Grading of Recommendations, Assessment, Development and Evaluation (GRADE): HEPLISAV-B

Aaron M. Harris, MD, MPH, FACP

Clinical Interventions Team Lead (Acting), Division of Viral Hepatitis

Advisory Committee on Immunization Practices

February 21, 2018

GRADE Process

- **Develop policy questions**
- **Consider critical outcomes**
- **Review and summarize evidence of benefits and harms**
- **Evaluate quality of evidence**
- Assess population benefit
- Evaluate values and preferences
- Review health economic data
- Considerations for formulating recommendations
- ACIP recommendation and GRADE category

Policy question: Should HEPLISAV-B vaccine be recommended for adults on a 2-dose schedule over 1 month?

Population	Adults ≥18 years of age
Intervention	HEPLISAV-B administered in 2 doses over 1 month
Comparison	Existing hepatitis B vaccines licensed for adults in the U.S.: TWINRIX, Engerix-B, Recombivax HB
Outcomes	• Hepatitis B infection • Mild adverse events • Serious adverse events • Cardiovascular safety

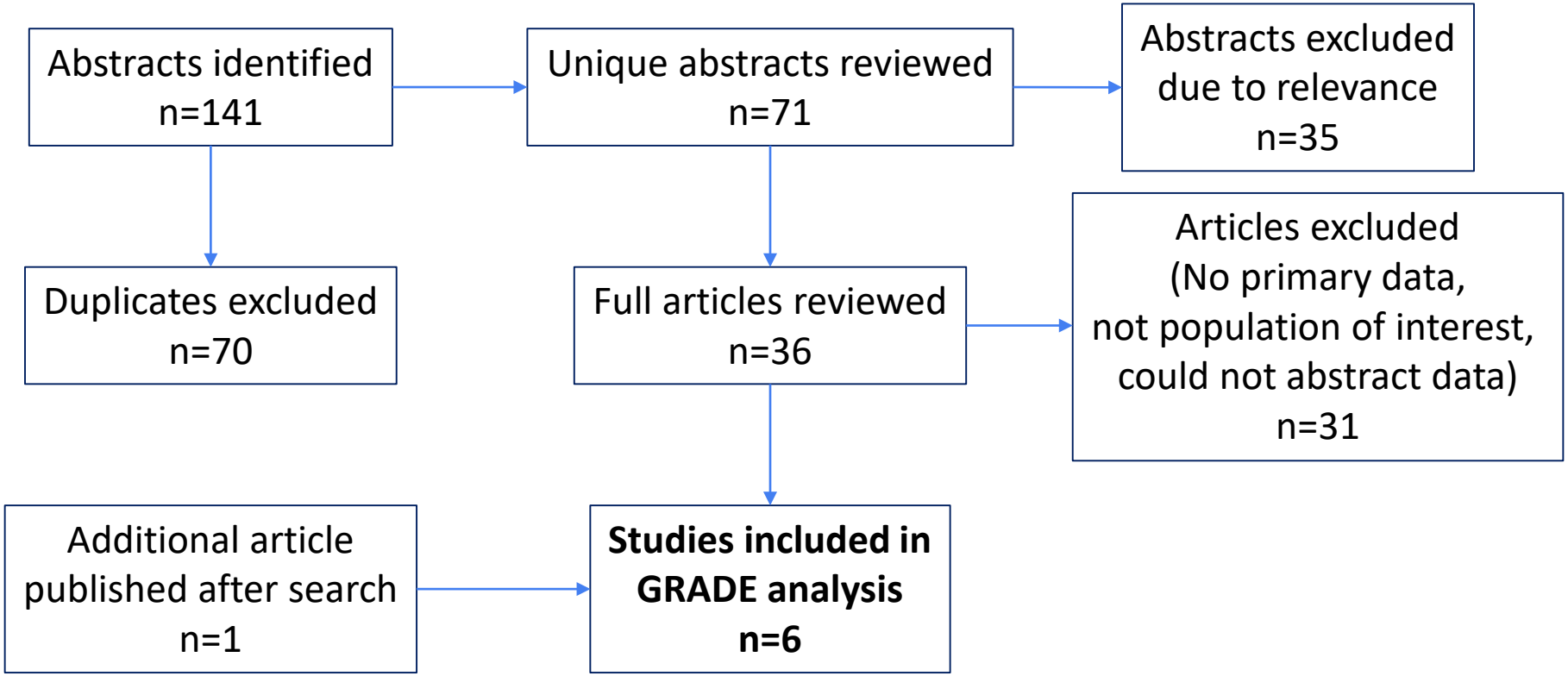
Outcome measures included in evidence profile

