

# Immune Response of Hepatitis B Vaccine Among Persons With Diabetes

## A systematic review of the literature

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In October 2011, the Advisory Committee on Immunization Practices (ACIP) recommended hepatitis B vaccination for adults with diabetes in the United States (1). Serosurvey data from the 1999–2010 National Health and Nutrition Examination Survey found that noninstitutionalized adults aged  $\geq 18$  years with diabetes have an increased seroprevalence of past or current hepatitis B virus (HBV) infection (1). Outbreaks of hepatitis B in elderly persons with diabetes in long-term care facilities have been linked to diabetes care procedures (including blood glucose monitoring), with likely vehicles for transmission including spring-loaded finger-stick devices used on multiple patients and blood glucose testing meters that were not cleaned between uses on different patients.

In the U.S., hepatitis B vaccination is routinely recommended for infants, children, and adolescents. It also is recommended for adults at increased risk of HBV infection, including persons with end-stage renal disease or chronic liver disease, health care personnel, injection-drug users, and men who have sex with men (2–4). A hepatitis B vaccination series results in protection in a high proportion (>95%) of infants, children, and young adults (5). As with other vaccines, the efficacy of the hepatitis B vaccine progressively declines with advancing age, as well as with the presence of obesity

and other comorbid conditions (6–12). Results of studies of the hepatitis B vaccine among persons with diabetes generally follow these patterns (13,14).

Primary hepatitis B vaccination usually consists of 3 (or 4) doses of 10 or 20  $\mu\text{g}$  of recombinant hepatitis B surface antigen (HBsAg) protein administered intramuscularly into the deltoid muscle on a 0-, 1-, and 6-month schedule (Table 1). Alternative schedules are U.S.-approved for routine vaccination for specific ages and vaccine formulations, and they elicit dose-specific and final rates of seroprotection similar to those obtained on a 0-, 1-, and 6-month schedule (4). Two single-antigen recombinant vaccines, Recombivax HB (Merck & Co, Inc., Whitehouse Station, NJ) and Engerix-B (GlaxoSmithKline Biologicals, Rixensart, Belgium), and one combination hepatitis A/hepatitis B vaccine, Twinrix (GlaxoSmithKline Biologicals), are approved for use in adults in the U.S. (15). Hepatitis B vaccines are safe for all age groups. Administration of additional vaccine doses for nonresponders is not associated with an increase in adverse events (16). Vaccination is not contraindicated in persons with autoimmune or chronic diseases, or in those who are pregnant (4).

No review has been published of the efficacy of the hepatitis B vaccine among persons with diabetes; results of studies

among persons with diabetes show some heterogeneity compared with adults without diabetes. Differences in diabetes type, management, and glycemic control, as well as vaccine, dosage, administration route, or schedule, may underlie this heterogeneity. The 2011 ACIP recommendation for hepatitis B vaccination for adults with diabetes, an increasing incidence of diabetes, and the high prevalence of diabetes among certain groups recommended for hepatitis B vaccination (e.g., persons with end-stage renal disease) suggests that a review of vaccine efficacy among persons with diabetes may be timely. We therefore performed a systematic review of the literature and summarized the evidence for seroprotection after hepatitis B vaccination among persons with diabetes.

## RESEARCH DESIGN AND METHODS

### Search strategy

Electronic searches of MEDLINE (via PubMed), EMBASE (via Ovid), Cochrane Library, and Web of Knowledge databases were performed. The search terms consisted of (hepatitis b vaccin\* OR hbv vaccin\* OR hepatitis b immuni\* OR hbv immuni\*) AND (immunogeni\* OR immune response OR antibody) AND (diabetes). The search terms also were used as Medical Subject Heading terms (MEDLINE) or key words (EMBASE), as applicable. Where possible, limits included publication date from 1986 through 30 April 2012, English language, and study of humans. The MEDLINE and EMBASE searches were limited to items containing abstracts. Studies conducted in the U.S. and other countries were eligible for inclusion.

