OREGON HEALTH AND SCIENCE UNIVERSITY
OFFICE OF CLINICAL INTEGRATION AND EVIDENCE-BASED PRACTICE

Evidence-Based Practice Summary
Hepatitis B Vaccination in Adults with Diabetes Mellitus

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BACKGROUND AND RATIONALE

Hepatitis B virus (HepB) is transmitted through percutaneous or mucosal exposure to infectious blood or body fluids. HepB is highly infectious, can be transmitted in the absence of visible blood, and remains viable on environmental surfaces for at least seven days. Persons with chronic infection serve as the main reservoir for HepB transmission. In 2015, a total of 3,370 cases of acute HepB infection were reported to CDC. However, due to under reporting, the actual number of acute cases is believed to be 6.5 times the number of reported cases in any year. The rate of reported acute HepB infections declined 88.5% since the commendations for HepB vaccination were first issued, from 9.6 cases per 100,000 population in 1982 to 1.1 cases per 100,000 population in 2015. [1]

Compared with adults without diabetes, adults with diabetes have a 60% higher prevalence of past or present HepB infection and twice the odds of acquiring acute HepB and a higher frequency of chronic infection with lower vaccination coverage. Data also suggest the possibility of a higher case-fatality proportion among persons with diabetes acutely infected with HepB compared with those without diabetes. [1]

ASK THE QUESTION

In adult patients with diabetes, what are the harms and benefits of the hepatitis B vaccine?

SEARCH FOR EVIDENCE

Databases included Ovid MEDLINE, MEDLINEinprocess, the Cochrane Central Register of Controlled Trials (CCRCT) & Cochrane Database of Systematic Reviews (CDSR).

See Appendix B for full search strategy.

CRITICALLY ANALYZE THE EVIDENCE

Primary Literature:

The literature search resulted in more than 60 articles that analyzed hepatitis B vaccines in adults with diabetes. Nine of the studies met eligibility criteria and were included in this review. The nine studies included systematic reviews, non-randomized studies and relevant modelling studies from 2008-2018.

1. Immunological Response: Seven studies investigated the immunological response of the HepB vaccine in adults with diabetes, 4 non randomized studies and 3 systematic reviews. The first non-randomized study (Al Saran 2014) was a retrospective cohort study that sought to determine the response to hepatitis B virus (HBV) vaccination in patients on hemodialysis (HD) and to identify the factors that could affect this response. Of the 144 patients on chronic HD involved in the study, 49 had diabetes. The authors found no statistical difference between responders and non-responders regarding the presence or absence of diabetes (P=0.5). The second non-randomized study (Lin 2012) was a retrospective cohort study that sought to determine the relationship between the immune response following a hepatitis B vaccination (HBV vaccination) and the survival of maintenance dialysis patients. This retrospective cohort study included 156 patients on HD, 50 of these patients had diabetes. The response rate was not statistically significant (P=0.111). Using the response rate as a predictor of infection-cause mortality, diabetes was a statistically significant predictor (P=0.0084). The third non-randomized study (Ocak 2008) was a prospective cohort study that investigated whether HD patients suffering from diabetes mellitus could be considered at risk for the development of the protective antibodies to hepatitis B (HB) vaccination and, to evaluate the effectiveness of tetanus toxoid (TT) administrated 2 days before HB vaccination. Their results indicated that after the completion of the course, the patients in group A (DM patients) were found to have a lower protective antibody rates than the patients in group B (57.8% vs 70%) (P > 0.05). The patients not having protective HBsAb levels were administered TT and HB vaccines, and after course, all of them have produced protective HBsAb levels. The final non-randomized study (Van Der Meeren 2016) assessed the safety and immunogenicity of recombinant hepatitis B vaccine in subjects with and without diabetes mellitus. They found that one month after the vaccine doses the seroprotection rate was 75.4% in the diabetes group and 82.0% in the control group. They found that age and BMI had a statistically significant negative effect on the likelihood of achieving seroprotection (P< 0.0001) but not gender or whether the subject was diabetic or not. The first systematic review (Alavian 2010) evaluated the immunological response to HBV vaccine in diabetic patients with chronic kidney disease (CKD) by conducting a meta-analysis of the current literature. Their review included 7 studies involving 15,073 subjects. Their aggregation of study results showed a significant decrease in response rates among the diabetic versus the non-diabetic patients [pooled odds ratio=0.58 (95% CI 0.37-0.89), P= 0.07]. The second systematic review (Fabrizi 2011) that evaluated the influence of diabetes mellitus on the immune response to HBV vaccine in dialysis population. The review included 12 studies involving 1002 unique patients on long-term dialysis. Their results indicated a significant decrease in seroprotection rates among patients with diabetes mellitus vs. nondiabetic patients was found; the pooled OR was = 0.52 [(95% CI 0.38-0.71), P = 0.001]. The final systematic review (Schille 2012) reviewed the literature and

summarized the evidence for seroprotection after hepatitis B vaccination among persons with diabetes. The review included 17 studies and 16,310 unique subjects, of which approximately 9,286 had diabetes. They reported that 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. They also reported that 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. Due to study heterogeneity, they were unable to conduct a meta-analysis.

