months or 0.7,21 days, even if they showed an anti-HBs level ≥ 10 IU/l 1–3 months after the third dose. Independently of an eventual risk of hepatitis B infection before completion of the vaccination schedule, long-term protection needs to be evidenced after a (super)accelerated schedule.⁵²

In these settings of risk group vaccination, the vaccination schedule should therefore rather be chosen by balancing the need for more rapid protection as compared with that offered by the standard 0.1.6-month vaccination schedule, with the need for offering long-term protection to persons who continue being at risk. That choice will be affected by the additional cost and the feasibility of offering a fourth vaccine dose.

There is a clear need to study the possible long-term (ie, 10 years and beyond) efficacy and protection of the three-dose (super) accelerated schedules. However, such studies are difficult to conduct in the at-risk groups—for example, sex workers. First, in case one managed to consistently follow-up at-risk persons over a number of years, it would be unethical not to offer them the fourth dose of hepatitis B vaccine. Second, in such an at-risk setting, there is a higher probability of intermediate exposure to hepatitis B virus, and thus of natural boosting. However, long-term observational studies could be considered in travellers or healthcare workers who did not receive their fourth dose and who could more easily be recalled compared with the setting of sex workers, for example.

As long as evidence demonstrating this long-term protection is lacking, a more “compact” standard schedule (ie, 0.1.4 months) might be an option worth considering, to maximise both seroprotection rates and compliance to offer early long-term protection with the least number of doses.⁴⁷ Confirmation of these observations is welcomed in further studies, comparing seroprotection with this compact schedule. After all, most at-risk groups are at continuous risk and thus clearly benefit from long-term protection.

To further improve the compliance of difficult-to-reach at-risk groups, other strategies (eg, reminder systems, outreaching activities, incentive schemes, etc) need to be considered.^{42 45–48 53–61} Additionally, the value of an alternative vaccine giving

equivalent immunogenicity with two doses only would be very useful in at-risk populations. The venue of new adjuvants could support these alternative approaches.

CONTRIBUTIONS OF EACH AUTHOR

EL and KVH performed the literature searches and prepared a draft manuscript. PVD was involved in interpreting the results and final editing of the manuscript.

Authors' affiliations

K Van Herck, E Leuridan, P Van Damme, Centre for the Evaluation of Vaccination, University of Antwerp, Belgium

K Van Herck, Research Fund Flanders (FWO), Brussels, Belgium

Conflict of interest statement: EL and PVD are employees of the University of Antwerp. KVH is a Postdoctoral Fellow of the Research Fund Flanders (FWO grant no. 1.2.695.07N00). PVD and KVH have been principal investigators of vaccine trials for several vaccine manufacturers, for which the University of Antwerp obtains research grants.