### Inclusion criteria

Peer-reviewed, published randomized clinical trials or observational studies (all types) assessing response to hepatitis B vaccine among persons with type 1 or type 2 diabetes were included. Studies among both children and adults were included to ascertain the effect of age upon vaccine response among persons with diabetes. Reports had to specify the proportion (numerator and denominator) of

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Table 1—Recommended dosages of hepatitis B vaccine for adults aged &gt;20 years\* (4)

	Single-antigen vaccine				Combination vaccine	
	Recombivax HB		Engerix-B		Twinrix	
	Dosage (μg)	Volume (mL)	Dosage (μg)	Volume (mL)	Dosage (μg)	Volume (mL)
Adults	10	1	20	1	20	1
Adult hemodialysis patients and other immunocompromised adults	40†	1	40‡	2	NA	NA

NA, not applicable. \*Please refer to package insert. †Dialysis formulation administered on a 3-dose schedule at 0, 1, and 6 months. ‡Two 1-mL doses administered in 1 or 2 injections on a 4-dose schedule at 0, 1, 2, and 6 months.

subjects seroprotected by diabetes status (or data available that allowed for calculation of the proportions), or available odds ratios from a multivariate analysis, which included diabetes as a predictor variable. Studies of specific subject populations of which persons with diabetes represented a subset were included.

### Exclusion criteria

Studies were excluded when immune response using an antibody to hepatitis B surface antigen (anti-HBs) threshold of 10 mIU/mL was not reported; immune response was not measured between 0 and 6 months after the last vaccine dose (because anti-HBs titers wane over time); 10 or fewer subjects with diabetes were included; vaccine was administered intradermally; or subjects were not naïve to the vaccine or had positive serology for HBsAg, anti-HBs, or antibody to hepatitis B core antigen, indicating past or current hepatitis B infection. When two studies reported results for duplicate subjects, one study was excluded. Studies were not excluded when subjects received additional vaccine dose(s) because they did not achieve seroprotective concentrations or when inclusion of a fraction of subjects meeting an exclusion criterion was deemed unlikely to affect the findings. The determination as to inclusion or exclusion was based on the above criteria and was made irrespective of study results.

### Data extraction and categorization

Data were manually extracted and electronically recorded. Studies were classified into one of three subject categories: adults (mean age >18 years), children (mean age ≤18 years), and hemodialysis/chronic kidney disease patients. Elements for extraction included study characteristics (e.g., study design, sample size,

publication year, country); subject characteristics (e.g., age, diabetes type); vaccine characteristics (e.g., vaccine, dosage, route, schedule); and the proportion of subjects attaining seroprotection, including the time interval (in months) from the last dose at which immune response was measured. When vaccine or route of administration differed by study arm, extraction elements were recorded for each arm when possible.

An anti-HBs threshold of 10 mIU/mL after series completion (an accepted marker of immune protection) defined seroprotection (4). When multiple immune response measurements were reported reflecting seroprotection at different intervals during the primary vaccine series, the result after the final dose was recorded. When immune response was measured more than once after vaccination, the result from the interval closest to 1 to 2 months after the last dose (corresponding to the recommended interval for postvaccination testing for serologic response in the U.S. [4]) was recorded. When immune response was measured after a booster dose(s) or novel adjuvant administration, results were recorded separately and noted.