Overall Level of Evidence: Low to indicate that the immunological response for the HepB vaccination is lower in adults with diabetes compared to adults without diabetes.

2. Complications from diabetes with hepatitis B: One non-randomized study (Deshpande 2016) measured healthcare utilization and costs for patients with both HBV infection and diabetes compared with patients with diabetes alone using a real-world population of adults enrolled in large commercial health plans. Their retrospective claims analysis included 918,488 patients (1,240 patients with diabetes and HBV infection [cases]; 917,248 patients with diabetes but no HBV infection [controls]). Their results indicated that the mean number of hospitalizations (0.6 vs 0.4), outpatient service visits (34.2 vs. 20.4), and office visits (10.9 vs. 9.8) were 41%, 68%, and 11% higher, respectively, in patients with both diabetes and HepB vs. patients with diabetes alone (all P<0.05). They also found that patients with HepB ($39,435) incurred $16,397 incremental total costs compared with controls ($23,038). Medical ($30,968 vs. $17,765) and pharmacy costs ($8,029 vs. $5,114) were both significantly higher for cases (P < 0.0001).

Overall Level of Evidence: Very Low to indicate that healthcare utilization and costs are higher in patients with both HepB and diabetes compared the patients with diabetes alone.

3. Adverse events from the HBV: One non-randomized prospective cohort study (Van Der Meeren 2016) assessed the safety and immunogenicity of recombinant hepatitis B vaccine in subjects with and without diabetes mellitus. They found that Grade 3 solicited symptoms (e.g headache, pain, dizziness etc.) were reported by 2.9% or fewer of participants in each group. With no difference between groups and that there was no increase in symptoms in either group with consecutive doses.

Overall Level of Evidence: Very Low to indicate that there is no difference in adverse events from the HepB vaccine between patients with and without diabetes.

Modeling Study Summary			
Author/Date	*Purpose of Study*	*Methods*	*Outcomes*
Journal: Diabetes **Author:** Hoerger, T. J., et al.. **Year Published:** 2013 **Location:** USA	To examine the cost-effectiveness of a hepatitis B vaccination program for unvaccinated adults with diagnosed diabetes in the U.S.	Cost-effectiveness simulation model of vaccination for hepatitis B and outcomes of HBV infection reflected the impact of hep B in adults with diagnosed di-abetes. The model accounted for higher incidence of HBV infection among adults with diagnosed diabetes, higher mortality among people with diabetes, and older age at peak diabetes prevalence. The analysis begins with the choice of vaccination	***Health Outcomes:*** With a 10% uptake rate, the intervention will vaccinate 528,047 people and prevent 4,271 acute and 256 chronic hepatitis B infections.

		strategy, which may include vaccination or no vaccination. Outcomes were assessed for the entire population of U.S. adults 20-59 years of age who cur-rently have diagnosed diabetes. The study population was stratified into 5-year age groups. The model tracks hepatitis-re-lated events from both acute and chronic HBV infections.	*Table 2—Acute and chronic health outcomes prevented by hepatitis B vaccination* Acute cases prevented Age-groups vaccinated | Number vaccinated with 10% uptake rate | Infected | Acute symptomatic | Hospitalizations | Fulminant cases | Transplants | Fulminant deaths 20–59 | 528,047 | 4,271 | 1,281 | 467 | 19 | 8 | 14 60+ | 774,394 | 723 | 217 | 79 | 3 | 1 | 2 All ages, 20+ | 1,302,441 | 4,994 | 1,498 | 547 | 23 | 9 | 16 Chronic cases prevented Age-groups vaccinated | Chronic cases | Cirrhosis | Decompensated cirrhosis | HCC | Transplants | Chronic deaths 20–59 | 256 | 146 | 56 | 33 | 5 | 116 60+ | 43 | 17 | 5 | 3 | 0 | 9 All ages, 20+ | 300 | 164 | 60 | 36 | 5 | 125 ***Cost effectiveness:*** Net health care costs will increase by $91.4 million, and 1,218 QALYs will be gained, producing a cost-effectiveness ratio of $75,094 per QALY gained. Results are most sensitive to age, the discount rate, the hepatitis B incidence ratio for people with diabetes, and hepatitis B infection rates. Cost-effectiveness ratios rise with age at vaccination; an alternative intervention that vaccinates adults with diabetes 60 years of age or older had a cost-effectiveness ratio of $2.7 million per QALY

External Guideline Recommendations:

In 2011, the **CDC** released their recommendations on the use of Hepatitis B Vaccination for Adults with Diabetes Mellitus:

1) Hepatitis B vaccination should be administered to unvaccinated adults with diabetes mellitus who are aged 19 through 59 years (recommendation category A; evidence type 2).
2) Hepatitis B vaccination may be administered at the discretion of the treating clinician to unvaccinated adults with diabetes mellitus who are aged ≥60 years (recommendation category B; evidence type 2)

In 2018, the **American Diabetes Association** released an updated set of Standards of Care for Diabetes Management:

1) Administer 3-dose series of hepatitis B vaccine to unvaccinated adults with diabetes ages 19 through 59 years. *Grade C*
2) Consider administering 3-dose series hepatitis B vaccine to unvaccinated adults with diabetes who are aged >60 years. *Grade C*

In 2018, the **CDC** released their updated Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices:

1) Adults recommended to receive HepB vaccine: Persons with diabetes aged 19–59 years; persons with diabetes aged ≥60 years at the discretion of the treating clinician.
2) In medical settings, health care personnel should implement standing orders to identify adults recommended for HepB vaccination and administer vaccination as part of routine services.

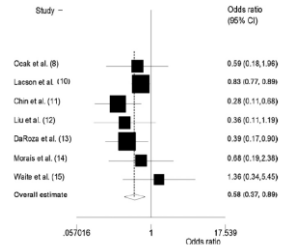
INTERNAL CLINICAL PRACTICE RECOMMENDATION

Hepatitis B vaccination should be administered to unvaccinated adults with diabetes mellitus who are aged 19 through 59 years. -*Strong Recommendation; Low Quality Evidence*

Hepatitis B vaccination may be administered at the discretion of the treating clinician to unvaccinated adults with diabetes mellitus who are aged ≥60 years. -*Consensus Statement*

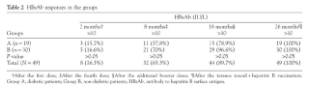
PICO Question: In adult patients with diabetes, what are the harms and benefits of the hepatitis B vaccine?						**Low Quality Rating if:** ☒ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*)
Outcome: Immunological Response						
Study Acronym; Author; Year Published; Location	**Aim of Study; Study Type; Study Size (N)**	**Patient Population**	**Study Intervention/ Study Comparator**	**Results (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**	
Total # of Studies: 7 # of Systematic Reviews: 3 # of RCTs: 0 # of Non-Randomized Studies: 4 # of Diagnostic Studies: 0						

Journal: *Saudi Journal of Kidney Diseases & Transplantation* **Author**: Al Saran, K., et al. **Year Published:** 2014 **Location:** The Prince Salman Center for Kidney Diseases, Saudi Arabia	**Aim**: To determine the response to hepatitis B virus (HBV) vaccination in patients on hemodialysis (HD) and to identify the factors that could affect this response. **Study Type**: retrospective study **Size**: 144 patients (78 males and 66 females)	**Inclusion Criteria**: adult patients on chronic hemodialysis (49 patients with diabetes mellitus) **Follow-Up:** 6 months	**Intervention**: hepatitis B vaccination **Comparator**: Patients were divided into two groups according to the level of hepatitis B surface antibodies (HBsAb): Responders group (>10 IU/L) and non-responders group (<10 IU/)	**Results**: There were 129 patients (89.6%) in the responders group including 69 males and 60 females and 15 patients (10.4%) in the non-responders group including nine males and six females. There was no statically significant difference between the two groups regarding the presence or absence of hepatitis C virus infection, age, gender, **diabetes mellitus (P=0.5)**, hemoglobin level and albumin level. HbA1C was used as an indicator of glycemic control for diabetic patients included in the study. There was no significant difference between the responder group and the non-responder group in the HbA1C, Hb and CRP levels	Study Limitations: ☒ None ***Non-Randomized*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☐ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)* ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* **Increase Quality Rating if:** ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect **Quality (certainty) of evidence for studies as a whole:** ☐ High ☐ Moderate ☒ Low

