Evidence to Recommendations Framework: Should all HepB-unvaccinated adults receive hepatitis B vaccination?

Presentation to ACIP

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Mona Doshani, MD, MPH

PICO Question

Population: Previously HepB-unvaccinated adults age ≥ 18 years

Intervention: Universal HepB vaccination strategy (2- and 3-dose schedules)

Comparison: Current risk-based HepB vaccination strategy (2- and 3-dose schedules)

Outcomes of interest

1. Incidence of hepatitis B
2. Morbidity related to hepatitis B
3. Mortality related to hepatitis B
4. Serious adverse events associated with the 2-dose vaccine*

* This outcome is solely aimed at assessing the 2-dose HEPLISAV-B (approved in 2017). The 3-dose HepB vaccines have already been evaluated for their adverse events profiles and recommended by ACIP based on their safety records.

Evidence to Recommendations (EtR) Framework

Domain	Question
Public Health Problem	• Is the problem of public health importance?
Benefits and Harms	• How substantial are the desirable anticipated effects? • How substantial are the undesirable anticipated effects? • Do the desirable effects outweigh the undesirable effects? • What is the overall certainty of evidence for the critical outcomes?
Values	• Does the target population feel the desirable effects are large relative to the undesirable effects? • Is there important variability in how patients value the outcome?
Acceptability	• Is the intervention acceptable to key stakeholders?
Resource Use	• Is the intervention a reasonable and efficient allocation of resources?
Equity	• What would be the impact of the intervention on health equity?
Feasibility	• Is the intervention feasible to implement?

1. EtR Domain: Public Health Problem

Burden of chronic hepatitis B virus (HBV) disease in the US remains significant[1,2,3]

- **Estimated prevalence of chronic HBV infection in US is 880,000 persons (95% CI: 580,000–1,170,000)[1]**
  - **Modeled estimate: 1.89 million persons (range, 1.49–2.40 million)[3]**

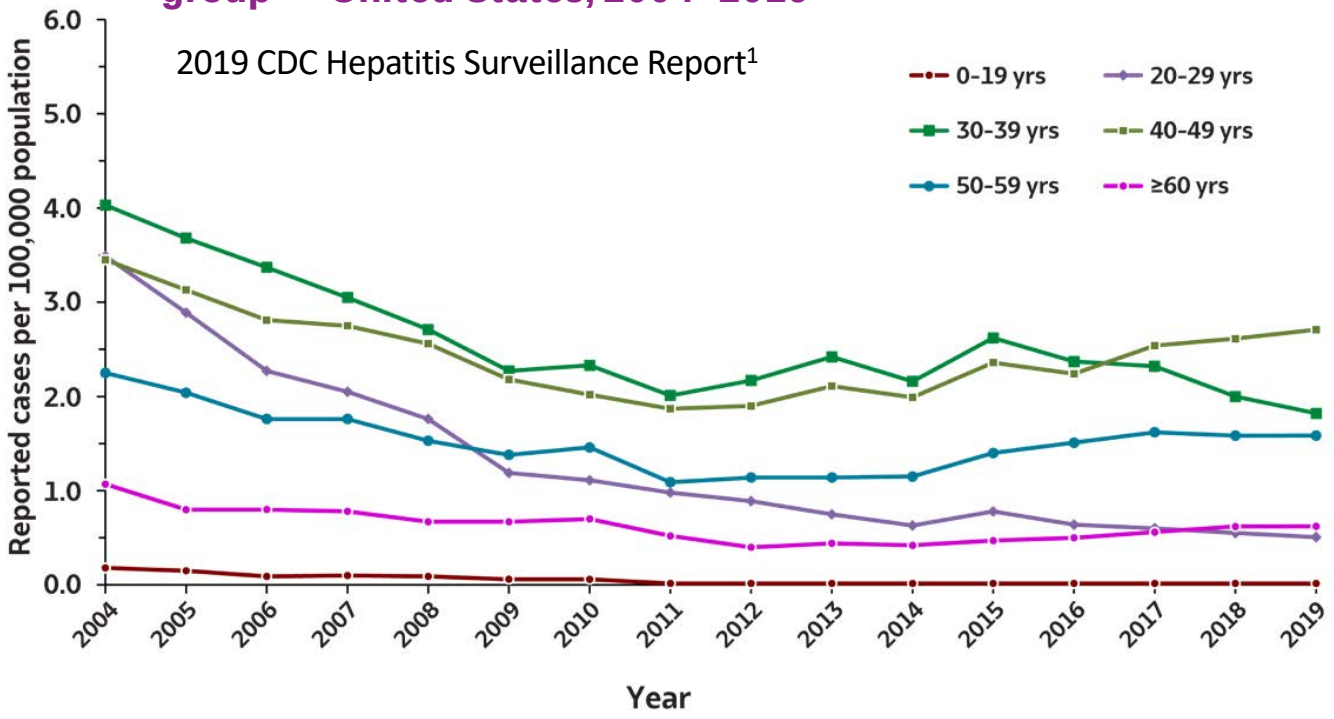
- **In 2019, age-adjusted death rate associated with hepatitis B in the US was 0.42 deaths per 100,000 population (n=1,662 deaths)[4]**