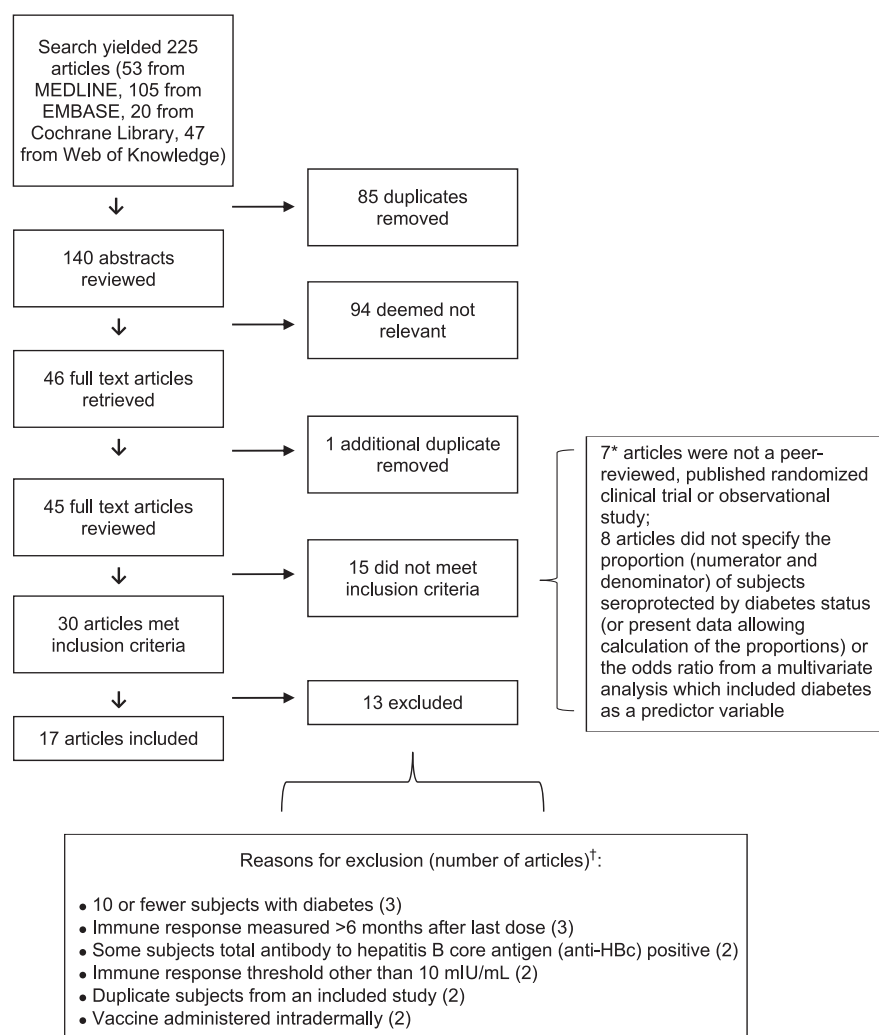
Odds ratios for attainment of seroprotection were recorded for studies reporting results from a multiple logistic regression model. When odds ratios and 95% CIs for the diabetes predictor variable were reported for *failure* to achieve seroprotection, the probability of attaining seroprotection was calculated by taking the inverse of the reported values.

**RESULTS**—The systematic electronic search yielded 225 studies (53 from MEDLINE, 105 from EMBASE, 20 from Cochrane Library, and 47 from Web of Knowledge; a list of these studies is available upon request). Of these 225 studies,

85 duplicates were identified. Abstracts from the remaining 140 studies (62.2%) were reviewed, and 94 (67.1%) were deemed not relevant. Forty-six (32.9%) full-text studies were retrieved and reviewed, and one additional duplicate was identified (Fig. 1). Fifteen studies did not fulfill inclusion criteria, and 13 met at least one criterion for exclusion (Table 2 and Fig. 1), leaving 17 studies.

The 17 studies included 2 randomized clinical trials, 12 prospective, and 3 retrospective studies published between 1989 and 2012 (Table 3). The 17 studies included 16,310 unique subjects, of which approximately 9,286 had diabetes. The subject categories consisted of adults for 4 studies (285 subjects, of whom 152 had diabetes); children for 4 studies (472 subjects, of whom 206 had diabetes); and hemodialysis/chronic kidney disease patients for 9 studies (15,553 subjects, of whom approximately 8,928 had diabetes). Subjects in the studies among adults and children generally lacked comorbidities (including kidney disease) other than diabetes. One study among hemodialysis/chronic kidney disease patients included only subjects with chronic kidney disease (i.e., no hemodialysis patients) (32), and three studies included both hemodialysis and chronic kidney disease patients (36,42,44), one of which also included peritoneal dialysis patients (44). The remainder were comprised entirely of hemodialysis patients. Seroprotection against hepatitis B virus infection was assessed in subjects by diabetes status in 16 studies (1,764 subjects, 633 with diabetes). Five studies included diabetes in a multivariate model (31,32,37,42,44). No serious vaccine-related adverse event was reported in any study.

The average age of subjects by study ranged from 8.4 to 79.5 years. Diabetes type was type 1 in five studies, type 2 in one study, and type 1 and type 2 in two studies. Diabetes type was not specified in eight of the nine studies among hemodialysis/chronic kidney disease patients; persons with type 2 diabetes constitute more than half of persons with diabetes starting dialysis in the U.S. (45). The vaccine type was exclusively recombinant in 15 studies, one of which used a combination hepatitis A/hepatitis B vaccine (43), and was exclusively plasma derived in one study; both recombinant and plasma-derived vaccines were used in one study. A novel adjuvant was administered to subjects in two studies (40,41). Vaccine dosage ranged from 3 to 40 μg. Route of



