PreHevbro for adult hepatitis B vaccination
Evidence to Recommendation and GRADE

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Hepatitis Vaccines Work Group, Advisory Committee on Immunization Practices
Wednesday February 23, 2022
## PICO and Policy Question

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

<table>
<thead>
<tr>
<th>Population</th>
<th>Adults greater than or equal to 18 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>PREHEVBRIO – 3 doses over 6 months</td>
</tr>
<tr>
<td>Comparison</td>
<td>Existing hepatitis B vaccines licensed for adults in the US (TWINRIX, Engerix-B, Recombivax-HB, HEPLISAV-B)*</td>
</tr>
</tbody>
</table>

**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

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

*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](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.
Studies identified through database search by Librarian (n= 4148)

Records removed before screening:
Duplicate records removed (n = 1660)
Records removed for other reasons (n = 51)
• Studies not involving the vaccines of interest
• Animal studies
• Conference notes/minutes

Records screened by titles (n = 2437)
Titles excluded using PICO criteria (n = 1739)

Shortlisted abstracts for review (n = 698)
Abstracts excluded using PICO criteria (n = 634)

Full text studies shortlisted for review (n = 64)

Full text studies excluded (n = 57):
• Duplicate studies with different titles
• Studies on non/hypo responders
• Single arm studies
• Studies with different schedules/doses of vaccine
• Review articles
• Clinical trial registries with no results
• Studies with wrong vaccine
• Others: Dose response studies, Lot to lot consistency studies, vertical transmission studies, therapeutic vaccination, patients with end stage renal disease

Studies included in review (n = 7 randomized trials)

*PreHevbrío vaccine is also known as: Sci-B-Vac, Bio-Hep-B, Hepimmune, 3AV, or TAV*
Benefits and Harms: GRADE Summary of Findings Table

<table>
<thead>
<tr>
<th># of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>PreHevBrio</th>
<th>Comparator (Engerix-B)</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B Infection (all studies considered seroprotection as anti-HBs ≥10 mIU/mL, between 1-3 months after completion of 3-dose series)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>7 randomized trials</td>
<td>serious(^a)</td>
<td>serious(^b)</td>
<td>not serious(^c)</td>
<td>not serious</td>
<td>none</td>
<td>2929/3500 (83.7%)</td>
<td>1611/2100 (76.7%)</td>
<td>RR 1.07 (1.01 to 1.14)</td>
<td>5,370 more per 100,000 (from 767 more to 10,740 more)</td>
<td>Low</td>
<td>CRITICAL</td>
<td></td>
</tr>
</tbody>
</table>

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. I² = 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. I² = 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.
<table>
<thead>
<tr>
<th>Domain</th>
<th>Question</th>
<th>Work Group Judgments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public Health</td>
<td><strong>Is the prevention of hepatitis B a problem of public health importance?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td>Problem</td>
<td><em>Is the problem of public health importance?</em></td>
<td></td>
</tr>
<tr>
<td>Benefits and</td>
<td><strong>For prevention of HBV infection (seroprotection), how substantially</strong></td>
<td>Minimal</td>
</tr>
<tr>
<td>Harms</td>
<td><strong>are the desirable anticipated effects of PreHevbrio compared with</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Engerix-B?</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>How substantial are the desirable anticipated effects?</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>For the outcomes of serious and mild adverse events, how substantially</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>are the undesirable anticipated effects of PreHevbrio compared with</strong></td>
<td>Minimal</td>
</tr>
<tr>
<td></td>
<td><strong>Engerix-B?</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>How substantial are the undesirable anticipated effects?</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Does the balance between desirable effects and undesirable effects</strong></td>
<td>Favors Both</td>
</tr>
<tr>
<td></td>
<td><strong>favor PreHevbrio or Engerix-B?</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Do the desirable effects outweigh the undesirable effects?</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>What is the overall certainty of evidence for the critical outcomes?</strong></td>
<td>Probably not important uncertainty</td>
</tr>
<tr>
<td>Equity</td>
<td><strong>What would be the impact of the PreHevbrio compared to Engerix-B on</strong></td>
<td>Probably no impact</td>
</tr>
<tr>
<td></td>
<td><strong>health equity?</strong></td>
<td></td>
</tr>
<tr>
<td>Values</td>
<td>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.</td>
<td></td>
</tr>
</tbody>
</table>
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:

<table>
<thead>
<tr>
<th>Balance of consequences</th>
<th>Undesirable consequences clearly outweigh desirable consequences in most settings</th>
<th>Undesirable consequences probably outweigh desirable consequences in most settings</th>
<th>The balance between desirable and undesirable consequences in closely balanced or uncertain</th>
<th>Desirable consequences probably outweigh undesirable consequences in most settings</th>
<th>Desirable consequences clearly outweigh undesirable consequences in most settings</th>
<th>There is insufficient evidence to determine the balance of consequences</th>
</tr>
</thead>
</table>

EtR Balance of Consequences
## ACIP Policy Statement for PreHevbrio

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>PreHevbrio may be used as a HepB vaccine in persons aged ≥18 years recommended for vaccination against HBV infection.</th>
</tr>
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<tr>
<td>Additional Considerations</td>
<td>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.</td>
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References


• Esaulenko EV, Yakovlev AA, Volkov GA, et. al. Efficacy and Safety of a 3-Antigen (Pre-S1/Pre-S2/S) Hepatitis B Vaccine: Results of a Phase 3 Randomized Clinical Trial in the Russian Federation. Clin Infect Dis. 2021 Nov 2;73(9).