1. Roberts H et al. Hepatology. 2021
2. Lim et al. Am J Gastroenterol. 2020
3. Wong et al. Am J Med. 2021
4. https://www.cdc.gov/hepatitis/statistics/2019surveillance/HepB.htm

Incidence: Over half of acute hepatitis B infections reported were among people aged 30–49 years[1]

- 3,192 acute hepatitis B cases reported to CDC in 2019[1]
  - Adjust for case under-ascertainment and under-reporting
  - Leads to an estimated 20,700 infections in the US in one year (95% CI: 11,800–50,800)

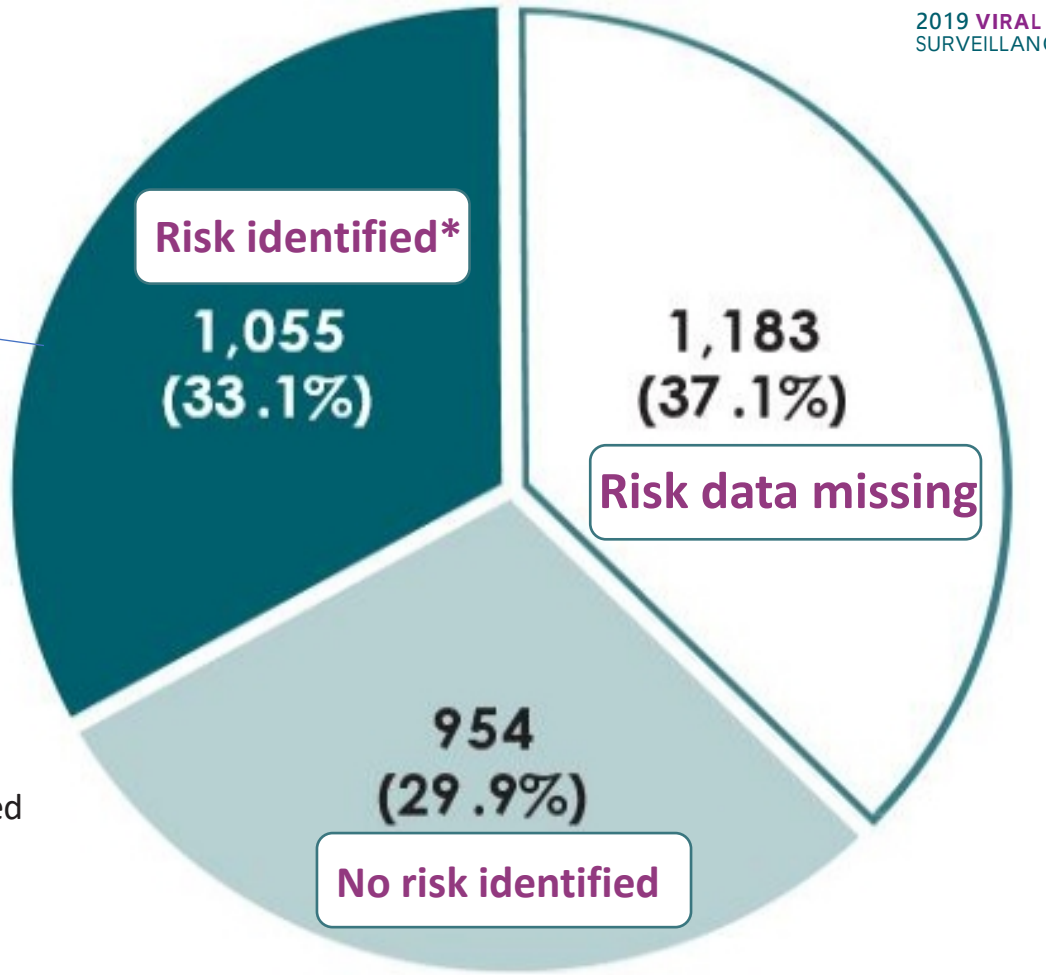
Rates of reported acute hepatitis B virus infection, by age group — United States, 2004–2019



1. https://www.cdc.gov/hepatitis/statistics/2019surveillance/HepB.htm

Availability of information regarding risk behaviors or exposures*† associated with reported cases of acute hepatitis B virus infection — US, 2019

Injection drug use (IDU) was the most commonly reported risk behavior/ exposure



Source: CDC, Nationally Notifiable Diseases Surveillance System

* Case reports with at least one of the following risk behaviors/exposures reported 6 weeks to 6 months prior to symptom onset or documented seroconversion if asymptomatic: 1) injection drug use; 2) multiple sexual partners; 3) underwent surgery; 4) men who have sex with men; 5) sexual contact with suspected/confirmed hepatitis B case; 6) sustained a percutaneous injury; 7) household contact with suspected/confirmed hepatitis B case; 8) occupational exposure to blood; 9) dialysis; and 10) transfusion. Reported cases may include more than one risk behavior/exposure.