**Figure 1**—Search results. \*Articles that were not a peer-reviewed, published randomized clinical trial or observational study were not double-counted (among articles that did not specify the proportion [numerator and denominator] of subjects seroprotected by diabetes status [or data available to allow the calculation of the proportions] or the odds ratio from a multivariate analysis that included diabetes as a predictor variable) so that the total would equal 15. †The number of articles does not total 13 because one article met two inclusion criteria.

administration was exclusively intramuscular in 15 studies and exclusively subcutaneous in one study; one study used intramuscular or intradermal administration routes in separate study arms. The standard 0-, 1-, and 6-month schedule was used exclusively or partially in 11 studies. Others were a 0-, 1-, 2-, and 12-month schedule and a 0-, 1-, 2-, and 6-month schedule (both U.S.-approved alternatives), as well as a 0-, 1-, and 2-month schedule (not approved in the U.S.). The sex distribution was generally equivalent for most studies, although men predominated in the studies among hemodialysis/chronic kidney disease patients. The type of vaccine, dosage, route of administration, schedule, and the interval after the last dose when seroprotection

was assessed were equivalent for the diabetes and comparison groups except as noted in Table 4.

Seroprotection proportions ranged from 31.3–100.0% (median, 73.4%) among persons with diabetes and 35.2–100.0% (median, 87.1%) for those without diabetes. The proportion protected was generally greatest among children, ranging from 54.2–100.0% (median, 93.9%) among children with diabetes and 98.0–100.0% (median 100.0%) among those without diabetes. Among adults, seroprotection proportions ranged from 31.3–94.4% (median, 88.2%) for those with diabetes compared with 35.2–96.9% (median, 93.6%) for those without diabetes. Seroprotection proportions were lowest for

hemodialysis/chronic kidney disease patients, ranging from 41.8–85.3% (median, 60.1%) for those with diabetes and 61.8–87.5% (median, 75.1%) for those without diabetes.

Seroprotection proportions among subjects with diabetes were generally lower when vaccine was administered on a 0-, 1-, and 2-month schedule (not approved in the U.S.) and greater when vaccine was administered on a 0-, 1-, 2-, and 12-month schedule (U.S.-approved alternative schedule) compared with the standard 0-, 1-, and 6-month schedule. Two studies using a 0-, 1-, and 2-month schedule reported relatively low seroprotection proportions for persons with diabetes in their corresponding subject categories (54.2% among children [35] and 45.8% among hemodialysis/chronic kidney disease patients [34]), and two studies using a 0-, 1-, 2-, and 12-month schedule reported relatively high seroprotection proportions among subjects with diabetes in their corresponding subject categories (88.6% and 94.4% [13] among adults and 66.7% among hemodialysis/chronic kidney disease patients [33]). When a fourth dose was administered to children with diabetes after a primary series on a 0-, 1-, and 2-month schedule, seroprotection increased from 54.2 to 100.0% in one study (35). Another study, however, achieved an 88.2% seroprotection proportion when vaccinating adults with diabetes subcutaneously using a 0-, 1-, and 2-month schedule with thymopentin as an adjuvant (41). Thymopentin is a synthetic pentapeptide with activity characteristic of the thymic hormone thymopietin and is not approved for use in the U.S. It has been used to enhance interleukin 2 production and function of macrophages (46).

Administration of additional hepatitis B vaccine doses may improve immune response among adults with diabetes. Douvin et al. (13) reported seroprotective anti-HBs levels in 91.5% of adult subjects with diabetes compared with 75.0% as reported by Bouter et al. (14). Subjects in both studies received 20- $\mu$ g dosages of recombinant hepatitis B vaccine intramuscularly. Subjects in the study by Douvin et al. were, on average, older than those in the study by Bouter et al. (mean age, 49.2 vs. 34.3 years). It is therefore reasonable that subjects from the study by Douvin et al. would have responded more poorly than those from the study by Bouter et al. because older age (6–9,31,47) is associated with a decline

