PreHevbrio for adult hepatitis B vaccination

Evidence to Recommendation and GRADE

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PICO and Policy Question

Should PREHEVBRIO be recommended as an option for adults recommended for hepatitis B (HepB) vaccination?

Population	Adults greater than or equal to 18 years of age
Intervention	PREHEVBRIO – 3 doses over 6 months
Comparison	Existing hepatitis B vaccines licensed for adults in the US (TWINRIX, Engerix-B, Recombivax-HB, HEPLISAV-B)*
Outcomes	• Hepatitis B virus infection (CRITICAL) • Serious adverse events (CRITICAL) • Mild adverse events (IMPORTANT but not critical)

Persons on hemodialysis, pregnant persons and persons who are breastfeeding are not discussed in this Evidence to Recommendations Framework. The safety and effectiveness of PREHEVBRIO have not been established in adults on hemodialysis. There are no adequate and well-controlled studies of PREHEVBRIO in pregnant women. Available human data on PREHEVBRIO administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy. Data are not available to assess the effects of PREHEVBRIO on the breastfed infant or on milk production/excretion.

*Studies that were ultimately included used only Engerix-B out of this list of possible comparators

Background

Adult HepB vaccine*	Derivation	Adjuvant	Dose of HBs Antigens	Schedule
PreHevbrio	mammalian (Chinese hamster ovary) Cell	alum	10µg	3 doses at 0, 1, 6 mo
Engerix-B	yeast	alum	20µg	3 doses at 0, 1, 6 mo
Recombivax HB	yeast	alum	10µg	3 doses at 0, 1, 6 mo
Heplisav-B	yeast	CpG 1018	20µg	2 doses at 0, 1 mo

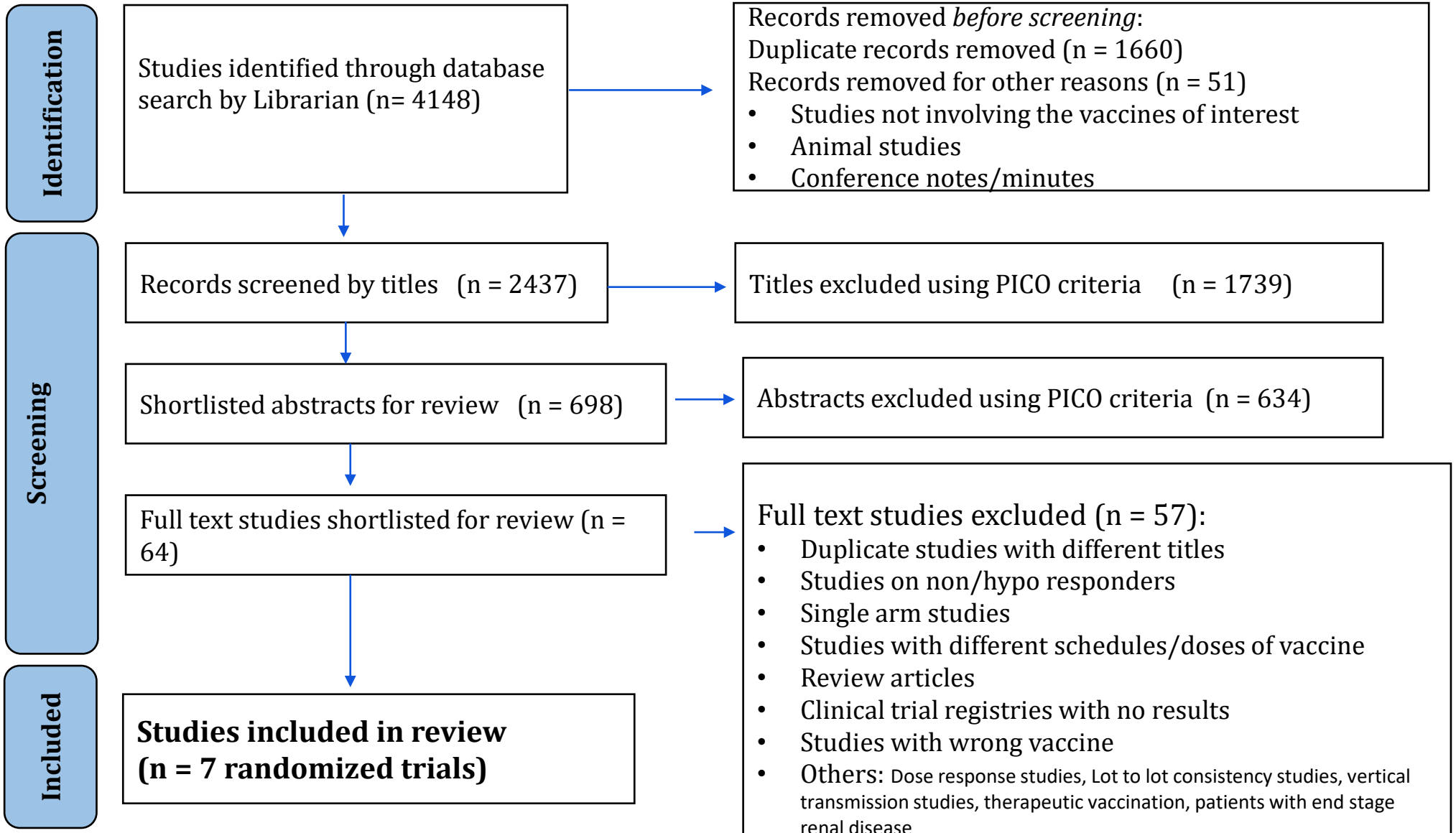
*See ACIP Recommended Immunization Schedule for Adults Aged 19 Years or Older — United States, 2022 for more dosing details (http://dx.doi.org/10.15585/mmwr.mm7107a1). Twinrix not shown (combination HepA-HepB). FDA Approval of PreHevbrio, a three-antigen HepB vaccine – Nov 30, 2021