† Risk behaviors/exposures data from one state was classified as 'missing' because of errors in reporting.

National Strategic Elimination Plans for Viral Hepatitis United States, 2021–2025[1]

A. Vision

The United States will be a place where new viral hepatitis infections are prevented, every person knows their status, and every person with viral hepatitis has high-quality health care and treatment and lives free from stigma and discrimination.

This vision includes all people, regardless of age, sex, gender identity, sexual orientation, race, ethnicity, religion, disability, geographical location, or socioeconomic circumstance.

B. Goals

In pursuit of this vision, the Hepatitis Plan establishes five goals:

1. **Prevent new viral hepatitis infections**
2. **Improve viral hepatitis–related health outcomes of people with viral hepatitis**
3. **Reduce viral hepatitis–related disparities and health inequities**
4. **Improve viral hepatitis surveillance and data usage**
5. **Achieve integrated, coordinated efforts that address the viral hepatitis epidemics among all partners and stakeholders**

HHS Target Measure: Reduce acute hepatitis B infections 90% by 2030

Over 95% of acute hepatitis B infections reported to CDC in 2019 were in adults ≥18 years[2]

1. https://www.hhs.gov/sites/default/files/Viral-Hepatitis-National-Strategic-Plan-2021-2025.pdf
2. 2019 CDC Hepatitis Surveillance Report. https://www.cdc.gov/hepatitis/statistics/2019surveillance/HepB.htm

Hepatitis B complications leads to higher healthcare demands

- **Chronic HBV infection can progress to advanced liver disease (such as decompensated cirrhosis, hepatocellular carcinoma (HCC), or liver transplant) and lead to higher healthcare resource demands.**

  - **US cancer data from the Surveillance, Epidemiology and End Results (SEER) Program:**
    - Over 38,000 HCC cases in 2020 and over 56,000 HCC cases in 2030
    - 10% to 15% of patients with HCC are infected with HBV

  - **Burden of US hepatitis B-related hospitalizations:**
    - Each year more than $1 billion is spent on hepatitis B-related hospitalizations, not including indirect costs (poor quality of life, reduced economic productivity, long-term disability, and premature death)

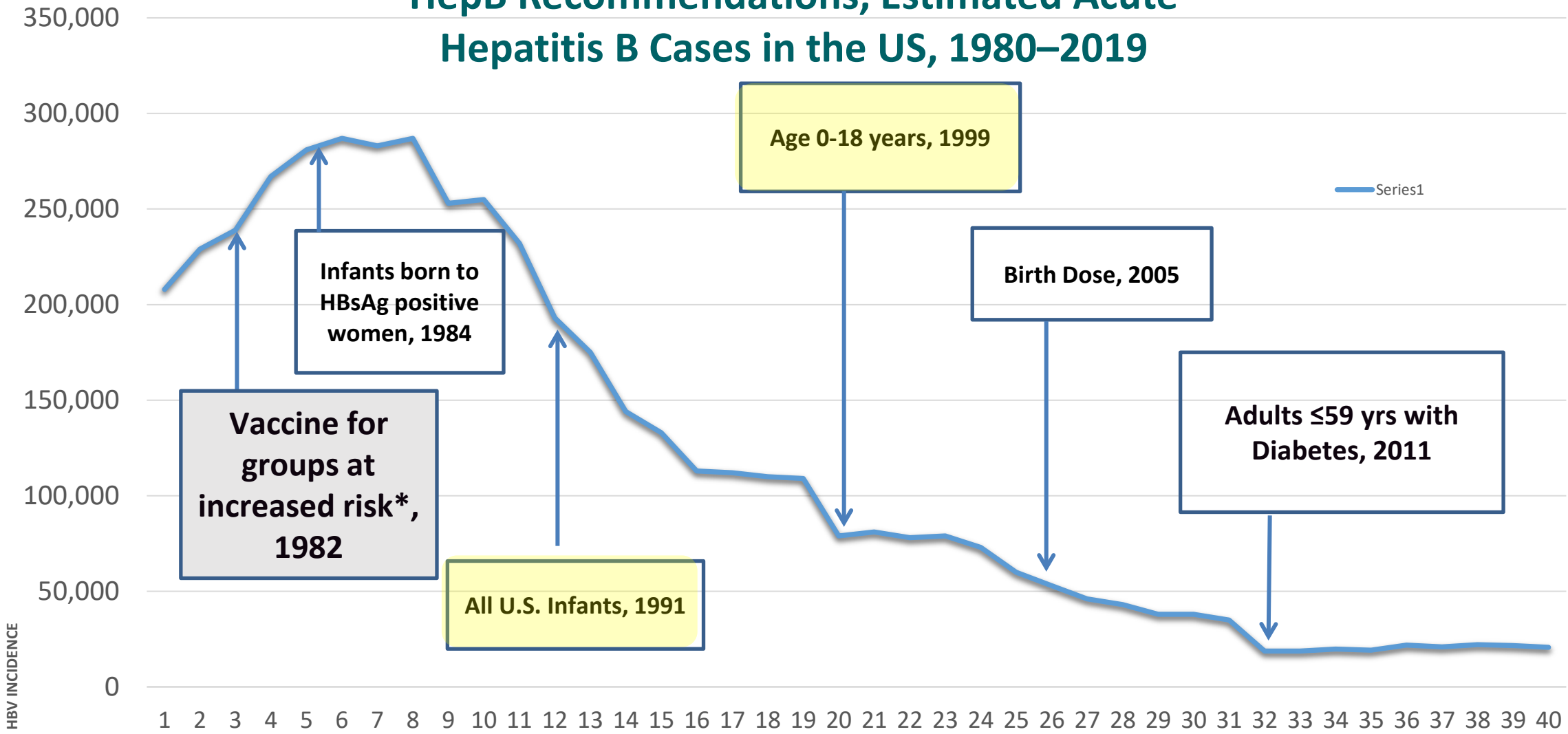
1. Nelson et al. Clinics in Liver Disease. 2016
2. Aly et al. Hepat Oncol. 2020
3. Bennett et al. Medscape.2021
4. Corte et al. J Gastroenterol Hepatol. 2014