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Nida Ali, for conducting the PreHevbrio systematic review and creating the GRADE evidence profiles
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?

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<td>Outcomes</td>
<td>• Hepatitis B virus infection (CRITICAL)</td>
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<td></td>
<td>• Serious adverse events (CRITICAL)</td>
</tr>
<tr>
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<td>• Mild adverse events (IMPORTANT)</td>
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Table 2: Outcomes and Rankings

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Importance*</th>
<th>Included in evidence profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B virus infection</td>
<td>Critical</td>
<td>Yes</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Critical</td>
<td>Yes</td>
</tr>
<tr>
<td>Mild adverse events</td>
<td>Important but not critical</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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

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

• 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
Exclusion Criteria

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

*PreHevbro vaccine is also known as: Sci-B-Vac, Bio-Hep-B, Hepimmune, 3AV, or TAV
Identification of PreHevbrío* studies

Studies identified through database search by Librarian (n = 4148)

Records removed before screening:
- Duplicate records removed (n = 1660)
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  - Studies not involving the vaccines of interest
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Studies included in review (n = 7 randomized trials)

*PreHevbrío vaccine is also known as: Sci-B-Vac, Bio-Hep-B, Hepimmune, 3AV, or TAV
<table>
<thead>
<tr>
<th>Last name first author, Publication year</th>
<th>Study design</th>
<th>Country (or more detail, if needed)</th>
<th>Age (mean/SD)</th>
<th>Total population</th>
<th>N Intervention</th>
<th>N comparison</th>
<th>Outcomes</th>
<th>Funding source</th>
</tr>
</thead>
</table>
| 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
| Study                                                                 | Age (study site), SPR measurement time after complete 3-dose series | N intervention | N comparison | Comparator vaccine | Absolute difference/effec
t estimate (RR) (95% CI) | Study limitations |
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Vesikari 2021, <em>JAMA Network Open</em> CONSTANT study</td>
<td>Healthy adults 18 – 45 years (United States [26%], Canada [4%], Europe/UK [69%]), 1 – 3 months</td>
<td>1753</td>
<td>592</td>
<td>Engerix-B</td>
<td>1.04 [0.99, 1.08]</td>
<td>not serious</td>
</tr>
<tr>
<td>Vesikari 2021, <em>Lancet Inf Dis Protect</em> study</td>
<td>healthy adults ≥18 years: mean age 56.6y (United States [42%], Canada [16%], and Europe [42%]), 28 days</td>
<td>796</td>
<td>811</td>
<td>Engerix-B</td>
<td>1.21 [1.14, 1.28]</td>
<td>not serious</td>
</tr>
<tr>
<td>Esaulenko 2021, <em>CID</em></td>
<td>healthy adults 18–45 years (Russian Federation), 30 days</td>
<td>50</td>
<td>50</td>
<td>Engerix-B</td>
<td>1.02 [0.92, 1.14]</td>
<td>not serious</td>
</tr>
<tr>
<td>Diaz-Mitoma 2021, <em>Vaccine</em></td>
<td>healthy adults, 18 – 45 years (Vietnam), 30 days</td>
<td>134 (Lot B)</td>
<td>134</td>
<td>Engerix-B</td>
<td>1.04 [0.95, 1.14]</td>
<td>serious</td>
</tr>
<tr>
<td>Etzion 2016, <em>J Crohn’s and Colitis</em></td>
<td>adults ≥18 years with Crohn’s disease or ulcerative colitis (Israel), 1–3 months</td>
<td>36</td>
<td>37</td>
<td>Engerix-B</td>
<td>0.82 [0.62, 1.09]</td>
<td>serious</td>
</tr>
<tr>
<td>Yap 1995, <em>J of Gastro and Hep</em></td>
<td>healthy adults 17 – 45 years (Singapore), 3 months</td>
<td>98</td>
<td>98</td>
<td>Engerix-B</td>
<td>1.05 [1.00, 1.11]</td>
<td>very serious</td>
</tr>
</tbody>
</table>