Public Health Problem: Work Group Interpretation

- **In 2021, ACIP approved universal HepB vaccine recommendations for adults ages 19 through 59 years.**

- **An additional HepB vaccine that is safe and non-inferior to existing ACIP-approved HepB vaccines could be a beneficial adjunct in achieving HHS goals of eliminating hepatitis B as a public health threat in the United States by 2030.**

PRISMA Flow Diagram: Identification of PreHevbrio* studies



*PreHevbrio vaccine is also known as: Sci-B-Vac, Bio-Hep-B, Hepimmune, 3AV, or TAV

Benefits and Harms: GRADE Summary of Findings Table

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PreHevbrio	Comparator (Engerix-B)	Relative (95% CI)	Absolute (95% CI)		
Hepatitis B Infection (all studies considered seroprotection as anti-HBs ≥10 mIU/mL, between 1-3 months after completion of 3-dose series)												
7	randomized trials	serious[a]	serious[b]	not serious[c]	not serious	none	2929/3500 (83.7%)	1611/2100 (76.7%)	RR 1.07 (1.01 to 1.14)	5,370 more per 100,000 (from 767 more to 10,740 more)	Low	CRITICAL
Severe Adverse Events (e.g. syncope, atrial fibrillation, congestive cardiac failure, death*)												
7	randomized trials	serious[d]	not serious[e]	not serious	serious[f]	none	75/3480 (2.2%)	28/2084 (1.3%)	RR 1.62 (0.50 to 5.22)	833 more per 100,000 (from 672 fewer to 5,670 more)	Low	CRITICAL
Mild Adverse Events (reported up to 6 months after completion of 3-dose series)												
4	randomized trials	not serious	serious[b]	not serious	serious[f]	none	1612/3864 (41.7%)	826/2481 (33.3%)	RR 1.09 (0.76 to 1.55)	3,266 more per 100,000 (from 8,709 fewer to 19,959 more)	Low	IMPORTANT BUT NOT CRITICAL

Explanations CI: confidence interval; RR: risk ratio

a. 3/7 studies contributing to 60% of the weight to the analysis and high risk of bias due to unclear random sequence generation /allocation concealment and blinding (Diaz-Mitoma, Raz, Yap)

b. I^2 = 89%, studies at high risk of bias may contribute to the heterogeneity observed

c. All studies considered seroprotection as anti-HBs ≥10 mIU/mL as a surrogate for prevention of HepB infection

d. 4/7 studies have high risk of bias for randomization/allocation concealment and blinding (Diaz-Mitoma, Etzion, Raz, Yap)

e. I^2 = 67%; heterogeneity due to 2 studies contributing 81% of the weight of this outcome analysis (CONSTANT and PROTECT)

f. 95% CI cannot exclude the possibility of no meaningful difference

*Sudden cardiac death (1 event) was later assessed as unrelated to vaccination, in a participant with history of open-heart surgery and biventricular hypertrophy