Outcome	Importance
Benefits	
1. Hepatitis B infection	Critical
Harms	
2. Mild adverse events (any)	Important
3. Serious adverse events (any)	Critical
4. Cardiovascular adverse events (any)	Critical

Evidence retrieval

- Systematic review of Medline (OVID), CAB Abstracts, Embase, Global Health (OVID), Scopus, Cochrane
- Search terms included: “HEPLISAV” or “HBV-ISS” or “HBsAg-1018” or “1018 immunostimulatory sequence” or “hepatitis B surface antigen-1018 ISS”
- Articles were included if they presented immunogenicity or disease endpoints or safety data on HEPLISAV
- Articles were excluded if:
  - Non-human primates, basic science
  - Secondary data analyses
  - Immunogenicity outcomes for non-licensed formulation or use of HEPLISAV
  - General review or opinion perspectives or unable to abstract data

Evidence retrieval



Evidence types for GRADE

Initial evidence type	Study design
1	Randomized controlled trials (RCTs), or overwhelming evidence from observational studies
2	RCTs with important limitations, or exceptionally strong evidence from observational studies
3	Observational studies, or RCTs with notable limitations
4	Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations

GRADE of evidence for HEPLISAV-B: Benefits

Outcome #1: Hepatitis B infection
Characteristics of included studies

Study	Type	Population	Intervention	Comparison	Main Outcomes*	Funding	Site
Halperin, 2006 *Vaccine*	RCT, phase II	99 healthy adults, 18-28 years	HEPLISAV at 0 and 8 weeks	Engerix-B at 0, 8, and 24 weeks	Seroprotection rate (anti-HBs ≥ 10mIU/mL)**	Dynavax	2 centers in Canada
Halperin, 2012 *Vaccine*	RCT, Phase III	2415 healthy adults, 18-55 years	HEPLISAV at 0 and 4 weeks	Engerix-B at 0, 4, and 24 weeks	Seroprotection rate (anti-HBs ≥ 10mIU/mL)**	Dynavax	Canada and Germany
Heyward, 2013 *Vaccine*	RCT Phase III	2452 healthy adults, 40-70 years	HEPLISAV at 0 and 4 weeks	Engerix-B at 0, 4, and 24 weeks	Seroprotection rate (anti-HBs ≥ 10mIU/mL)**	Dynavax	29 sites in US, 3 in Canada
Jackson, 2017 *Vaccine*	RCT Phase III	8374 adults, 18-70 years, excluding HIV and history of autoimmune disease	HEPLISAV at 0 and 4 weeks	Engerix-B at 0, 4, and 24 weeks	Seroprotection rate (anti-HBs ≥ 10mIU/mL)**	Dynavax	USA

* No studies included disease endpoints

** Seroprotection rate after receiving complete vaccine series

Outcome #1: Hepatitis B infection
Seroprotection rate (SPR), estimates of effect

Outcome*	No. of subjects (# studies)	SPR in HEPLISAV	SPR in Comparison	Difference in SPRs	NNV
Seroprotection rate at 24 weeks in adults 18-28 years	48 in HEPLISAV; 51 in Engerix-B (1)	100%	90.2%	9.8%	10
Seroprotection rate at 28 weeks in adults 18-55 years	1511 in HEPLISAV; 521 in Engerix-B (1)	97.9% (97.9–98.7)	81.1% (77.7-84.4)	16.8% (14.3–20.2)	6
Seroprotection rate at 28 weeks in adults 40-70 years	1121 in HEPLISAV; 353 in Engerix-B (1)	90.0% (88.2–91.8)	70.5 (65.5–75.2)	19.5% (14.7–24.7)	5
Seroprotection rate at 28 weeks in adults 18-70 years, excluding HIV and autoimmune	4376 in HEPLISAV; 2289 in Engerix-B (1)	95.4% (94.8–96.0)	81.3% (79.6–82.8)	14.2% (12.5–15.9)	7