REFERENCES

- Expanded programme on immunization. Global Advisory Group—Part I. *Wkly Epidemiol Rec* 1992;**67**(3):11–5.
- Vryheid RE, Kane MA, Muller N, et al. Infant and adolescent hepatitis B immunization up to 1999: a global overview. *Vaccine* 2000;**19**(9–10):1026–37.
- Banatvala J, Van Damme P, Emiruglu N. Hepatitis B immunisation in Britain: time to change? *BMJ* 2006;**332**:804–5.
- Mast E, Mahoney F, Kane M, et al. Hepatitis B vaccine. In: Plotkin S, Orenstein WA, eds. *Vaccines*. 4th edn. Philadelphia: W.B. Saunders, 2004:299–337.
- Zimmerman RK, Middleton DB, Burns IT, et al. Routine vaccines across the life span, 2005. *J Fam Pract* 2005;**54**(1 Suppl):S9–26.
- Centers for Disease Control and Prevention. *Epidemiology and prevention of vaccine-preventable diseases*. 10th edn. Washington, DC: Public Health Foundation, 2007.
- World Health Organisation. Hepatitis B vaccines. WHO Position Paper. *Wkly Epidemiol Rec* 2004;**79**:253–64.
- Banatvala J, Kane M, Da Villa G, et al. Are booster immunisations needed for lifelong hepatitis B immunity? *Lancet* 2000;**355**:561–65.
- Health Protection Agency. *Immunisation against infectious disease*, 3rd edn, 2006 edn. Norwich, UK: The Stationery Office, 2006.
- National Health & Medical Research Council. *The Australian immunisation handbook*. 8th edn, 2003 edn. Canberra: Australian Government Department of Health and Ageing, 2003.
- Centers for Disease Control and Prevention. *Health information for international travel 2005–2006*. 2005–2006 edn. Atlanta: US Department of Health and Human Services, Public Health Service, 2005.
- Migrant Clinicians Network. http://www.migrantclinician.org/_resources/hep_mcn_position_paper.pdf (accessed 9 Mar 2007).
- Royal College of General Practitioners. http://www.rcgp.org.uk/pdf/drug_hepb.pdf (accessed 9 Mar 2007).
- Royal Australian College of General Practitioners. <http://www.racgp.org.au/content/navigationmenu/clinicalresources/racgpguidelines/immunisation/vaccines/hepatitisb/default.htm#dosage> (accessed 9 Mar 2007).
- British Association of Sexual Health and HIV. UK national guideline on the management of viral hepatitis A, B, and C. http://www.bashh.org/guidelines/2005/hepatitis_abc_final_0905.pdf (accessed 9 Mar 2007).
- Mast EE, Weinbaum CM, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. *MMWR Recomm Rep* 2006;**55**:1–33; quiz CE1–4.
- Chowdhury A, Santra A, Habibullah CM, et al. Immune response to an indigenously developed r-hepatitis B vaccine in mixed population: study of an accelerated vaccination schedule. *World Journal of Gastroenterology* 2005;**11**:1037–9.
- Wilkinson SE, Morath M, Bennett DL, et al. Accelerated schedule of hepatitis B vaccination in high-risk youth. *J Paediatr Child Health* 1996;**32**:60–2.
- Bosnak M, Dikici B, Bosnak V, et al. Accelerated hepatitis B vaccination schedule in childhood. *Pediatr Int* 2002;**44**:663–5.
- Cassidy WM, Watson B, Ioli VA, et al. A randomized trial of alternative two- and three-dose hepatitis B vaccination regimens in adolescents: antibody responses, safety, and immunologic memory. *Pediatrics* 2001;**107**:626–31.
- Jilg W, Schmidt M, Deinhardt F. Vaccination against hepatitis B: comparison of three different vaccination schedules. *J Infect Dis* 1989;**160**:766–9.
- Scheierrmann N, Gesemann M, Maurer C, et al. Persistence of antibodies after immunization with a recombinant yeast-derived hepatitis B vaccine following two different schedules. *Vaccine* 1990;**8**(Suppl):S44–6; discussion S60–2.
- Marchou B, Excler JL, Bourderieux C, et al. A 3-week hepatitis B vaccination schedule provides rapid and persistent protective immunity: a multicenter, randomized trial comparing accelerated and classic vaccination schedules. *J Infect Dis* 1995;**172**:258–60.
- Marsano LS, Greenberg RN, Kirkpatrick RB, et al. Comparison of a rapid hepatitis B immunization schedule to the standard schedule for adults. *Am J Gastroenterol* 1996;**91**:111–5.
- Carlsson T, Struve J, Sonnerborg A, et al. The anti-HBs response after 2 different accelerated intradermal and intramuscular schemes for hepatitis B vaccination. *Scand J Infect Dis* 1999;**31**:93–5.
- Saltoğlu N, Inal AS, Tasova Y, et al. Comparison of the accelerated and classic vaccination schedules against Hepatitis B: three-week Hepatitis B vaccination schedule provides immediate and protective immunity. *Ann Clin Microbiol Antimicrob* 2003;**2**:10.
- Hussain Z, Ali SS, Hussain SA, et al. Evaluation of immunogenicity and reactogenicity of recombinant DNA hepatitis B vaccine produced in India. *World J Gastroenterol* 2005;**11**:7165–8.
- Marcho L, Vildozola H, Valencia E, et al. [Comparative study on the protective effect of two immunization schemes using a hepatitis B recombinant vaccine in vulnerable health science students]. *Rev Gastroenterol Peru* 2005;**25**:313–9.
- Bock HL, Loscher T, Scheierrmann N, et al. Accelerated schedule for hepatitis B immunization. *J Travel Med* 1995;**2**:213–7.
- Kallinowski B, Benz C, Buchholz L, et al. Accelerated schedule of hepatitis B vaccination in liver transplant candidates. *Transplant Proc* 1998;**30**:797–9.
- Engler SH, Sauer PW, Golling M, et al. Immunogenicity of two accelerated hepatitis B vaccination protocols in liver transplant candidates. *Eur J Gastroenterol Hepatol* 2001;**13**:363–7.
- Gellin BG GR, Hart RH, Bertino JS, et al. Immunogenicity of two doses of yeast recombinant hepatitis B vaccine in healthy older adults. *J Infect Dis* 1997;**175**:1494–7.
- Rosman AS, Basu P, Galvin K, et al. Efficacy of a high and accelerated dose of hepatitis B vaccine in alcoholic patients: a randomized clinical trial. *Am J Med* 1997;**103**:217–22.
- Nothdurft HD, Dietrich M, Zuckerman JN, et al. A new accelerated vaccination schedule for rapid protection against hepatitis A and B. *Vaccine* 2002;**20**:1157–62.
- Zuckerman J. The place of accelerated schedules for hepatitis A and B vaccinations. *Drugs* 2003;**63**:1779–84.
- Keystone JS. Travel-related hepatitis B: risk factors and prevention using an accelerated vaccination schedule. *Am J Med* 2005;**118**(Suppl 10A):635–685.
- Lugoboni F, Quaglio G, Pajusco B, et al. Immunogenicity, reactogenicity and adherence to a combined hepatitis A and B vaccine in illicit drug users. *Addiction* 2004;**99**:1560–4.
- Quaglio G, Talamini G, Lugoboni F, et al. Compliance with hepatitis B vaccination in 1175 heroin users and risk factors associated with lack of vaccine response. *Addiction* 2002;**97**:985–92.
- Dal-Re R, Gonzalez A, Ramirez V, et al. Compliance with immunization against hepatitis B. A pragmatic study in sexually transmitted disease clinics. *Vaccine* 1995;**13**:163–7.
- Asboe D, Rice P, de Ruiter A, et al. Hepatitis B vaccination schedules in genitourinary medicine clinics. *Genitourin Med* 1996;**72**:210–2.
- van Steenberghe JE. Results of an enhanced-outreach programme of hepatitis B vaccination in the Netherlands (1998–2000) among men who have sex with men, hard drug users, sex workers and heterosexual persons with multiple partners. *J Hepatol* 2002;**37**:507–13.
- Mak R, Traen A, Claeysens M, et al. Hepatitis B vaccination for sex workers: do outreach programmes perform better? *Sex Transm Infect* 2003;**79**:157–9.
- Jones O, Sankar KN. Audit of outcome of super-accelerated hepatitis B vaccination schedule in a genitourinary medicine clinic. *Int J STD AIDS* 2005;**16**:636–7.
- McMillan A. Hepatitis B vaccination of men who have sex with men: experience with an accelerated course of vaccination in a genitourinary medicine clinic. *Int J STD AIDS* 2005;**16**:633–5.
- Sethi G, Holden BM, Greene L, et al. Hepatitis B vaccination for male sex workers: the experience of a specialist GUM service. *Sex Transm Infect* 2006;**82**:84–5.
- Opamey AA, Bashford J. Audit of hepatitis B immunization at the genitourinary medicine department in Middlesbrough, UK. *Int J STD AIDS* 2002;**13**:268–70.
- Wouters K, Leuridan E, Van Herck K, et al. Compliance and immunogenicity of two hepatitis B vaccination schedules in sex workers in Belgium. *Vaccine* 2007;**25**:1893–900.
- Rogers N, Lubman DI. An accelerated hepatitis B vaccination schedule for young drug users. *Aust NZ J Public Health* 2005;**29**:305–7.
- Wright NM, Campbell TL, Tompkins CN. Comparison of conventional and accelerated hepatitis B immunisation schedules for homeless drug users. *Commun Dis Public Health* 2002;**5**:324–6.
- Christensen PB, Fisker N, Krarup HB, et al. Hepatitis B vaccination in prison with a 3-week schedule is more efficient than the standard 6-month schedule. *Vaccine* 2004;**22**:3897–901.
- Zuckerman JN. The place of accelerated schedules for hepatitis A and B vaccinations. *Drugs* 2003;**63**:1779–84.
- Zuckerman JN, Connor BA, von Sonnenburg F. Hepatitis A and B booster recommendations: implications for travelers. *Clin Infect Dis* 2005;**41**:1020–6.
- Seal KH, Kral AH, Lorrwick J, et al. A randomized controlled trial of monetary incentives vs. outreach to enhance adherence to the hepatitis B vaccine series among injection drug users. *Drug Alcohol Depend* 2003;**71**:127–31.
- Vilella A, Bayas JM, Diaz MT, et al. The role of mobile phones in improving vaccination rates in travelers. *Prev Med* 2004;**38**:503–9.
- Leuridan E, Wouters K, Stalpaert M, et al. Male sex workers in Antwerp, Belgium: a descriptive study. *Int J STD AIDS* 2005;**16**:744–8.
- Van Ardenne N, Roelofs I, Leuridan E, et al. Audit on offering and accepting hepatitis B vaccine by sex workers. *Int J STD AIDS* 2004;**15**:493–4.