Table 2—Exclusion criteria as applicable for 13 studies

Authors (reference)	Publication year	Exclusion criteria
Ahishali et al. (17)	2008	≤10 subjects with diabetes
Chow et al. (18)	2006	≤10 subjects with diabetes
Eldesoky et al. (19)	2009	Immune response measured >6 months after last dose
Elwell et al. (20)	2003	Immune response measured >6 months after last dose
Halota et al. (21)	2002	Some subjects anti-HBc positive
Kramer et al. (22)	2009	Immune response threshold other than 10 mIU/mL
Marseglia et al. (23)	2000	Immune response measured >6 months after last dose, duplicate subjects from Marseglia et al., 1996
Morais et al. (24)	2007	Vaccine administered ID
Pascasio et al. (25)	2008	Some subjects anti-HBc positive
Pozzilli et al. (26)	1987	Immune response threshold other than 10 mIU/mL
Somboonsilp et al. (27)	2003	Vaccine administered ID
Tsouchnikas et al. (28)	2007	≤10 subjects with diabetes
Wismans et al. (29)	1991	Duplicate subjects from Bouter et al., 1992

Anti-HBc, antibody to hepatitis B core antigen (total or not specified); ID, intradermally.

in response. However, differences in the number of doses administered likely contributed to higher seroprotective proportions in the Douvin et al. study, in which 30 subjects (42.3%) receiving vaccine on a 0-, 1-, 2-, and 12-month schedule also received a booster dose at month 4 (for an anti-HBs titer <10 mIU/mL, according to the study protocol). Therefore these subjects received five total doses, compared with three total doses on a 0-, 1-, and 6-month schedule reported by Bouter et al.

Five studies among hemodialysis/chronic kidney disease patients included diabetes in a multivariate model (31,32,37,42,44) (Table 5). All studies controlled for age, and three controlled for obesity. Four studies, with a total of 587 subjects (186 with diabetes), reported that diabetes was independently associated with failure to achieve seroprotection (odds ratio [OR] 0.23–0.50 [95% CI 0.09–0.96]) (31,32,42,44). In their study of 14,546 predominantly hemodialysis

patients, Lacson et al. (37) reported no decrease in seroprotection associated with diabetes (OR 1.02 [95% CI 0.93–1.12]), although a subanalysis of 814 pairs (including subjects with and without diabetes) matched for age, sex, race, dialysis vintage, and dialysis modality reported a decrease in seroprotection associated with diabetes (OR 0.71 [95% CI 0.52–0.97]).

A lower seroprotection proportion was achieved among children with diabetes who received the vaccine using intradermal administration, which is not a U.S.-approved route of administration. Li Volti et al. (38) reported 77.8% seroprotection with intradermal administration compared with 100.0% seroprotection with intramuscular administration. Among children without diabetes, 100.0% in both intradermal and intramuscular arms achieved seroprotection (38). Other studies have found improved results with intradermal administration of the hepatitis B vaccine in dialysis patients (48).

Thymopentin or priming with tetanus toxoid (TT) was used in two studies to enhance the immune response to the hepatitis B vaccine. Thymopentin was administered to adults with diabetes three times per week for a week before hepatitis B vaccination and for 3 weeks afterward. The results were compared with hepatitis B vaccination among normal control subjects (41). TT was administered 2 days before an additional dose of hepatitis B vaccine to hemodialysis/chronic kidney disease patients who were nonresponders after 6 or 7 doses of hepatitis B vaccine that had been administered during the previous 18 months (40). Although differences in route of administration and number of booster doses administered prevent comparison with other studies, seroprotection was reported in 88.2% of adults with diabetes who received the thymopentin adjuvant and in 100.0% of previously nonresponding hemodialysis/chronic kidney disease patients with diabetes who had received TT before vaccination. Subsequent meta-analysis of studies using thymopentin adjuvant with hepatitis B vaccine in end-stage renal disease patients (with and without diabetes) found limited benefit from the addition of thymopentin to hepatitis B schedules (46).

**CONCLUSIONS**—When hepatitis B vaccination is performed in accordance with standard administration procedures, children and young adults with diabetes

Table 3—Characteristics of included studies

Author(s) (reference)	Publication year	Country	Study design	N
Arslanoğlu et al. (30)	2002	Turkey	Prospective	150
Bouter et al. (14)	1992	Netherlands	Prospective	64
Chin (31)	2003	U.S.	Retrospective	97
DaRoza et al. (32)	2003	Canada	Prospective	165
Douvin et al. (13)	1997	France	RCT	71
Eardley et al. (33)	2002	U.K.	Prospective	86
Fabrizi et al. (34)	1996	Italy	Prospective	188
Fiçicioğlu et al. (35)	1995	Turkey	Prospective	41
Hashemi et al. (36)	2011	Iran	Prospective	167
Lacson et al. (37)	2005	U.S.	Retrospective	14,546
Li Volti et al. (38)	1998	Italy	RCT	42
Marseglia et al. (39)	1996	Italy	Prospective	239
Ocak et al. (40)	2008	Turkey	Prospective	49
Pagani et al. (41)	1989	U.K.	Prospective	64
Taheri et al. (42)	2005	Iran	Prospective	125
Williams et al. (43)	2012	U.S.	Prospective	86
Zitt et al. (44)	2012	Austria	Retrospective	200

RCT, randomized clinical trial.