Benefits and Harms: Conclusions from GRADE*

- **The evidence suggests that seroprotection conferred by PreHevbrio is non-inferior (little or no difference) compared with seroprotection conferred by Engerix-B.**

- **PreHevbrio may result in little to no difference in serious adverse events when compared with serious adverse events due to Engerix-B.**

- **PreHevbrio may result in little to no difference in mild adverse events when compared with mild adverse events due to Engerix-B.**

***Assumption: equivalent non-inferiority among currently U.S.-recommended 3-dose HepB vaccines for the population of interest, since all currently recommended HepB vaccines have undergone ACIP review**

Domain	Question	Work Group Judgments
Public Health Problem	Is the prevention of hepatitis B a problem of public health importance? *Is the problem of public health importance?*	**Yes**
Benefits and Harms	For prevention of HBV infection (seroprotection), how substantially different are the desirable anticipated effects of PreHevbrio compared with Engerix-B? *How substantial are the desirable anticipated effects?*	**Minimal**
	For the outcomes of serious and mild adverse events, how substantially different are the undesirable anticipated effects of PreHevbrio compared with Engerix-B? *How substantial are the undesirable anticipated effects?*	**Minimal**
	Does the balance between desirable effects and undesirable effects favor PreHevbrio or Engerix-B? *Do the desirable effects outweigh the undesirable effects?*	**Favors Both**
	What is the overall certainty of evidence for the critical outcomes?	**Probably not important uncertainty**
Equity	What would be the impact of the PreHevbrio compared to Engerix-B on health equity?	**Probably no impact**
Values	Based on similarities of dosage schedule, adjuvant, and vaccine mechanism, ACIP Hepatitis Work Group perceived that these domains of Values, Acceptability, Resource Use and Feasibility for PreHevbrio are comparable with Values, Acceptability, Resource Use and Feasibility of Engerix-B.	
Acceptability		
Resource Use		
Feasibility		

EtR Balance of Consequences

Based on EtR considerations, the balance between PreHevbrio and currently used HepB vaccines is closely balanced, and therefore the Work Group judgment on adding PreHevbrio as an option for HepB vaccination of adults is as follows:

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences in *closely balanced* or *uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings	There is insufficient evidence to determine the balance of consequences

ACIP Policy Statement for PreHevbrio

Recommendation	**PreHevbrio may be used as a HepB vaccine in persons aged ≥18 years recommended for vaccination against HBV infection.**
Additional Considerations	**Persons on hemodialysis, pregnant persons and persons who are breastfeeding are not discussed in this Evidence to Recommendations Framework.** The safety and effectiveness of PREHEVBRIO have not been established in adults on hemodialysis. There are no adequate and well-controlled studies of PREHEVBRIO in pregnant women. Available human data on PREHEVBRIO administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy. Data are not available to assess the effects of PREHEVBRIO on the breastfed infant or on milk production/excretion.

References

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- Review Manager (RevMan) [Computer program]. Version 5.4. The Cochrane Collaboration, 2020.

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Thank you

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

GRADE Tables

Table 1: Policy Question and PICO
Should PREHEVBRIO be recommended as an option for adults recommended for hepatitis B vaccination?

Population	Adults greater than or equal to 18 years of age
Intervention	PREHEVBRIO – 3 doses over 6 months
Comparison	Existing hepatitis B vaccines licensed for adults in the US (TWINRIX, Engerix-B, Recombivax-HB, HEPLISAV-B)
Outcomes	• Hepatitis B virus infection (CRITICAL) • Serious adverse events (CRITICAL) • Mild adverse events (IMPORTANT)

Persons on hemodialysis, pregnant persons and persons who are breastfeeding are not discussed in this Evidence to Recommendations Framework. The safety and effectiveness of PREHEVBRIO have not been established in adults on hemodialysis. There are no adequate and well-controlled studies of PREHEVBRIO in pregnant women. Available human data on PREHEVBRIO administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