Journal: *Vaccine* **Author:** Alavian, S. M. and S. V. Tabatabaei **Year Published:** 2010 **Location:** Baqiyatallah University of Medical Sciences, Research Center for Gastroenterology and Liver Disease, Tehran, Iran	**Aim**: To evaluate the immunological response to HBV vaccine in diabetic patients with CKD by conducting a meta-analysis of the current literature. **Study Type**: Systematic Review with meta-analysis **Size**: 7 studies involving 15,073 subjects	**Inclusion Criteria**: prospective and retrospective studies comparing the response rate in diabetic CKD patients (study group) vs. non-diabetic CKD patients (control group). Also included studies that had reported response rates in both diabetic and non-diabetic subjects separately. Studies that recruited dialysis patients were considered still eligible. Trials of the plasma-derived and recombinant DNA HBV vaccine were included. All dose schedules and routes of vaccine administration were accepted as qualifying. **Exclusion Criteria**: Studies that reported inadequate data on measures of response, or included the individuals with positive serology for hepatitis B virus surface antigen (HBsAg), antibodies to HBsAg (HBsAb) and antibodies to hepatitis B virus core antigen (HBcAb) or HIV and patients with concurrent administration of immunosuppressive medicines were excluded.	**Intervention**: HBV vaccine **Comparator**: diabetic versus the non-diabetic CKD patients	**Results**: ***Serological response to HBV vaccine*:** Aggregation of study results showed a **significant decrease in response rates among the diabetic versus the non-diabetic patients [pooled odds ratio=0.58** (95% CI 0.37-0.89), P= 0.07]  Fig. 2. Summary estimate of ORs of seroprotection rate of HBV vaccine in DM vs. non-DM patients with CKD. Square areas do not correspond to study weights in meta-analysis.	Study Limitations: ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies	☐ Very Low

Journal: *Alimentary Pharmacology & Therapeutics* **Author:** Fabrizi, F., et al. **Year Published:** (2011) **Location:** Milan, Italy and Miami, Florida	**Aim**: To evaluate the influence of diabetes mellitus on the immune response to HBV vaccine in dialysis population. **Study Type**: A systematic review with a meta-analysis **Size**: 12 studies involving 1002 unique patients on long-term dialysis	**Inclusion Criteria**: Adults undergoing maintenance hemodialysis and peritoneal dialysis. studies that (i) specified either a relative risk and a measure of variance for vaccine response among dialysis patients with diabetes mellitus, compared with nondiabetic individuals, or (ii) presented data in a form that could be used to construct a 2 x 2 contingency table were considered for final inclusion **Exclusion Criteria**: Students, military recruits or cohorts of subjects <19 years	**Intervention**: HBV vaccine **Comparator**: seroprotection rate after completion of HBV vaccination schedule in patients with diabetes mellitus vs. nondiabetic patients.	**Results:** A **significant decrease in seroprotection rates among patients with diabetes mellitus vs. nondiabetic patients was found**; the pooled OR was = 0.52 (95% CI 0.38-0.71), P = 0.001.	Study Limitations: ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies	

Journal: *BMC Nephrology* **Author:** Lin, S. Y., et al. **Year Published:** 2012 **Location:** China Medical University Hospital in Taichung, Taiwan	**Aim**: To determine the relationship between the immune response following a hepatitis B vaccination (HBV vaccination) and the survival of maintenance dialysis patients. **Study Type**: Retrospective Cohort Study **Size**: 156 patients (103 on hemodialysis and 53 on continuous ambulatory peritoneal dialysis, 50 patients with diabetes)	**Inclusion Criteria**: Patients who underwent dialysis therapy between March 2002-March 2008 **Follow-Up**: 5 years	**Intervention**: All patients were given four doses (40 µg per dose) of the hepatitis B vaccine in the deltoid muscles at 0, 1, 2, and 6 months. Anti-HBs titers were measured at one month after the final dose and annually thereafter. **Comparator**: responders and non-responders were define according to the level of anti-HBs one month after the final injec-tion (non-responders: < 10 IU/L; responders: ≥ 10 IU/L).	**Results:** The response rate to the hepatitis B vaccination was 70.5%. There was no significant association between the immune response and the 5-year survival rate (p =0.600) or between the post-vaccination anti-HBs titers and the 5-year survival rate (p = 0.201). **The response rate of the patients with DM was not statistically significant (P=0.111)** The logistic prediction model with the coefficient as non-response following HBV vaccination, diabetes mellitus, old age, and low albumin level could significantly predict infection-cause mortality (sensitivity = 0.842, specificity = 0.937). **Table 3 The predictive model of infection-cause mortality in dialysis patients Logit (probability of infection-cause mortality) =β0 + β1*Retiter + β2*DM + β3*Age + β4*Albumin + β5*DM*Albumin + β6*Age*Albumin** **Covariates** / **Coefficient** / **p-value** Intercept / 143.4122 / 0.0232 Seroconversion following HBV vaccination / −4.7392 / 0.0068 Presence of DM / −5.3569 / 0.0084 Age / −1.9758 / 0.3333 Albumin / −40.2689 / 0.0234 DM*Albumin / 13.1720 / 0.0089 Age*Albumin / 0.5699 / 0.0317	Study Limitations: ☐ None ***Non-Randomized*** ☐Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☒ Differences in important prognostic factors at baseline	