*All studies considered seroprotection as anti-HBs ≥10 mIU/mL*
<table>
<thead>
<tr>
<th>Study</th>
<th>Journal</th>
<th>Age (study site)</th>
<th>N intervention</th>
<th>N comparison</th>
<th>Comparator vaccine</th>
<th>Absolute difference/effect estimate (RR) (95% CI)</th>
<th>Study limitations (Risk of Bias)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vesikari 2021, JAMA Network Open</td>
<td>CONSTANT study</td>
<td>Healthy adults 18 – 45 years (United States [26%], Canada [4%], Europe/UK [69%])</td>
<td>2124</td>
<td>712</td>
<td>Engerix-B</td>
<td>1.04 [0.99, 1.08]</td>
<td>not serious</td>
</tr>
<tr>
<td>Vesikari 2021, Lancet Inf Dis</td>
<td>PROTECT study</td>
<td>Healthy adults ≥18 years: mean age 56.6y (United States [42%], Canada [16%], and Europe [42%])</td>
<td>796</td>
<td>811</td>
<td>Engerix-B</td>
<td>1.21 [1.14, 1.28]</td>
<td>not serious</td>
</tr>
<tr>
<td>Esaulenko 2021, CID</td>
<td></td>
<td>Healthy adults 18–45 years (Russian Federation)</td>
<td>50</td>
<td>50</td>
<td>Engerix-B</td>
<td>no SAE reported</td>
<td>not serious</td>
</tr>
<tr>
<td>Diaz-Mitoma 2021, Vaccine</td>
<td></td>
<td>Healthy adults, 18 – 45 years (Vietnam)</td>
<td>131</td>
<td>133</td>
<td>Engerix-B</td>
<td>0.25 [0.03, 2.24]</td>
<td>serious</td>
</tr>
<tr>
<td>Etzion 2016, J Crohn’s and Colitis</td>
<td></td>
<td>Adults ≥18 years with Crohn’s disease or ulcerative colitis (Israel)</td>
<td>35</td>
<td>37</td>
<td>Engerix-B</td>
<td>no SAE reported</td>
<td>serious</td>
</tr>
<tr>
<td>Raz 2001, IMAJ</td>
<td></td>
<td>Healthy adults 18 – 60 years (Israel)</td>
<td>249</td>
<td>246</td>
<td>Engerix-B</td>
<td>no SAE reported</td>
<td>very serious</td>
</tr>
<tr>
<td>Yap 1995, J of Gastro and Hep</td>
<td></td>
<td>Healthy adults 17 – 45 years (Singapore), 3 months</td>
<td>98</td>
<td>98</td>
<td>Engerix-B</td>
<td>no SAE reported</td>
<td>very serious</td>
</tr>
</tbody>
</table>

*participants reporting ≥1 serious adverse event
### Table 3c. Studies reporting mild adverse events (MAE)*

<table>
<thead>
<tr>
<th>Study and Year</th>
<th>Age (study site)</th>
<th>N intervention</th>
<th>N comparison</th>
<th>Comparator vaccine</th>
<th>Absolute difference/efffect estimate (RR) (95% CI)</th>
<th>Study limitations (Risk of Bias)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vesikari 2021, <em>JAMA Network Open</em> CONSTANT study</td>
<td>Healthy adults 18 – 45 years (United States [26%], Canada [4%], Europe/UK [69%])</td>
<td>2124</td>
<td>712</td>
<td>Engerix-B</td>
<td>1.00 [0.92, 1.09]</td>
<td>not serious</td>
</tr>
<tr>
<td>Vesikari 2021, <em>Lancet Inf Dis</em> PROTECT study</td>
<td>Healthy adults ≥18 years: mean age 56.6y (United States [42%], Canada [16%], and Europe [42%])</td>
<td>796</td>
<td>811</td>
<td>Engerix-B</td>
<td>0.89 [0.76, 1.05]</td>
<td>not serious</td>
</tr>
<tr>
<td>Esaulenko 2021, <em>CID</em></td>
<td>Healthy adults 18–45 years (Russian Federation)</td>
<td>47</td>
<td>47</td>
<td>Engerix-B</td>
<td>0.23 [0.07, 0.76]</td>
<td>not serious</td>
</tr>
<tr>
<td>Diaz-Mitoma 2021, <em>Vaccine</em></td>
<td>Healthy adults, 18 – 45 years (Vietnam)</td>
<td>131</td>
<td>133</td>
<td>Engerix-B</td>
<td>2.46 [1.67, 3.63]</td>
<td>serious</td>
</tr>
</tbody>
</table>

*participants reporting ≥1 mild adverse event
### Benefits and Harms: GRADE Summary of Findings Table

<table>
<thead>
<tr>
<th></th>
<th>Certainty assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No of studies</strong></td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
</tr>
<tr>
<td><strong>Hepatitis B Infection</strong> (all studies considered seroprotection as anti-HBs ≥10 mIU/mL, between 1-3 months after completion of 3-dose series)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 randomized trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>serious^a</td>
<td>serious^b</td>
<td>not serious^c</td>
<td>not serious</td>
<td>none</td>
</tr>
</tbody>
</table>

| **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. I² = 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. I² = 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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Importance*</th>
<th>Included in evidence profile</th>
<th>Certainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B virus infection</td>
<td>Critical</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Critical</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Mild adverse events</td>
<td>Important but not critical</td>
<td>Yes</td>
<td>Low</td>
</tr>
</tbody>
</table>

*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.