Table 2: Outcomes and Rankings

Outcome	Importance*	Included in evidence profile
Hepatitis B virus infection	Critical	Yes
Serious adverse events	Critical	Yes
Mild adverse events	Important but not critical	Yes

*Three options: 1. Critical; 2. Important but not critical; 3. Not important for decision making

Evidence retrieval

- Systematic review of data for Hepatitis B vaccination including a search of PubMed, Medline and EMBASE from 1987 through 2021
- No language restrictions on initial searches and included articles from any country

Search Terms

Hepatitis b vaccines/ OR ((hepatitis b ADJ5 vaccin*) OR (hepb ADJ5 vaccin*) OR (HBV ADJ5 vaccin*))

(Sci-B-Vac OR 3 antigen* OR tri-antigen* OR three antigen* OR 3AV OR 3A-HBV OR pre-s* OR pres1* OR s?preS1?preS2 OR s?pre-S1?pre-S2 OR pres?s OR TAV OR third generation* OR Bio-Hep-B OR Hepimmune OR AG-3 OR Hepagene OR 3 dose* OR three dose*).

TI (Sci-B-Vac OR "3 antigen*" OR tri-antigen* OR "three antigen*" OR 3AV OR 3A-HBV OR pre-s* OR pres1* OR s?preS1?preS2 OR s?pre-S1?pre-S2 OR pres?s OR TAV OR "third generation*" OR Bio-Hep-B OR Hepimmune OR AG-3 OR Hepagene OR "3 dose*" OR "three dose*")) OR (AB (Sci-B-Vac OR "3 antigen*" OR tri-antigen* OR "three antigen*" OR 3AV OR 3A-HBV OR pre-s* OR pres1* OR s?preS1?preS2 OR s?pre-S1?pre-S2 OR pres?s OR TAV OR "third generation*" OR Bio-Hep-B OR Hepimmune OR AG-3 OR Hepagene OR "3 dose*" OR "three dose*"))

(TI (Trial* OR study OR studies OR randomi?ed OR "double blind" OR rct* OR efficacy OR effective* OR evidence* OR immunogenicity)) OR (AB (Trial* OR study OR studies OR randomi?ed OR "double blind" OR rct* OR efficacy OR effective* OR evidence* OR immunogenicity))

Trial* OR study OR studies OR randomised OR double blind OR rct* OR efficacy OR effective* OR evidence* OR immunogenicity