Journal: *Nephrology* **Author:** Ocak, S. and A. F. Eskiocak **Year Published:** 2008 **Location:** Antakya Hemodialysis Center, Turkey	**Aim**: To investigate whether hemodialysis (HD) patients suffering from diabetes mellitus could be considered at risk for the development of the protective antibodies to hepatitis B (HB) vaccination and, to evaluate the effectiveness of tetanus toxoid (TT) administrated 2 days before HB vaccination. **Study Type**: Prospective Cohort Study **Size**: 49 HD patients were divided into two groups: group A (19 diabetic patients) and group B (30 non-diabetic patients).	**Inclusion Criteria**: Patients who underwent dialysis therapy in January 2003 **Follow-Up**: 26 months	**Intervention**: All patients were given four doses (40 µg per dose) of the hepatitis B vaccine in the deltoid muscles at 0, 1, 2, and 6 months. HBsAb levels were measured at two-month intervals for 12 months. In the cases with HBsAb levels <10 IU/L, the additional booster doses of the vaccine were administered intramuscularly with 2 month intervals, for two or three times. After the additional booster doses, the patients not having protective HBsAb levels were administered TI (tetanus toxoid vaccine) as a vaccine adjuvant intra-muscularly into the right deltoid muscle at a dose of 0.5 ml (40 JU) after HD session. In the second day after the administration of TI, a dose of 40 µg of HepB vaccine was given intramuscularly into the left deltoid muscle of the patients. **Comparator**: responders and non-responders were defined according to HBsAb levels (non-responders: < 10 IU/L; responders: ≥ 10 IU/L).	**Results**: After the completion of the course, **the patients in group A (DM patients) were found to have a lower protective antibody rates than the patients in group B (57.8% vs 70%) (P > 0.05).** After the administration of additional booster doses during 12 months, the protective antibody to hepatitis B surface antigen (HBsAb) levels were detected in 78.9% and 96.6% of the patients in group A and group B, respectively (P > 0.05). **The patients not having protective HBsAb levels were administered TT and HB vaccines, and after course, all of them have produced protective HBsAb levels.**  **Table 3** HBsAb titres in groups at 26 months after tetanus toxoid + hepatitis B vaccination HBsAb (IU/L) Groups: <10 / 10–100 / ≥100 A (n = 19): 0 (0%) / 9 (47.3%) / 10 (52.6%) B (n = 30): 0 (0%) / 10 (33.3%) / 20 (66.6%) Total (N = 49): 0 (0%) / 19 (38.7%) / 30 (61.2%) Group A, diabetic patients; Group B, non-diabetic patients; HBsAb, antibody to hepatitis B surface antigen.	Study Limitations: ☐ None ***Non-Randomized*** ☐Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☒ Differences in important prognostic factors at baseline	

Journal: *Diabetes Care* **Author:** Schillie, S. F., et al. **Year Published:** 2012 **Location:** USA	**Aim**: To review the literature and summarize the evidence for seroprotection after hepatitis B vaccination among persons with diabetes. **Study Type**: Systematic Review **Size**: 17 studies and 16,310 unique subjects, of which approximately 9,286 had diabetes.	**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. **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 naive 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.	**Intervention**: HepB vaccine **Comparator**: Seroprotection proportion defined according to HBsAb levels (non-responders: < 10 IU/L; responders: > 10 IU/L) in patients with and without diabetes	**Results**: **Due to heterogeneity, a statistical analysis was not possible.** 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.	Study Limitations: ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	

Journal: *Human Vaccines & Immunotherapeutics* **Author:** Van Der Meeren, O., et al. **Year Published:** 2016 **Location:** 21 centers in Australia, Canada, New Zealand and the US.	**Aim**: To assess the safety and immunogenicity of recombinant hepatitis B vaccine in subjects with and without diabetes mellitus. **Study Type**: Prospective, multi-country controlled study in 21 centers **Size**: 416 participants with Type-2 diabetes and 258 controls matched for age and body mass index	**Inclusion Criteria**: The diabetes group comprised subjects with type-2 DM diagnosed within the past 5 y according to criteria specified by the American Diabetes Association, or who had commenced treatment with any form of anti-diabetic medication within the past 5 y. Participants in the control group had no documented history of DM and had serum glycated hemoglobin (HbA1c) <6.5% (48 mmol/ml IFCC) at the time of screening. **Follow-Up**: 1 month after intervention	**Intervention**: Screening was conducted 2 to 28 d before the first vaccine dose. Serum creatinine, HBsAg, anti-HBs antibodies, anti-HBc antibodies and HbA1c were measured in all participants at central laboratories using validated commercial assays. All participants received 3 doses of hepatitis B vaccine at 0, 1 and 6 months. The vaccine was administered as an intramuscular injection into the deltoid muscle of the non-dominant arm. Blood samples were collected at the screening visit and one month after the third vaccine dose. Anti-HBs antibodies were measured with a level of detection of 6.2 mIU/mL defining seropositivity. **Comparator**: responders and non-responders were defined according to HBsAb levels (non-responders: < 10 IU/L; responders: ≥ 10 IU/L).	**Results**: One month after the 3 vaccine doses, the seroprotection rate was 75.4% in the diabetes group and 82.0% in the control group (P=0.0741). **Age and BMI had a statistically significant negative effect on the likelihood of achieving seroprotection (P< 0.0001) but not gender or whether the subject was diabetic or not.**	Study Limitations: ☒ None ***Non-Randomized*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