Missed opportunities in HepB vaccination coverage among adults ≥19 years

- Low HepB vaccination coverage among US adults
  - 2018 National Health Interview Survey: HepB vaccination coverage (≥3 doses)[1]
    - 40.3% for adults 19-49 years
    - 19.1% for adults ≥50 years
  - 2013 – 2018 NHANES: 21.4% (95% CI: 20.2%–22.6%) of adults aged ≥25 years had vaccine-induced immunity to hepatitis B[4]
- In particular, risk groups likely represent a substantial proportion of the adult population (e.g., people with diabetes, healthcare workers), but have had low vaccination coverage[5]
  - Hyer et al. reported 87% of individuals > 60 years with DM were unvaccinated[2]
  - More than half of women with 1+ risk factor who visited or talked to a health professional in the past year were unvaccinated[3]

1. Vaccination Coverage Among US Adults, NHIS, 2018 | CDC
2. Hyer et al. Vaccine. 2019
3. Miller et al. Conference abstract. 2016
4. Roberts H et al. Hepatology. 2021
5. Ladak et al. Infection. 2012

HepB Recommendations, Estimated Acute Hepatitis B Cases in the US, 1980–2019



Source: National Notifiable Diseases Surveillance System (NNDSS)

*Health care providers, MSM, IDU, hemodialysis patients, household & sexual partners of persons with chronic HBV, persons in certain institutional settings, e.g., inmates of long-term correctional facilities.

Public Health Problem: Work Group Interpretation

Is the problem of public health importance?

- No
- Probably no
- Probably yes
- **Yes**
- Varies
- Don’t know

2. EtR Domain: Benefits and Harms
Summary of Evidence

Benefits: Seroprotection

- **>90% protection among healthy adults who complete the 3-dose HepB series[1-4]**

- **Immunity to hepatitis B infection is estimated to last for decades after vaccination.[1]**
  - Estimated ≥90% of persons had evidence of protection 30 years after receiving the primary series.[5]

1. Assad et al. Vaccine. 1999
2. Venters et al. Expert Rev Vaccines. 2004
3. Andre et al. Am J Med. 1989
4. Schillie et al. MMWR. 2018
5. Bruce et al. J Infect Dis. 2016

Benefits: Vaccine effectiveness

- **The incidence of HBV infection among US children decreased dramatically because of routine vaccination of infants.**
  - Within 10 years of initiation of universal hepatitis B vaccination in 1991, a 68% decrease in HBV infection prevalence among children was observed.[1]

- **No studies on universal vaccination among adults and a few studies with weak evidence on vaccination among adults with increased risk factors[2]**

1. Nelson et al. Clinics in Liver Disease. 2016
2. Tressler et al. Preventive Medicine. 2020
3. Sizemore et al. Sexually Transmitted Diseases. 2018

Harms: Summary of Evidence

Pregnancy

- **VSD study: Hepatitis B vaccines administered in 1,399 pregnancies: showed no increased risk of adverse events among pregnant people or their children[1]**
- **Insufficient data available on HepB-CpG (HEPLISAV-B) administered to pregnant people[2]**
  - **Ongoing pregnancy registry: collecting information from 250-300 pregnant people on outcomes following pregnancy exposure to Heplisav-B (Completion date: August 9, 2023)[3]**

Co-administration with other vaccines

- **MenACWY-CRM administered concomitantly with hepatitis A and/or B vaccine: No increased safety concerns or compromised immune responses to any of the vaccine antigens [4, 5]**