Table 4—Studies included in review: demographic data, vaccination schedule, and seroprotection (SP) proportion (anti-HBs cutoff of 10 mIU/mL)

Authors (reference)	Study population	Age (years)*	Diabetes type	Vaccine	Dose (µg)	Route	Schedule (months)	When seroprotection assessed (months)	Seroprotection proportion	
									Diabetes, % (n/N)	No diabetes, % (n/N)
Bouter et al. (14)	Adults	34.3	1	Recombinant	20	IM	0, 1, and 6	1	75.0 (24/32)	96.9 (31/32)
Douvin et al. (13)	Adults	52.4	1 and 2	Engerix-B	20	IM	0, 1, 2, and 12†	1	94.4 (34/36)	NR
		46.0		GenHevac B	20	IM	0, 1, 2, and 12†	1	88.6 (31/35)	NR
Pagani et al. (41)	Adults	50	1 and 2	Haevac B (+thymopentin if diabetes)	5	SC	0, 1, and 2	3	88.2 (15/17)	93.6 (44/47)
Williams et al. (43)	Adults	79.5*	NR	Twinrix	20	IM	0, 1, and 6	1–2	31.3 (10/32)	35.2 (19/54)
Arslanoglu et al. (30)	Children	10.8	1	Engerix-B‡	10	IM	0, 1, and 6	1–6§	93.9 (93/99)	98.0 (50/51)
Fiçioğlu et al. (35)	Children	11.5	1	GenHevac B	20	IM	0, 1, and 2 ± 5	2	54.2 (13/24)	100.0 (17/17)
Li Volti et al. (38)	Children	8.4	1	Engerix-B	10–20	IM	0, 1, and 6	1	100.0 (9/9)	100.0 (12/12)
		9.8			3	ID	0, 0.5, 1, 1.5–2	1	77.8 (7/9)	100.0 (12/12)
Marseglia et al. (39)	Children	17.3	1	Recombivax HB	10¶	IM	0, 1, and 6	2	95.4 (62/65)	98.3 (171/174)
Chin (31)	HD/CKD	53.7*	NR	Recombivax HB	40	IM	0, 1, and 6**	4–6	52.1†† (25/48)	79.6†† (39/49)
DaRoza et al. (32)#	HD/CKD	59.8*	NR	Recombinant or plasma	40	IM	0, 1, 2, and 6	3	71.7 (33/46)	86.6 (103/119)
Eardley et al. (33)	HD/CKD	61*	NR	HB Vax II	40	IM	0, 1, 2, and 12	1.5–2	66.7 (8/12)	74.3 (55/74)
Fabrizi et al. (34)§§	HD/CKD	63.4*	NR	Engerix-B	40	IM	0, 1, and 2	1	45.8 (11/24)	72.3 (68/94)
Hashemi et al. (36)	HD/CKD	57.4*	NR	Engerix-B	40	IM	0, 1, and 6	2–3	85.3 (29/34)	75.9 (101/133)
Lacson et al. (37)	HD/CKD	59*	NR	Recombivax HB	40	IM	0, 1, and 6	6	NR	NR
				Engerix-B	40	IM	0, 1, 2, and 6	6	NR	NR
Ocak et al. (40)	HD/CKD	61.6*	2	Euvax B ± tetanus toxoid	40	IM	0, 1, 2, and 6 ± 2	2	57.9    (11/19)	70.0    (21/30)
							OR 3 boosters			
Taheri et al. (42)	HD/CKD	50*	NR	Heberbiovac HB	40	IM	0, 1, and 6	1–6	62.2 (23/37)	87.5 (77/88)
Zitt et al. (44)	HD/CKD	64*	NR	HBVaxPro or Engerix-B	40	IM	0, 1, and 6	2	41.8 (23/55)	61.8 (89/144)