* All studies considered seroprotection as anti-HBs $\geq$ 10mIU/mL

Outcome #1: Hepatitis B infection
Type of evidence

Outcome	Design (# of studies)	Initial evidence level	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Evidence Type
Hepatitis B infection	RCT, Phase II (1)	1	No serious	No serious	Serious (-1)[a,b]	No serious	Yes[c]	2
Hepatitis B infection	RCT, Phase III (3)	1	No serious	No serious	Serious (-1)[a]	No serious	Yes[c]	2

a. There were no studies that looked at hepatitis B infection as outcome; anti-HBs response was used as a surrogate

b. Intervention was HEPLISAV series at 0 and 8 weeks, which is not the licensed series

c. All studies funded by Dynavax Technologies Corporation

GRADE of evidence for HEPLISAV-B: Harms

Outcomes #2, 3, 4: Adverse events
Characteristics of included studies

Study	Type	Population	Intervention	Comparison	Main Outcomes*	Funding	Site
Halperin, 2006, *Vaccine*	RCT Phase II	99 healthy adults, 18–28 years	HEPLISAV at 0 and 8 weeks	Engerix-B at 0, 8, and 24 weeks	Any mild adverse events (local, systemic), SAE	Dynavax	2 sites in Canada
Halperin, 2012, *Vaccine*	RCT Phase III	2415 healthy adults, 18–55 years	HEPLISAV at 0 and 4 weeks	Engerix-B at 0, 4, and 24 weeks	Any mild adverse events (local, systemic), SAE (related not reported)	Dynavax	Canada, Germany
Sablan, 2012, *Vaccine*	RCT Phase III	412 healthy adults, 40–70 years	HEPLISAV at 0, 8, and 24 weeks (placebo at week 4)	Engerix-B at 0, 4, and 24 weeks (placebo at week 8)	Any mild adverse events (local, systemic), SAE	Dynavax	5 sites in Korea, 2 sites in Philippines, and 1 site in Singapore
Heyward, 2013, *Vaccine*	RCT Phase III	2452 healthy adults, 40–70 years	HEPLISAV at 0 and 4 weeks	Engerix-B at 0, 4, and 24 weeks	Any mild adverse events (local, systemic), SAE, cardiovascular events	Dynavax	29 sites in US, 3 sites in Canada

Outcomes #2, 3, 4: Adverse events
Characteristics of included studies, continued

Study	Type	Population	Intervention	Comparison	Main Outcomes*	Funding	Site
Janssen, 2013, *Vaccine*	RCT Phase III	521 adults with chronic kidney disease, 18–75 years	HEPLISAV at 0, 4, and 24 weeks	Engerix-B at 0, 4, 8, and 24 weeks	Any adverse events, SAE, cardiovascular events	Dynavax	46 sites in US, 3 sites in Canada, 9 sites in Germany
HBV 23	RCT Phase III	8368 adults, 18–70 years, excluding HIV and history of autoimmune disease	HEPLISAV at 0 and 4 weeks	Engerix-B at 0, 4, and 24 weeks	Any mild adverse events, SAE (related not reported), cardiovascular events	Dynavax	US

Outcome #2: Mild adverse events
Estimates of effect

Outcome	No. of subjects (# studies)	No. reported in HEPLISAV (%)	No. reported in Comparison (%)	Difference
Any mild adverse events	14256 (6)	4497 (45.6%)	2003 (45.7%)	-0.1%
Injection-site reaction	5888 (5)	1519 (35.5%)	494 (30.8%)	4.6%
Systemic reaction	5888 (5)	1205 (28.1%)	483 (30.1%)	-2.0%

Outcome #3: Serious adverse events (SAE) Estimates of effect

Outcome	No. of subjects (# studies)	No. reported in HEPLISAV (%)	No. reported in Comparison (%)	Difference
Any SAE	14256 (6)	529 (5.4%)	276 (6.3%)	-0.9%
SAE considered related to vaccine*	3473 (4)	1 (0.04%)	1 (0.10%)	-0.06%

*1 related SAE in HEPLISAV was progression of chronic kidney disease stage IV to end-stage renal disease 28 days after receiving dose 1.

*1 related SAE in Engerix-B was reactive airway disease due to Churg-Strauss syndrome (ANCA+ vasculitis) 42 days after receiving dose 3.