1. Groom et al. Vaccines. 2018
2. Schillie et al. MMWR. 2018
3. HEPLISAV-B -fda.gov. FDA approval letter. November 9, 2017
4. Haber et al. Vaccine. 2018
5. Alberer et al. Travel Medicine. 2015

Benefits: Vaccinate general population before chronic liver disease (CLD) and other comorbidities (e.g., obesity, diabetes) develop

Patients with chronic liver disease are known to have decreased immunogenicity with the conventional (3-dose) vaccine.[1, 2]

- **Only 64% of patients with CLD developed immunity with the new vaccine, in contrast to 90% reported in healthy volunteers in their registration trial.**

- **Lower seroprotection rates (45%) among persons with cirrhosis**

1. Roni, D.A. et al. Advances in Virology. 2013
2. Moreno-Fernandez et al. Primary Care Diabetes. 2020

Benefits: universal adult vaccination against HBV infection with either vaccine series[1]

1. Hall et al. ACIP Feb. 2021

- **Increase percent of people protected, moving from model baseline current strategy (23.7%) to universal strategy (44.9%, 3-dose strategy; 45.7%, 2-dose strategy)**

- **Avert additional HBV-related outcomes, with either 2- or 3-dose series, compared with baseline current strategy:**

	Baseline Strategy	3-dose strategy		2-dose strategy	
Outcome	Number (No.)	Number (No.)	Percent averted (%)	Number (No.)	Percent averted (%)
Acute HBV infections	570,735	428,485	24.8	428,733	24.6
Chronic HBV infections	45,847	34,200	24.2	34,447	24.0
HBV related deaths	104,953	78,808	22.8	78,808	22.2
Hepatocellular carcinoma	81,410	59,477	28.8	60,964	28.1

*Analytic horizon is the lifetime of the cohort, (on average, ~35 years per person). U.S. adult population of 247,822,574.
Each policy option is compared to the current vaccine recommendation and not across options

Benefits: Summary of Evidence

- **Economic analysis was not meant to compare 3-dose to 2-dose but rather to assess the cost benefit of the universal strategy.**
  - **Indicates that HepB vaccination does provide population benefits, regardless of HepB vaccine option chosen for this question.**

- **Base case did not vary vaccination coverage among adults at increased risk (since vaccination is already recommended for adults at increased risk)**
  - **However, in addition to the intended effects among the general population, actual implementation of a universal adult vaccination recommendation would likely result in an increase in vaccination among adults at increased risk.**

- **Similarity of impact of the 3-dose and 2-dose strategies driven by the balance of:**
  - **Higher proportion of adults that complete the full series in the 2-dose strategy**
  - **Small proportion of people receiving protection from an incomplete series**

1. Hall et al. ACIP Feb. 2021

Harms: Rare side effects/adverse reactions[1,4]

1. Assad et al. Vaccine. 1999
2. Schillie et al. MMWR. 2018
3. McCarthy et al. Pediatrics. 2016
4. Haber et al. Vaccine. 2018

- **Commonly reported mild adverse events: injection site pain (3-29%), erythema (3%), swelling (3%), fever (1%–6%), and headache (3%)[1,2]**

- **Estimated incidence of anaphylaxis among vaccine recipients is 1.1 per million doses. Likely causal relationship among yeast-sensitive persons**

- **Vaccine Safety Datalink, (VSD):**
  - **Over the 7-year study period, after the administration of 876,209 HepA and HepB vaccines; No deaths were reported in the 0-to-30-day window after vaccination[3]**

- **VAERS 2005-2015: 2,365 reports in adults, 15 deaths, 139 serious reports including general disorders/administration site conditions, musculoskeletal conditions and connective tissue disorders, and central nervous system disorders[4]**

Harms: Summary of Evidence

HepB-CpG vaccine (HEPLISAV-B):
minimal mild and severe adverse events

Adverse Events	HepB-CpG (HEPLISAV-B)	HBsAg-Eng (ENGERIX-B)
Mild adverse event	45.6%	45.7%
Serious adverse event	5.4%	6.3%
Cardiovascular event	0.27%	0.14%

1. Schillie et al. MMWR. 2018

Summary of GRADE

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HBsAg-1018	HBsAg-Eng	Relative (95% CI)	Absolute (95% CI)		
Cardiovascular events - RCTs												
4	randomised trials	not serious	serious [a]	not serious	serious [b]	none	41/9619 (0.4%)	16/4129 (0.4%)	RR 1.33 (0.58 to 3.08)	128 more per 100,000 (from 163 fewer to 806 more)	Type 3 LOW	CRITICAL
Cardiovascular events - observational												
1	observational studies	not serious	not serious	not serious	serious [b]	none	52/31183 (0.2%)	71/38442 (0.2%)	HR 0.92 (0.63 to 1.32)	15 fewer per 100,000 (from 68 fewer to 59 more)	Type 4 VERY LOW	CRITICAL
Serious adverse events												
6	randomised trials	not serious	not serious	not serious	not serious	none	528/9876 (5.3%)	277/4383 (6.3%)	RR 0.96 (0.79 to 1.16)	253 fewer per 100,000 (from 1,327 fewer to 1,011 more)	Type 1 HIGH	CRITICAL

CI: Confidence interval; RR: Risk ratio; HR: Hazard Ratio

a. Heterogeneity of estimates across studies. I2 = 43%

b. Few events suggest fragility of the estimate. 95% CI cannot exclude the possibility of meaningful harm.