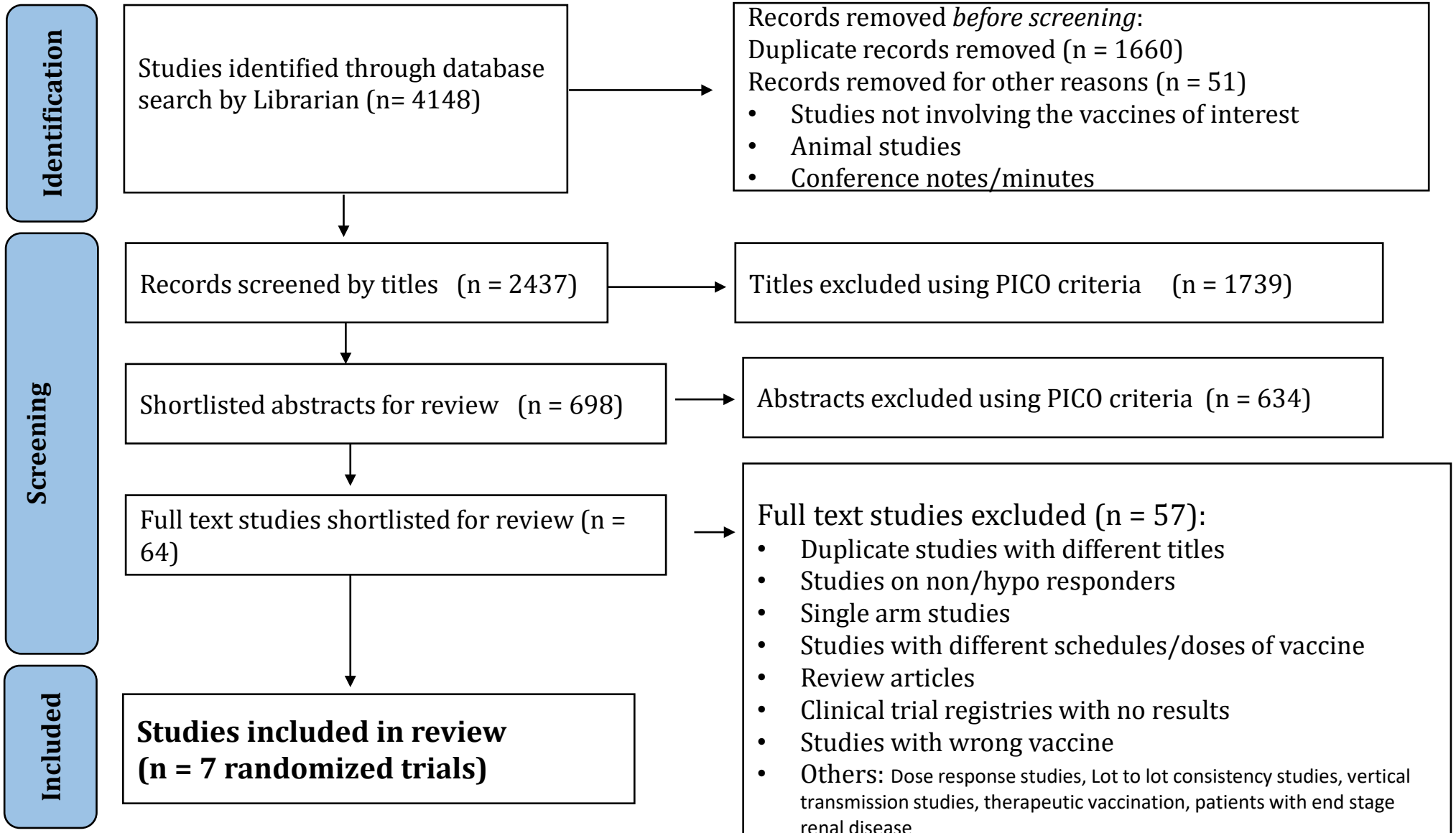
Evidence retrieval

Exclusion Criteria

- Non-human studies
- Studies addressing population <18 year old (pediatric studies)
- Studies addressing pregnant people
- Studies without the vaccine of interest (PreHevbrio*)
- Studies without a U.S. HepB vaccine as comparator
- Non-RCTs

*PreHevbrio vaccine is also known as: Sci-B-Vac, Bio-Hep-B, Hepimmune, 3AV, or TAV

Identification of PreHevbrio* studies



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Studies Included in the PreHevbrio* Review of Evidence

Last name first author, Publication year	Study design	Country (or more detail, if needed)	Age (mean/SD)	Total population	N Intervention	N comparison	Outcomes	Funding source
Vesikari 2021 (CONSTANT)	RCT	United States (26%), Canada (4%), Europe/UK (69%)	Median 35.0 years (range 18-45)	2838	2126	712	• Prevention of Hepatitis B infection/ seroprotection • Any severe or mild adverse events	VBI Vaccines Inc.
Vesikari 2021 (PROTECT)	RCT	United States (42%), Canada (16%), and Europe (42%)	56.6 years range 18-90y intervention, 18-86y comparison	1607	796	811	• Prevention of Hepatitis B infection/ seroprotection • Any severe or mild adverse events	VBI Vaccines Inc.
Esaulenko 2021	RCT	Russian Federation	18–45 years 28.38 ± 7.72, intervention; 30.56 ± 8.13 comparison	100	50	50	• Prevention of Hepatitis B infection/ seroprotection • Any severe or mild adverse events	VBI Vaccines Inc. and Pharmsynthez PAO
Diaz-Mitoma 2021	RCT	Vietnam	18 – 45 years 20.6 (1.6) intervention 20.5 (1.7) comparison	268	134 (Lot B)	134	• Prevention of Hepatitis B infection/ seroprotection • Any severe or mild adverse events	VBI Vaccines Inc.
Etzion 2016	RCT	Israel	≥18 years 37.6 (14.5) intervention 38.0 (12.7) comparison	73	36	37	• Prevention of Hepatitis B infection/ seroprotection • Any severe or mild adverse events	Scigen Ltd. (previous iteration of VBI Vaccines Inc)
Raz 2001	RCT	Israel	18 – 60 years 42.81 (18-60) intervention 42.99 (20-60) comparison	518	260	258	• Prevention of Hepatitis B infection/ seroprotection • Any severe or mild adverse events	Not Available
Yap 1995	RCT	Singapore	17 – 45 years 26 (18-45) intervention 25 (17-44) comparison	200	100	100	• Prevention of Hepatitis B infection/ seroprotection • Any severe or mild adverse events	Scitech Genetics Ltd