PICO Question: In adult patients with diabetes, what are the harms and benefits of the hepatitis B vaccine?	**Low Quality Rating if:** ☒ Studies inconsistent
Outcome: Complications from diabetes with hepatitis B	

Study Acronym; Author; Year Published; Location	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention/ Study Comparator	Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Design Limitations	*(wide variation of treatment effect across studies, population, interventions, or outcomes varied)* ☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☐ Studies are imprecise *(when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* **Increase Quality Rating if:** ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect **Quality (certainty) of evidence for studies as a whole:** ☐ High ☐ Moderate ☐ Low ☒ Very Low
Total # of Studies: 1 # of Systematic Reviews: 0 # of RCTs: 0 # of Non-Randomized Studies: 1 # of Diagnostic Studies: 0						
Journal: *Human Vaccines & Immunotherapeutics* **Author:** Deshpande, G., et al. **Year Published:** 2016 **Location:** USA	**Aim**: To measure healthcare utilization and costs for patients with both HBV infection and diabetes compared with patients with diabetes alone using a real-world population of adults enrolled in large commercial health plans. **Study Type**: retrospective claims analysis **Size**: 918,488 patients (1,240 patients with diabetes and HBV infection [cases]; 917,248 patients with diabetes but no HBV infection [controls])	**Inclusion Criteria**: Patients with diabetes and patients with diabetes and Hep B **Follow-Up**: N/A	**Intervention**: Cases were matched with 4 controls using propensity score matching. **Comparator**: Healthcare utilization and costs comparing patients with diabetes and HBV with those with diabetes alone.	**Results:** ***Utilization:*** **the mean number of hospitalizations** (0.6 vs 0.4), **outpatient service visits** (34.2 vs. 20.4), **and office visits** (10.9 vs. 9.8) **were 41%, 68%, and 11% higher, respectively, in cases vs. controls (all P<0.05)**. **Costs:** **Cases** ($39,435) **incurred $16,397 incremental total costs compared with controls** ($23,038). **Medical** ($30,968 vs. $17,765) **and pharmacy costs** ($8,029 vs. $5,114) **were both significantly higher for cases (P < 0.0001)**.	Study Limitations: ☐ None ***Non-Randomized*** ☐Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☒ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

PICO Question: In adult patients with diabetes, what are the harms and benefits of the hepatitis B vaccine?						**Low Quality Rating if:** ☒ Studies inconsistent *(wide variation of treatment effect across studies, population, interventions, or outcomes varied)*
Outcome: Adverse Events						
Study Acronym; Author; Year Published; Location	**Aim of Study; Study Type; Study Size (N)**	**Patient Population**	**Study Intervention/ Study Comparator**	**Results (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**	

Total # of Studies: 8 # of Systematic Reviews: 3 # of RCTs: 0 # of Non-Randomized Studies: 5 # of Diagnostic Studies: 0						
Journal: *Human Vaccines & Immunotherapeutics* **Author:** Van Der Meeren, O., et al. **Year Published:** 2016 **Location:** 21 centers in Australia, Canada, New Zealand and the US.	**Aim**: To assess the safety and immunogenicity of recombinant hepatitis B vaccine in subjects with and without diabetes mellitus. **Study Type**: Prospective, multi-country controlled study in 21 centers **Size**: 416 participants with Type-2 diabetes and 258 controls matched for age and body mass index	**Inclusion Criteria**: The diabetes group comprised subjects with type-2 DM diagnosed within the past 5 y according to criteria specified by the American Diabetes Association, or who had commenced treatment with any form of anti-diabetic medication within the past 5 y. Participants in the control group had no documented history of DM and had serum glycated hemoglobin (HbA1c) <6.5% (48 mmol/ml IFCC) at the time of screening. **Follow-Up**: 1 month after intervention	**Intervention**: Screening was conducted 2 to 28 d before the first vaccine dose. Serum creatinine, HBsAg, anti-HBs antibodies, anti-HBc antibodies and HbA1c were measured in all participants at central laboratories using validated commercial assays. All participants received 3 doses of hepatitis B vaccine at 0, 1 and 6 months. The vaccine was administered as an intramuscular injection into the deltoid muscle of the non-dominant arm. Blood samples were collected at the screening visit and one month after the third vaccine dose. Anti-HBs antibodies were measured with a level of detection of 6.2 mIU/mL defining seropositivity. **Comparator**: responders and non-responders were defined according to HBsAb levels (non-responders: < 10 IU/L; responders: ≥ 10 IU/L).	**Safety:** Grade 3 solicited symptoms were reported by 2.9% or fewer of participants in each group. **With no difference between groups** **There was no increase in symptoms in either group with consecutive doses.** Other adverse events occurring within 31 d after each vaccination were reported by 36.1% of participants with DM and 37.2% of controls. Grade 3 adverse events were reported by 8.4% and 6.2% of participants, respectively. Grade 3 events reported by more than one participant in the diabetes group were sinusitis (reported by 1.0% of participants), headache (0.7%), tonsillitis, arthralgia, musculoskeletal pain, and dizziness (each reported by 0.5% of participants).	**Study Limitations:** ☒ None ***Non-Randomized*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	☒ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☐ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)* ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* **Increase Quality Rating if:** ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect **Quality (certainty) of evidence for studies as a whole:** ☐ High ☐ Moderate ☐ Low ☒ Very Low