- 57 **Prévost C**, Bertrand, Tonglet. Pertinence et faisabilité d'un programme de vaccination contre l'hépatite B proposé à un groupe de prostituées à Bruxelles, Belgique. *Arch Public Health* 2000;**58**:37–48.
- 58 **Weinstock HS**, Bolan G, Moran JS, *et al*. Routine hepatitis B vaccination in a clinic for sexually transmitted diseases. *Am J Public Health* 1995;**85**:846–9.
- 59 **Baker AM**, McCarthy B, Gurley VF, *et al*. Influenza immunization in a managed care organization. *J Gen Intern Med* 1998;**13**:469–75.
- 60 **Sansom S**, Rudy E, Strine T, *et al*. Hepatitis A and B vaccination in a sexually transmitted disease clinic for men who have sex with men. *Sex Transm Dis* 2003;**30**:685–8.
- 61 **Jacobson VJ**, Szilagyi P. Patient reminder and patient recall systems to improve immunization rates. *Cochrane Database Syst Rev* 2005:CD003941.
- 62 **Jaleel H**, Allan PS, Huengsberg M, *et al*. Offering the vaccine and accepting it: an audit of hepatitis B vaccination in West Midlands region. *Int J STD AIDS* 2003;**14**:632–5.
- 63 **Wouters K**. Sexually transmitted infections (STI) among prostitutes in Antwerp, Belgium. *Arch Public Health* 2002;**60**:27–38.
- 64 **Das S**, Brassington M, Drake SM, *et al*. Response to hepatitis-B vaccination in healthy homosexual individuals: retrospective case control study. *Vaccine* 2003;**21**:3701–5.
- 65 **Brown AE**, Tomkins SE, Logan LE, *et al*. Monitoring the effectiveness of HIV and STI prevention initiatives in England, Wales, and Northern Ireland: where are we now? *Sex Transm Infect* 2006;**82**:4–10.