*PreHevbrio vaccine is also known as: Sci-B-Vac, Bio-Hep-B, Hepimmune, 3AV, or TAV

Tables 3a-b: Summary of Studies Reporting Outcomes

Table 3a. studies reporting seroprotection (SPR)*	Age (study site), SPR measurement time after complete 3-dose series	N intervention	N comparison	Comparator vaccine	Absolute difference/effect estimate (RR) (95% CI)	Study limitations (Risk of Bias)
Vesikari 2021, *JAMA Network Open* CONSTANT study	Healthy adults 18 – 45 years (United States [26%], Canada [4%], Europe/UK [69%]), 1 – 3 months	1753	592	Engerix-B	1.04 [0.99, 1.08]	not serious
Vesikari 2021, *Lancet Inf Dis* PROTECT study	healthy adults ≥18 years: mean age 56.6y (United States [42%], Canada [16%], and Europe [42%]), 28 days	796	811	Engerix-B	1.21 [1.14, 1.28]	not serious
Esaulenko 2021, *CID*	healthy adults 18–45 years (Russian Federation), 30 days	50	50	Engerix-B	1.02 [0.92, 1.14]	not serious
Diaz-Mitoma 2021, *Vaccine*	healthy adults, 18 – 45 years (Vietnam), 30 days	134 (Lot B)	134	Engerix-B	1.04 [0.95, 1.14]	serious
Etzion 2016, *J Crohn's and Colitis*	adults ≥18 years with Crohn's disease or ulcerative colitis (Israel), 1–3 months	36	37	Engerix-B	0.82 [0.62, 1.09]	serious
Raz 2001, *IMAJ*	healthy adults 18 – 60 years (Israel), 1 month	260	258	Engerix-B	1.14 [1.07, 1.21]	very serious
Yap 1995, *J of Gastro and Hep*	healthy adults 17 – 45 years (Singapore), 3 months	98	98	Engerix-B	1.05 [1.00, 1.11]	very serious

*All studies considered seroprotection as anti-HBs ≥10 mIU/mL

Table 3b. Studies reporting serious adverse events (SAE)*	Age (study site)	N intervention	N comparison	Comparator vaccine	Absolute difference/effect estimate (RR) (95% CI)	Study limitations (Risk of Bias)
Vesikari 2021, *JAMA Network Open* CONSTANT study	Healthy adults 18 – 45 years (United States [26%], Canada [4%], Europe/UK [69%])	2124	712	Engerix-B	1.04 [0.99, 1.08]	not serious
Vesikari 2021, *Lancet Inf Dis* PROTECT study	healthy adults ≥18 years: mean age 56.6y (United States [42%], Canada [16%], and Europe [42%])	796	811	Engerix-B	1.21 [1.14, 1.28]	not serious
Esaulenko 2021, *CID*	healthy adults 18–45 years (Russian Federation)	50	50	Engerix-B	no SAE reported	not serious
Diaz-Mitoma 2021, *Vaccine*	healthy adults, 18 – 45 years (Vietnam)	131	133	Engerix-B	0.25 [0.03, 2.24]	serious
Etzion 2016, *J Crohn's and Colitis*	adults ≥18 years with Crohn's disease or ulcerative colitis (Israel)	35	37	Engerix-B	no SAE reported	serious
Raz 2001, *IMAJ*	healthy adults 18 – 60 years (Israel)	249	246	Engerix-B	no SAE reported	very serious
Yap 1995, *J of Gastro and Hep*	healthy adults 17 – 45 years (Singapore), 3 months	98	98	Engerix-B	no SAE reported	very serious