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

The published clinical guidelines were evaluated for this review using the **University of Pennsylvania's Center for Evidence-Based Practice Trustworthy Guideline rating scale.** The scale is based on the Institute of Medicine's "Standards for Developing Trustworthy Clinical Practice Guidelines" (IOM), as well as a review of the AGREE Enterprise and Guidelines International Network domains.

Guideline Issuer	ACIP/CDC 2011	American Diabetes Association 2016	CDC/ACIP 2018
1. Transparency	C	A	A
2. Conflict of interest	C	A	A
3. Development group	A	A	A
4. Systematic Review	C	B	A
5. Supporting evidence	A	A	C
6. Recommendations	A	A	B
7. External Review	NR	A	A
8. Currency and updates	NR	A	A

See appendix C for full description of the Trustworthy Guideline grading system.

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Appendix A. GRADE criteria for rating a body of evidence on an intervention

Developed by the GRADE Working Group

Grades and interpretations:

High: Further research is very unlikely to change our confidence in the estimate of effect. **Moderate**: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low**: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low**: Any estimate of effect is very uncertain.

Type of evidence and starting level

Randomized trial – high Observational study – low Any other evidence – very low

Criteria for increasing or decreasing level

Reductions Study quality has serious (–1) or very serious (–2) problems

Important inconsistency in evidence (–1) Directness is somewhat (–1) or seriously (–2) uncertain Sparse or imprecise data (–1) Reporting bias highly probable (–1) **Increases** Evidence of association† strong (+1) or very strong (+2) †Strong association defined as significant relative risk (factor of 2) based on consistent evidence from two or more studies with no plausible confounders Very strong association defined as significant relative risk (factor of 5) based on direct evidence with no threats to validity.

Appendix B. Search Strategy

Search strategy included:

1 exp Glucose Metabolism Disorders/ (276026)
2 exp Hepatitis B/ (32678)
3 exp Hepatitis B virus/ (17066)
4 2 or 3 (37225)
5 1 and 4 (360)
6 exp Immunization/ (83144)
7 exp vaccines/ (130806)
8 6 or 7 (169169)
9 5 and 8 (31)
10 exp Hepatitis B Vaccines/ (6349)
11 1 and 10 (50)
12 9 or 11 (54)
13 ((diabet* or dm) adj7 ((hepatitis b or hbv) adj5 (vaccin* or immuniz*))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (50)
14 12 or 13 (69)

15 (vaccin* or immuniz*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (238099)
16 5 and 15 (37)
17 14 or 16 (74)
18 limit 17 to yr="2008 -Current" (50)
Filters/limits included articles published in English in the last 10 years.

Appendix C. Trustworthy Guideline rating scale

The University of Pennsylvania's Center for Evidence-Based Practice Trustworthy Guideline rating scale is based on the Institute of Medicine's "Standards for Developing Trustworthy Clinical Practice Guidelines" (IOM), as well as a review of the AGREE Enterprise and Guidelines International Network domains.

The purpose of this scale is to focus on the weaknesses of a guideline that may reduce the trust a clinical user can have in the guideline, and distinguish weaknesses in documentation (e.g. guide-line does not have a documented updating process) from weaknesses in the guidance itself (e.g. recommendations are outdated). Current quality scales like AGREE emphasize documentation. They are important checklists for developers of new guidelines, but are less useful for grading existing guidelines. These scales also are harder for clinicians and other persons who are not methodology experts to apply, and their length discourages their use outside formal technology assessment reports. This new scale is brief, balanced, and easy and consistent to apply.

We do not attempt to convert the results of this assessment into a numeric score. Instead we present a table listing the guidelines and how they are rated on each standard. This facilitates qualitative understanding by the reader, who can see for what areas the guideline base as a whole is weak or strong as well as which guidelines are weaker or stronger.