HD/CKD, hemodialysis/chronic kidney disease patients; ID, intradermally; IM, intramuscularly; NR, not reported; SC, subcutaneously. \*Mean age for subjects with and without diabetes. †Thirty subjects received one booster at month 4 because of anti-HBs <10 mIU/mL. ‡GenHevac B used in 23 of 51 controls. §Time in months after last dose when measured range of anti-HBs among persons with diabetes was 0.1–23.4; range among controls 1–6 months. ||Response 100.0% after fourth dose. ¶One subject aged 4.5 years received a 5-µg dose. #DaRoza et al. (32) included only included patients before dialysis initiation. \*\*Second series given if no response. ††Response assessed on two occasions; subjects responding on only the first occasion were not classified as responder or nonresponder. §§Some subjects were antibody to hepatitis B core antigen positive. ||||Responses of 78.9% and 96.6% after additional doses in diabetes and comparison groups, respectively; response 100.0% in each group after administration of tetanus toxoid and vaccine.

Table 5—Multiple logistic regression model results for attainment of seroprotective response

Authors (references)	Predictor variable	Other variables in model	Matching	Odds ratio	95% CI
Chin (31)	Diabetes	Age, weight, initial nPCR	—	0.29*†	0.11–0.77*
DaRoza et al. (32)	Diabetes	Age, sex, use of erythropoietin, albumin level, hemoglobin level, urea level, weight, GFR	—	0.27	0.10–0.71
Lacson et al. (37)‡	Diabetes	Age, sex, race, vaccine type, albumin, BSA, hemoglobin, vintage (square root), modality, hepatitis C	Age, sex, race, vintage, modality§	1.02§	0.93–1.12
Taheri et al. (42)	Diabetes	Age, sex, dialysis treatment	—	0.23	0.09–0.59*
Zitt et al. (44)	Diabetes	Age, sex, modality, 25(OH)D, VDRA treatment	—	0.50	0.26–0.96

25(OH)D, 25-hydroxyvitamin D; BSA, body surface area; GFR, glomerular filtration rate; nPCR, normalized protein catabolic rate; VDRA, vitamin D receptor activator. \*Inverse of values reported by author because reported values were for failure to achieve seroprotection response. †Diabetes was no longer significant when the parameter for baseline serum albumin was added into the model. ‡Seroprotection response threshold of 10 mIU/mL was confirmed by personal communication with author. §Authors performed a matched analysis on a subset of 814 pairs (for this subset analysis, matched variables were excluded from multivariate model); odds ratio and 95% CI from matched analysis were 0.71 and 0.52–0.97, respectively.

generally have responses similar to persons of comparable age without diabetes. Older adults have a reduced response, and older adults with diabetes seem to have further impairment in vaccine response, particularly those with coexisting kidney conditions.

There are several hypotheses about the biological basis for potentially impaired response to vaccination among persons with diabetes. Although persons with diabetes have appropriate humoral immune responses to vaccination (49), impaired cellular response may account for less robust antibody production after hepatitis B vaccination (14). Proposed explanations include a reduction in the number of circulating helper T cells, the CD4-to-CD8 lymphocyte ratio, and lymphocyte blastogenesis (23) and defects with antigen presentation (39). Impaired vaccine response also has been linked to the presence of DR3, DR7, and DQ2 human leukocyte antigen alleles among persons with diabetes (13). However, no association between seroprotection and glycemic control (13,14,30,39), duration of diabetes (13,30,39), insulin requirement (30,39), or microangiopathic complications (39) was demonstrated in studies included in this review.

Obesity is a major risk factor for type 2 diabetes; 53% of adults with diabetes are obese (50). Studies have demonstrated an association between obesity and a reduced response to hepatitis B vaccine in adults (51). A needle length that is inadequate to penetrate the deltoid fat pad and reach the muscle mass may account for the reduced immune response among persons with obesity (4,52). The less abundant blood supply in adipose

tissue may delay antigen presentation to the B and T cells responsible for the immune response (52). However, the needle should not be so long that it involves the underlying bone (4).

In addition to obesity (52), older age (6–9,47), comorbid conditions (11), and medication use (12) have been associated with impaired vaccine response and may confound the relationship between diabetes and immune response. Four multivariate analyses among hemodialysis/chronic kidney disease patients included in this review, all of which controlled for age and three of which controlled for obesity, found diabetes to be an independent factor for impaired vaccine response (31,32,42,44). Lacson et al. (37), however, reported a null association with diabetes and seroprotection among hemodialysis/chronic kidney disease patients ( $N = 14,546$ ; OR 1.02 [95% CI 0.93–1.12]) in their principal multivariate analysis.