*participants reporting ≥1 serious adverse event

Table 3c. Studies reporting mild adverse events (MAE)*	Age (study site)	N intervention	N comparison	Comparator vaccine	Absolute difference/effect estimate (RR) (95% CI)	Study limitations (Risk of Bias)
Vesikari 2021, *JAMA Network Open* CONSTANT study	Healthy adults 18 – 45 years (United States [26%], Canada [4%], Europe/UK [69%])	2124	712	Engerix-B	1.00 [0.92, 1.09]	not serious
Vesikari 2021, *Lancet Inf Dis* PROTECT study	healthy adults ≥18 years: mean age 56.6y (United States [42%], Canada [16%], and Europe [42%])	796	811	Engerix-B	0.89 [0.76, 1.05]	not serious
Esaulenko 2021, *CID*	healthy adults 18–45 years (Russian Federation)	47	47	Engerix-B	0.23 [0.07, 0.76]	not serious
Diaz-Mitoma 2021, *Vaccine*	healthy adults, 18 – 45 years (Vietnam)	131	133	Engerix-B	2.46 [1.67, 3.63]	serious

*participants reporting ≥1 mild adverse event

Benefits and Harms: GRADE Summary of Findings Table

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PreHevbrio	Comparator (Engerix-B)	Relative (95% CI)	Absolute (95% CI)		
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Severe Adverse Events (e.g. syncope, atrial fibrillation, congestive cardiac failure, death*)												
7	randomized trials	serious[d]	not serious[e]	not serious	serious[f]	none	75/3480 (2.2%)	28/2084 (1.3%)	RR 1.62 (0.50 to 5.22)	833 more per 100,000 (from 672 fewer to 5,670 more)	Low	CRITICAL
Mild Adverse Events (reported up to 6 months after completion of 3-dose series)												
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Explanations CI: confidence interval; RR: risk ratio

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b. I^2 = 89%, studies at high risk of bias may contribute to the heterogeneity observed

c. All studies considered seroprotection as anti-HBs ≥10 mIU/mL as a surrogate for prevention of HepB infection

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e. I^2 = 67%; heterogeneity due to 2 studies contributing 81% of the weight of this outcome analysis (CONSTANT and PROTECT)

f. 95% CI cannot exclude the possibility of no meaningful difference

*Sudden cardiac death (1 event) was later assessed as unrelated to vaccination, in a participant with history of open-heart surgery and biventricular hypertrophy

Table 5: Summary of Evidence for Outcomes of Interest

Outcome	Importance*	Included in evidence profile	Certainty
Hepatitis B virus infection	Critical	Yes	Low
Serious adverse events	Critical	Yes	Low
Mild adverse events	Important but not critical	Yes	Low

*Three options: 1. Critical; 2. Important but not critical; 3. Not important for decision making

GRADE Summary

GRADE Evidence Type

- **High certainty**: We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Very low certainty**: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

GRADE Criteria

- Initial evidence type (certainty level) determined by study design
  - Initial evidence (high certainty): A body of evidence from randomized controlled trials
  - Initial evidence (low certainty): A body of evidence from observational studies
- **Risk of bias:** Can include failure to conceal allocation, failure to blind, loss to follow-up. Risk of bias may vary across outcomes.
- **Inconsistency:** Criteria for evaluating include similarity of point estimates, extent of overlap of confidence intervals, and statistical criteria including tests of heterogeneity and I^2.
- **Indirectness:** Considers the generalizability of the evidence to the original PICO components
- **Imprecision:** Considers the fragility of the relative and absolute effect measures based on the interpretation of the 95% CIs and the optimal information size.
- Other considerations: Includes publication bias or indications of dose-response gradient, large or very large magnitude of effect, and opposing residual confounding.

GRADE Conclusions*

- The evidence suggests that there may be little to no difference in seroprotection conferred by PreHevbrio compared with other U.S.-recommended 3-dose HepB vaccines.

- PreHevbrio may result in little to no difference in serious adverse events when compared with other U.S.-recommended 3-dose HepB vaccines.

- PreHevbrio may result in little to no difference in mild adverse events when compared with other U.S.-recommended 3-dose HepB vaccines.

*Assumption: equivalent non-inferiority among currently U.S.-recommended 3-dose HepB vaccines for the population of interest, since all currently recommended HepB vaccines have undergone ACIP review