1. Transparency

A	Guideline development methods are fully disclosed.
B	Guideline development methods are partially disclosed.
C	Guideline development methods are not disclosed.

The grader must refer to any cited methods supplements or other supporting material when evaluating the guideline. Methods should include:
- Who wrote the initial draft.

- How the committee voted on or otherwise approved recommendations.
- Evidence review, external review and methods used for updating are not addressed in this standard.

2. Conflict of interest

A	Funding of the guideline project is disclosed, disclosures are made for each individual panelist, and financial or other conflicts do not apply to key authors of the guideline or to more than 1 in 10 panel members).
B	Guideline states that there were no conflicts (or fewer than 1 in 10 panel members), but does not disclose funding source.
C	Lead author, senior author, or guideline panel members (at least 1 in 10) have conflict of interest, or guideline project was funded by industry sponsor with no assurance of independence.
NR	Guideline does not report on potential conflict of interests.

For purposes of this checklist, conflicts of interest include employment by, consulting for, or holding stock in companies doing business in fields affected by the guideline, as well as related financial conflicts. This definition should not be considered exclusive. As much as anything, this is a surrogate marker for thorough reporting, since it may be assumed that guideline projects are funded by the sponsoring organization and many authors think it unnecessary to report a non-conflict.

3. Guideline development group

A	Guideline development group includes 1) methodological experts and clinicians and 2) representatives of multiple specialties.
B	Guideline development group includes one of the above, but not both.
C	Guideline developers all from one specialty or organization, and no methodologists.
NR	Affiliations of guideline developers not reported

The purpose of this standard is to ensure that supporters of competing procedures, or clinicians with no vested interest in utilization of one procedure or another, are involved in development of the guideline. Both AGREE II and IOM call for patient or public involvement: very few guideline panels have done so to date, so this is not necessary for guidelines to be rated A. Involvement of methodologists or HTA specialists in the systematic review is sufficient involvement in the guideline development group for our purposes. In the absence of any description of the guideline group, assume the named authors are the guideline group.

4. Systematic review

A	Guideline includes a systematic review of the evidence or links to a current review.
B	Guideline is based on a review which may or may not meet systematic review criteria.
C	Guideline is not based on a review of the evidence.

In order to qualify as a systematic review, the review must do all of the following:
Describe itself as systematic or report search strategies using multiple databases
Define the scope of the review (including key questions and the applicable population)
Either include quantitative or qualitative synthesis of the data or explain why it is not indicated

Note: this element does not address the quality of the systematic review: simply whether or not it exists. Concerns about quality or bias of the review will be discussed in text, where the analyst will explain whether the weaknesses of the review weaken the validity or reliability of the guideline.

Note: a guideline may be rated B on this domain even if the review on which it is based is not available to us. This potential weakness of the guideline should be discussed in text of the report.

5. Grading the supporting evidence

A	Specific supporting evidence (or lack thereof) for each recommendation is cited and graded
B	Specific supporting evidence (or lack thereof) for each recommendation is cited but the recommendation is not graded.
C	Recommendations are not supported by specific evidence.

To score a B on this domain there should be specific citations to evidence tables or individual references for each relevant recommendation in the guideline, or an indication that no evidence was available. Any standardized grading system is acceptable for purposes of this rating. If a guideline reports that there is no evidence available despite a thorough literature search, it may be scored B on this domain, or even A if evidence for other recommendations is cited and graded.

6. Recommendations

A	Considerations for each recommendation are documented (i.e. benefits and harms of a particular action, and/or strength of the evidence); and recommendations are presented in an actionable form.
B	Either one or the other of the above criteria is met.
C	Neither of the above criteria are met

In order to be actionable, the guideline should specify the specific population to which the guideline applies, the specific intervention in question, and the circumstances under which it should be carried out (or not carried out). The language used in the recommendations should also be consistent with the strength of the recommendation (e.g. directive and active language like “should” or “should not” for strong recommendations, and passive language like “consider” for weak recommendations). A figure or algorithm is considered actionable as long as it is complete enough to incorporate all the applicable patients and interventions. Please see the forthcoming NICE manual (24) for a good discussion of actionability in guidelines.

7. External review

A	Guideline was made available to external groups for review.
B	Guideline was reviewed by members of the sponsoring body only.
C	Guideline was not externally reviewed.
NR	No external review process is described.

8. Updating and currency of guideline

A	Guideline is current and an expiration date or update process is specified.
B	Guideline is current but no expiration date or update process is specified.
C	Guideline is outdated.

A guideline is considered current if it is within the developers’ stated validity period, or if no period or expiration data is stated, the guideline was published in the past three years (NOTE: the specific period may be changed at the analyst’s discretion, based on whether the technology is mature and whether there is a significant amount of recent evidence). A guideline must address new evidence when it is updated. A guideline which is simply re-endorsed by the panel without searching for new evidence must be considered outdated.