Administration of additional doses of hepatitis B vaccine improves the proportion of persons responding to it. Additional doses have not caused unusual adverse reactions (16). It is recommended that health care personnel at continuing risk of hepatitis B exposure and infants with perinatal hepatitis B exposure repeat a primary series of hepatitis B vaccine if they are found to be nonresponsive to the initial series (4,5). Among health care personnel who did not respond after a primary series, 67.6% mounted a protective response up to three additional doses (11). Data exclusively on revaccination of nonresponding persons with diabetes are sparse. Although postvaccination serology to determine responses among adults with diabetes is not cost

effective (Centers for Disease Control and Prevention, 2011, unpublished data) and not recommended, using schedules requiring four rather than three doses or administering additional doses of hepatitis B vaccine remains an option.

A longer interval between the final two doses of the primary hepatitis B vaccine series has been associated with higher final anti-HBs levels in general (4). Findings from this review suggest that a longer interval between the final two doses also is associated with increased seroprotection proportions among persons with diabetes. Excessively long intervals have the drawback of increasing the risk for acquisition of HBV infection among those with an incomplete series (4).

Other strategies that may augment the response to hepatitis B vaccine in persons with diabetes include the use of novel adjuvants, higher dosages, or combination vaccines. No hepatitis B vaccine with a novel adjuvant is currently licensed for use in the U.S. Recent prelicensure trials using a two-dose schedule with a hepatitis B vaccine containing a toll-like receptor 9 (HBsAg-1018 ISS) agonist as the adjuvant seems promising (53). Other strategies that could be explored in clinical trials include the use of the combined hepatitis A virus and HBV vaccine Twinrix (GlaxoSmithKline Biologicals) (54,55) or hemodialysis dosage of the hepatitis B vaccine (56). Because response declines with advancing age and comorbidities (11), vaccination soon after diabetes diagnosis likely would constitute the most practical way to optimize seroprotection.

This review has several limitations. It is possible that all relevant studies may not have been identified in the literature search, especially those studies in which

persons with diabetes represented a subset of the population. There is the potential for publication bias. Studies with significant results are more likely to be published than those with null results, and this review consisted only of published studies. A null result for some studies in this review would consist of an equivalent vaccine response in persons with and without diabetes. It is therefore unlikely that publication bias would lead to a reported overestimate of vaccine response among persons with diabetes. Only 17 of the identified studies were included in this review (and only 5 multivariate analyses), and data pertaining to adults with diabetes but without hemodialysis/chronic kidney disease were sparse. Observational studies were included, and the results of these studies may not be as robust as randomized clinical trials. The matched comparison groups and objective outcome measure (i.e., anti-HBs levels) strengthen the data quality. Outcomes consisted of serological correlates of protection (anti-HBs levels), which may not correlate with maintaining full vaccine effectiveness over time. Immunocompetent persons found to have anti-HBs levels of  $\geq 10$  IU/L after the primary series, consistent with the threshold used by studies included in this review, are considered to be protected (4,5,57). Duration of protection was not assessed in this review, although other evidence suggests protection lasts for two decades in healthy primary vaccine responders. However, data on the duration of immune memory in immunocompromised persons are limited (4). Although general conclusions were drawn from a synthesis of the results, no attempt was made to test for statistically significant differences. A meta-regression was not conducted because colinearity likely exists among sources of heterogeneity (e.g., children most likely have type 1 diabetes and are treated with insulin). Heterogeneity between studies by diabetes type, management, glycemic control, and vaccine type, dosage, administration route, and schedule limit synthesis of results.

High levels of seroprotection from recombinant hepatitis B vaccine are achieved safely in children with diabetes. Data from studies reviewed here suggest that adults with diabetes have a reduced response to vaccination. Seroprotection is decreased among older adults and persons on hemodialysis in general, including those with diabetes. Administration of schedules using an extended interval to

the final dose, four vs. three doses, or additional vaccine doses may achieve seroprotection in a greater proportion of adults with diabetes, including those who do not respond to an initial series. Other strategies to increase response among older adults with diabetes, including those with other comorbid conditions, should be explored.

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