Benefits and Harms: Work Group Interpretation

How substantial are the **desirable** anticipated effects?

- Minimal
- Small
- Moderate
- **Large**
- Varies
- Don’t know

Benefits and Harms: Work Group Interpretation

How substantial are the **undesirable** anticipated effects?

- **Minimal**
- Small
- Moderate
- Large
- Varies
- Don’t know

Benefits and Harms: Work Group Interpretation

Do the desirable effects outweigh undesirable effects?

- **Favors intervention**
- Favors comparison
- Favors both
- Favors neither
- Unclear

Benefits and Harms: Work Group Interpretation

What is the overall certainty of evidence for the critical outcomes?

- Important uncertainty
- Probably important uncertainty
- **Probably not important uncertainty**
- No important uncertainty

3. EtR Domain: Values and Preferences

Values: Summary of Evidence

Values and preferences vary by risk status/group

- **Among adult patients in high-risk settings, 47% did not respond to questions about risk factors for hepatitis B but expressed interest in getting vaccinated.[1]**

Limited information on low-risk persons

- **Systematic review of perceptions of immigrants and refugees (mostly Southeast Asians) from highly HBV endemic areas residing in low HBV endemic countries (US, Canada, Australia) found that 54-96% of participants knew that hepatitis B was vaccine-preventable.[2]**
  - **Differing attitudes toward vaccination: some studies noted confusion around benefits, efficacy, and side-effects while others found positive perception of vaccination following provider recommendation.**

- **In a convenience sample of Chinese American immigrant adults surveyed in Southern California, 60% reported "feeling well/no health problems" as a barrier for vaccination.[3]**

- **In a convenience sample of Vietnamese American immigrant adults, participants were not worried about HBV or liver cancer. However, they stated that they would not worry about liver disease after getting vaccinated.[4]**

1. Bridges et al. Vaccine. 2019
2. Owiti et al. BMC Pub Hlth. 2015
3. Zhao et al. JAANP. 2015
4. Ma et al. J Im Min Hlth. 2007

Values: Work Group Interpretation

Does the target population feel that the desirable effects are large relative to undesirable effects?

- No
- Probably no
- **Probably yes**
- Yes
- Varies
- Don’t know

Values: Work Group Interpretation

Is there important uncertainty about or variability in how much people value the main outcomes?

- Important uncertainty or variability
- Probably important uncertainty or variability
- **Probably not important uncertainty or variability**
- No important uncertainty or variability
- No known undesirable outcomes

4. EtR Domain: Acceptability

Acceptability: Summary of Evidence

Stakeholder support for universal adult HepB vaccine recommendation and improving adult immunization rates[1-5]

- **Expert meeting sponsored by a vaccine manufacturer, specialists in primary care, GI/hepatology, infectious diseases, travel medicine and public health concluded a universal adult HepB vaccination strategy would be the most practical approach to control hepatitis B in adults.**

- **AHIP Stakeholder Roundtable held on improving adult immunization rates**
  - **Primary care providers, consumers, pharmacies and public and private payers including health plans discussed the importance of reducing vaccine-preventable diseases by increasing vaccination rates across the lifespan of a person and reducing ethnic and racial disparities.**

- **State stakeholders expressed willingness to invest in hepatitis B vaccination program for adults at increased risk.**

1. Schiff et al. J Appl Res. 2007.
2. Time for a bold advance to defeat hepatitis B | The Hill)
3. https://www.ahip.org/wp-content/uploads/2016/04/Vaccine_Report_8.26.15-1.pdf
4. Harris et al. MMWR. 2016.
5. https://www.nfid.org/wp-content/uploads/2019/08/cta-hep-b-at-risk-adults.pdf

National Provider Survey: Assessing current approaches of adult hepatitis B vaccination practices

	Definitely/Somewhat a barrier (%)[a]	A minor/not at all a barrier (%)
Patients not disclosing their high-risk behaviors	68	32
Lack of adequate reimbursement for vaccination	35	65
The “up-front” costs of purchasing the vaccine	33	67
Feeling too pressed for time to routinely assess patients for risk factors	44	56
Other preventive care issues taking precedence over hepatitis B vaccination	42	57
Difficulty ensuring that patients complete the three-dose vaccine series	36	64
High-risk patients refusing vaccination	17	83
Patient concerns about vaccine safety	6	94
Provider concerns about vaccine safety	2	98