BMJ Clinical Evidence—Call for contributors

BMJ Clinical Evidence is a continuously updated evidence-based journal available worldwide on the internet which publishes commissioned systematic reviews. *BMJ Clinical Evidence* needs to recruit new contributors. Contributors are healthcare professionals or epidemiologists with experience in evidence-based medicine, with the ability to write in a concise and structured way and relevant clinical expertise.

Areas for which we are currently seeking contributors:

- Secondary prevention of ischaemic cardiac events
- Acute myocardial infarction
- MRSA (treatment)
- Bacterial conjunctivitis

However, we are always looking for contributors, so do not let this list discourage you.

Being a contributor involves:

- Selecting from a validated, screened search (performed by in-house Information Specialists) valid studies for inclusion.
- Documenting your decisions about which studies to include on an inclusion and exclusion form, which we will publish.
- Writing the text to a highly structured template (about 1500–3000 words), using evidence from the final studies chosen, within 8–10 weeks of receiving the literature search.
- Working with *BMJ Clinical Evidence* editors to ensure that the final text meets quality and style standards.
- Updating the text every 12 months using any new, sound evidence that becomes available. The *BMJ Clinical Evidence* in-house team will conduct the searches for contributors; your task is to filter out high quality studies and incorporate them into the existing text.
- To expand the review to include a new question about once every 12 months.

In return, contributors will see their work published in a highly-rewarded peer-reviewed international medical journal. They also receive a small honorarium for their efforts.

If you would like to become a contributor for *BMJ Clinical Evidence* or require more information about what this involves please send your contact details and a copy of your CV, clearly stating the clinical area you are interested in, to CECommissioning@bmjgroup.com.

Call for peer reviewers

BMJ Clinical Evidence also needs to recruit new peer reviewers specifically with an interest in the clinical areas stated above, and also others related to general practice. Peer reviewers are healthcare professionals or epidemiologists with experience in evidence-based medicine. As a peer reviewer you would be asked for your views on the clinical relevance, validity and accessibility of specific reviews within the journal, and their usefulness to the intended audience (international generalists and healthcare professionals, possibly with limited statistical knowledge). Reviews are usually 1500–3000 words in length and we would ask you to review between 2–5 systematic reviews per year. The peer review process takes place throughout the year, and our turnaround time for each review is 10–14 days. In return peer reviewers receive free access to *BMJ Clinical Evidence* for 3 months for each review.

If you are interested in becoming a peer reviewer for *BMJ Clinical Evidence*, please complete the peer review questionnaire at www.clinicalevidence.com/cweb/contribute/peerreviewer.jsp