Outcome #4: Cardiovascular adverse events
Estimates of effect

Outcome	No. of subjects (# studies)	No. reported in HEPLISAV (%)	No. reported in Comparison (%)	Difference
Cardiovascular adverse event	11333 (3)	21 (0.27%)*	5 (0.14%)	0.13%

*All subjects with cardiovascular adverse event reported more than 1 cardiovascular disease risk factor

Outcomes #2, 3, 4: Adverse events Type of evidence

Outcome	Design (# of studies)	Initial evidence level	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Evidence Type
Mild adverse events	RCT (6)	1	No serious	No serious	No Serious	No serious	Yes*	1
Serious adverse events	RCT (6)	1	No serious	No serious	No Serious	No serious	Yes*	1
Cardiovascular adverse events	RCT (3)	1	No serious	No serious	No Serious	No serious	Yes*	1

*All studies funded by Dynavax Technologies Corporation;

*Adverse events from HBV23 is unpublished

GRADE Summary

Outcomes #1,2, 3, 4: Adverse events
Characteristics of excluded studies

Study	Type	Population	Intervention	Comparison	Main Outcomes*	Funding	Site
[a]Halperin, 2012, *Vaccine*	Obs	41 healthy adults, 18–39 years	HEPLISAV at 0 and 4 or 8 weeks	None	SPR, any adverse events, SAE	Dynavax	1 site in Canada
[b]Halperin, 2013, *Human Vaccines & Immunotherapeutics*	RCT	Healthy adults, 18–65 years who did not respond to 3 doses (N=35) or 4-6 doses (N=24) of licensed HBV vaccine	HEPLISAV 1 dose followed by 2 additional Engerix-B doses	Engerix-B followed by up to 2 additional Engerix-B doses	SPR, any adverse events, SAE	Dynavax	2 sites in Canada
[c]Janssen, 2015, *Vaccine*	Subgroup analysis	328 adults with chronic kidney disease	HEPLISAV at 0, 4, and 24 weeks	Engerix-B at 0, 4, 8, and 24 weeks, double doses	SPR, any adverse events, SAE	Dynavax	US, Canada, Germany

a. Unable to abstract data since safety data presented in Figure only and non control/placebo
b. Unable to abstract safety data from the way data presented in Table 4; recipients only received 1 dose of HEPLISAV
c. Subgroup analysis of data from Janssen.2013.Vaccine, already included data in estimates of effect

Limitations

- All data are from same funding source (Dynavax Technologies Corporation)
- Generalizability
  - 21% of patients in 3 of 6 studies were not in the United States
    - 18% of patients in 2 studies from Canada and Germany, which may be similar populations to U.S.
    - 3% of patients in 1 study from Korea, Philippines, Singapore
- All data from clinical trials, no real world data
- No disease endpoints
- Cardiovascular events were not reported in all studies
- No long term data published on immunogenicity and adverse events

GRADE SUMMARY

Compared to licensed hepatitis B vaccine (Engerix-B)

Outcome	Design (# of studies)	Findings	Evidence type	Overall evidence type
BENEFITS				
Hepatitis B infection	RCT (4)	HEPLISAV non-inferior seroprotection rate	**2**	**2**
HARMS				
Mild adverse events	RCT (6)	No differences detected between vaccinated and comparison populations for mild adverse events HEPLISAV had 4.6% more local injection site reactions	**1**	**1**
Serious adverse events	RCT (6)	No differences detected between vaccinated and comparison populations for serious adverse events	**1**	
Cardiovascular adverse events	RCT* (1) RCT** (2)	More events in HEPLISAV group, but not statistically significant	**1**	

*Not yet published, data abstracted from HEPLISAV package insert; **Data abstracted from studies that stated most were cardiac deaths not related to vaccine

Future considerations

Information gaps

- Indirectness since no study looking at hepatitis B infection as outcome
- No real world cohort data
- Long term protective immunity unknown
- Cost-effectiveness analysis*
  - 1 industry funded study showed HEPLISAV ICER < $25,000 compared to Engerix-B for diabetic patients, patients with chronic kidney disease, patients with ESRD, healthcare workers, and travelers
  - Other populations needed
- Post licensure studies will be included in future workgroup considerations

*Kuan.2013.Vaccine

Acknowledgement

- Dr. Ruth Link-Gelles for providing assistance with GRADE process

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

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.