National survey of 433 family medicine physicians and 420 internists assessed[1]

1. Daley et al. Am J Prev Med. 2009

National Provider Survey:

Perceived barriers to nurses/medical assistants using standing orders to identify and vaccinate adults with risk factors

- **~50% of providers stated that nurses/medical assistants had questions about who should be immunized.**
- **~50% felt the assessment of risk factors required a higher level of medical knowledge than some nurses/medical assistants had.**
- **66% of providers stated that nurses/medical assistants are too pressed for time to assess patients for risk factors.**

National survey of 433 family medicine physicians and 420 internists assessed[1]

1. Daley et al. Am J Prev Med. 2009

Acceptability: Summary of Evidence

Physicians report that the main barriers to stocking and administering adult hepatitis B vaccines were financial

- **In a survey of physicians, 40-60% of internists and family medicine physicians reported assessing the need for hepatitis B vaccine and 65-80% reported stocking hepatitis B vaccines[1]**
- **Patient resistance/vaccine hesitancy, and not having enough time or effective materials to address patient resistance were also top challenges for surveyed family medicine physicians[2]**
- **Simplifying hepatitis B vaccine recommendations may encourage practitioners to administer hepatitis B vaccines to adults**

1. Hurley et al. Ann Intern Med. 2014
2. Equils et al. Hum Vac Imm. 2019

Acceptability: Work Group Interpretation

Is the universal vaccination strategy acceptable to key stakeholders?

- No
- Probably no
- **Probably yes**
- **Yes**
- Varies
- Don’t know

5. EtR Domain: Resource Use

Resource Use: Cost Utility Study[1]

Scenarios:	**Base case:** 50% vaccination coverage in general population; ~30% coverage* among people with risk factors	**Sensitivity analysis 1:** 50% vaccination coverage in general population; +20% *additional* coverage among people with risk factors	**Sensitivity analysis 2:** 70% vaccination coverage in general population; +60% *additional* coverage among people with risk factors
Outcome			
3-dose strategy			
ICER (USD/QALY)	$152,722	$137,111	$121,189
Total incremental cost (2019 USD, billion)	~$32	~$36	~$57
NNV (acute infection)	372	334	314
2-dose strategy			
ICER (USD/QALY)	$155,429	$134,589	$122,208
Total incremental cost (2019 USD, billion)	~$32	~$36	~$57
NNV (acute infection)	386	350	324

*Base case: Summary vaccination coverage input based on 35.8% protected, with varying age-group specific coverages.

Note: Analytic horizon is the lifetime of the cohort, (on average, ~35 years per person). U.S. adult population of 247,822,574.

Each policy option is compared to the current vaccine recommendation and not across options.

1. Hall et al. ACIP Feb 2021

Universal adult HepB vaccination strategy results in additional costs, but also additional QALYs, compared to the current strategy[1]

- **The purpose of this economic analysis was to show that regardless of which HepB vaccine option was chosen for this particular question, HepB vaccination provides a benefit to the US population.**

- **Results hold true across a range of vaccination coverage scenarios and are robust against the influence of any single model assumption or input.**

- **Higher vaccination coverage in the intervention strategies resulted in better health outcomes —the average QALYs gained, life-years gained, number of acute HBV infections averted, and number of HBV-related deaths averted all increased as vaccination coverage in the intervention strategy increased.**

1. Hall et al. ACIP Feb 2021

Resource Use: Work Group Judgment

Is the universal vaccination strategy a reasonable and efficient allocation of resources?

