CDC Recommendation for Hepatitis B Vaccination among Adults with Diabetes:

Grading of Scientific Evidence in Support of Key Recommendations

GRADE Tables: Hepatitis B Vaccination Among Persons with Diabetes Referenced in MMWR Dec 23, 2011 / Vol 60(50);1709-11

Methods for Grading of Recommendations Assessment, Development, and Evaluation (GRADE) According to ACIP Guidelines

Evidence of benefits, harms, values and preferences, and cost effectiveness were reviewed in accordance with GRADE methods to determine the recommendation category (Ahmed F, Temte JL, Campos-Outcalt D, Schünemann HJ; for the ACIP Evidence Based Recommendations Work Group (EBRWG). Methods for developing evidence-based recommendations by the Advisory Committee on Immunization Practices (ACIP) of the U.S. Centers for Disease Control and Prevention (CDC). *Vaccine* 29(49):9171-6, 2011). Pooled data from 6 placebo-controlled randomized trials (5798 subjects) indicated a relative risk for hepatitis B infection events of 0.37 (95% CI 0.29, 0.48) among vaccinated subjects, although evidence type was downgraded for indirectness as trials did not focus on subjects with diabetes. Pooled data from 5 observational studies (285 subjects with diabetes) indicated 91.6% of subjects with diabetes achieved seroprotection, although evidence type was downgraded for imprecision due to small numbers. No serious vaccine-related adverse events were reported in any study. The Institute of Medicine found evidence supporting a causal relationship between hepatitis B vaccination and anaphylaxis in yeast-sensitive individuals; the risk of anaphylaxis following hepatitis B vaccine is estimated at 1.1 per million doses. [IOM (Institute of Medicine). 2011. Adverse Effects of Vaccines: Evidence and Causality. Washington, DC: The National Academies Press; Bohlke K, Davis RL, Marcy SM, Braun MM, DeStefano F, Black SB, Mullooly JP, Thompson RS; Vaccine Safety Datalink Team. Risk of anaphylaxis after vaccination of children and adolescents, *Pediatrics* 2003;112:815-20].

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Table 1: Benefits and Harms of Hepatitis B Vaccination Among Persons with Diabetes[a]

Outcome	No. of subjects (# studies)	Incidence in controls	Incidence in vaccinated	Relative risk (95% CI) of hepatitis B infection events among vaccinated	Seroprotection proportion among subjects with diabetes (95% CI)	Risk difference per 1000 (95% CI), vaccinated versus not vaccinated	Number needed to vaccinate (NNV)
BENEFITS							
Hepatitis B infection events	5798 (6 RCTs)	10.7%[b]	4.1%[b]	0.37 (0.29, 0.48)[b]	--	-67 (-76, -56)[c]	261[d]
Seroprotection	285 (5 Obs)	--	--	--	91.6% (87.6%, 94.4%)	--	--
HARMS							
Serious adverse events	6251 (6 RCTs and 3 Obs)	0.0%[e]	0.0%[e]	--	--	--	--
Anaphylaxis	6251 (6 RCTs and 3 Obs)	0.0%[e]	0.0%[e]	--	--	--	--

[a] Some studies include persons with and without diabetes

[b] Follow-up ranged from 12-29 months; figures do not account for person-time of follow-up for all studies; relative risk and 95% CI calculated from RevMan software version 5.1

[c] Calculated from GRADE profiler software version 3.6 assuming fixed effects

[d] Number needed to treat (number needed to vaccinate) calculated from modeling analysis of adults with diabetes ages ≥20 years (lifetime perspective)

[e] No serious events reported. Study sizes not sufficient to detect rare serious adverse events

Table 2: Type of Evidence for Hepatitis B Vaccination Benefits and Harms among Persons with Diabetes[a]

Outcome	Design (# studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Evidence type
Benefits							
Hepatitis B infection events	RCT (6)	No serious	No serious	Yes (-1)[b]	No serious	No serious	2
Seroprotection	Obs (5)	No serious	No serious	No serious	Yes (-1)[c]	No serious	4
Harms							
Serious adverse events	RCT (6) Obs (3)	No serious	No serious	Yes (-1)[b]	No serious	No serious	2[d]
Anaphylaxis	RCT (6) Obs (3)	No serious	No serious	Yes (-1)[b]	No serious	No serious	2[d]

[a] Some studies include persons with and without diabetes

[b] Subjects with diabetes not focus of RCT studies; one RCT used 3 mcg dose on 0,1,2 month schedule; one study used 5 mcg dose on 0,1,2 month schedule with subcutaneous administration

[c] Total number of events <300, 95% CI 0.88, 0.94

[d] Study sizes not sufficient to detect rare adverse events: rate of anaphylaxis estimated 1.1 per million doses (95% CI 0.1, 3.9 per million doses); (Bohlke K. et al. *Pediatrics* 2003;112:815-20). Widespread vaccine use for 30 years has not revealed other serious adverse events (IOM (Institute of Medicine). 2011. Adverse Effects of Vaccines: Evidence and Causality. Washington, DC: The National Academies Press)

Table 3: Summary of Evidence for Benefits and Harms of Hepatitis B Vaccination among Adults with Diabetes[a]

Comparison	Outcome	Study design (# studies)	Findings	Evidence type	Overall evidence type
Hepatitis B vaccination vs. no vaccination	Hepatitis B infection events	RCT (6)	Decreased risk among vaccinated	2	2
	Seroprotection	Obs (5)	Seroprotection among subjects with diabetes similar to that among subjects without diabetes	4	
	Serious adverse events	RCT (6) Obs (3)	No serious vaccine-related adverse events	2[b]	
	Anaphylaxis	RCT (6) Obs (3)	No serious vaccine-related adverse events	2[b]	

[a] Some studies include persons with and without diabetes

[b] Study sizes not sufficient to detect rare adverse events

Table 4. Considerations for Formulating Recommendations: Hepatitis B Vaccine for Adults with Diabetes

Key factors	Comments
Balance between benefits and harms	Benefits are greater than potential harms
Evidence type for benefits and harms	Benefits: Evidence type 2 Harms: Approximately 30 year hepatitis B vaccine history indicates serious adverse events and anaphylaxis extremely rare
Values	High values on preventable outcomes[a] for persons <60 years and moderate to high values for persons ≥60 years assigned by ACIP Hepatitis Work Group
Cost-effectiveness	Vaccination is most cost effective for adults with diabetes for ages <60 years

[a]Preventable outcomes consist of acute hepatitis, fulminant hepatitis, chronic hepatitis, cirrhosis, hepatocellular carcinoma, liver transplantation, death

Summary: Benefits are greater than potential harms; overall evidence is type 2. High values were placed on prevention of the morbidity and mortality of hepatitis B virus infection among adults with diabetes.

Study References

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