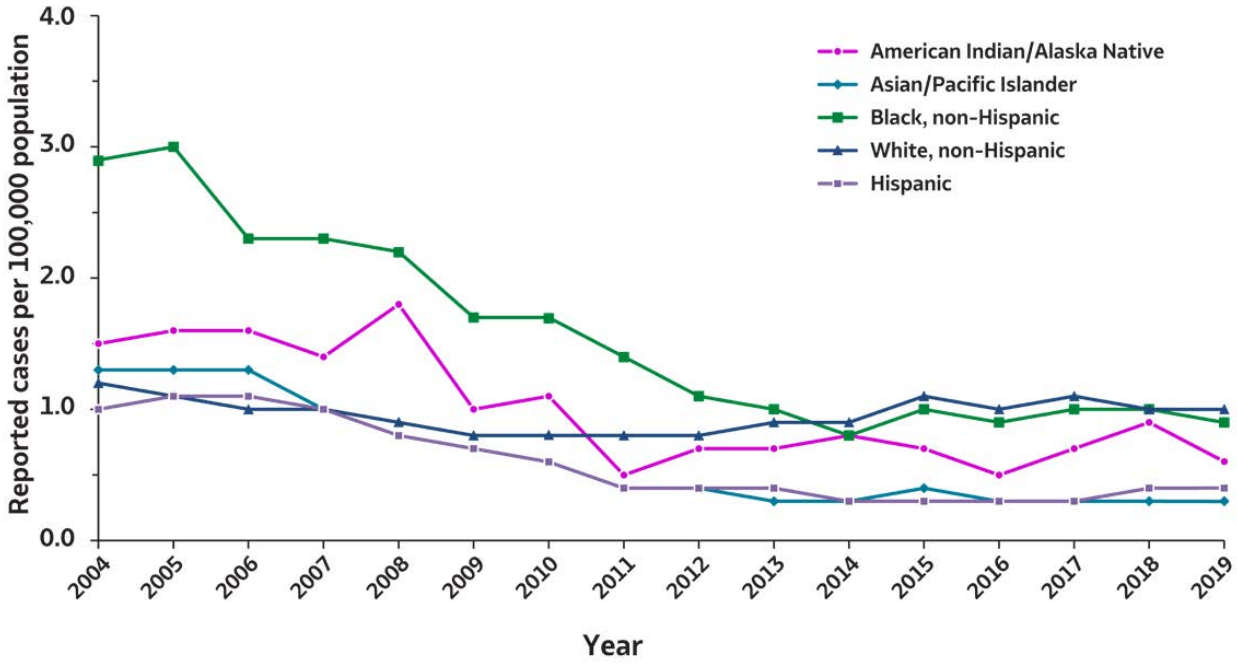
- No
- Probably no
- Probably yes
- **Yes**
- Varies
- Don’t know

6. EtR Domain: Equity

Racial disparity in hepatitis B infection rates: slow improvement

- In 2006, HBV infections rates among non-Hispanic Black people remained over twice as high as among other racial/ethnic populations.[1]
- Recent rates among Black Americans are now up to 3x those of other racial/ethnic minority groups.
- Recently, HBV infection rates have increased among non-Hispanic White people.[2, 3, 4]
- Rates of HBV disease for children and adolescents of all races did converge to a lower rate after a universal vaccination strategy was implemented for this group.[3]

Figure 2.6. Rates of reported acute hepatitis B virus infections, by race/ethnicity — United States, 2004–2019



1. Wasley et al. MMWR. 2008
2. Harris et al. MMWR. 2016
3. https://www.cdc.gov/hepatitis/statistics/2019surveillance/HepB.htm
4. Schiff et al. Journal of Applied Research. 2007

Estimated proportion of adults aged ≥19 years who received hepatitis B vaccination, by age group, race/ethnicity†

Age group, race/ethnicity	Sample size	%	(95% CI)
19–49 years	9,479	40.3	(38.8, 41.8)
White	5,809	43.6	(41.8, 45.4)
Black	1,140	35.4	(31.4, 39.6)¶¶
Hispanic	1,612	33.1	(30.1, 36.2)¶¶
Asian	597	45.2	(40.1, 50.4)
Other	321	37.8	(31.2, 44.8)

National Health Interview Survey, United States, 2018[1]

1. Vaccination Coverage Among US Adults, NHIS, 2018 | CDC

Abbreviations: CI = confidence interval

† Race/ethnicity was categorized as follows: white, black, Hispanic, Asian and "other." In this report, persons identified as white, black, Asian, or other race are non-Hispanic. Persons identified as Hispanic might be of any race. "Other" includes American Indian/Alaska Native and persons who identified multiple races. The five racial/ethnic categories are mutually exclusive.

§ Respondents were asked if they had ever received the hepatitis B vaccine, and if yes, if they had received at least 3 doses or less than 3 doses.

¶ $p<0.05$ by t-test for comparisons between 2018 and 2017 within each level of each characteristic.

¶¶ $p<0.05$ by t–test for comparisons with white as the reference.

Risk factors assessed include socio-structural factors that may criminalize and stigmatize[1]

- In the ongoing opioid crisis[2], stigma associated with drug use may keep people from reporting risk factors to their clinicians.[1]

- Currently, health care providers may rely on self-reported vaccine history to determine need for vaccination, but self-reported vaccination history does not predict immunity well.[3,4,5]

- A universal vaccination recommendation could eliminate the need for risk factor assessment prior to vaccination
  - Reduce stigma among people who have been marginalized and at increased risk, and immigrants with concerns about stigma associated with HBV-related care [6, 7, 8]

1. Taylor J, et al. BMC Infect Dis. 2019
2. Harris A, et al. MMWR. 2016
3. Figgatt M, et al. Public Health Rep. 2020
4. Collier, MG et al. Vaccine. 2015
5.Topp, L et al. Drug Alcohol Rev. 2009
6. Kim, MJ et al. Asia-Pacific J Onc Nurs. 2015
7. Mokaya j et al. Wellcome Open Research. 2018
8. Owiti, JA et al. BMJ Public Health. 2015

Equity: Work Group Interpretation

What would be the impact of the universal vaccination strategy on health equity?

- Reduced
- Probably reduced
- Probably no impact
- Probably increased
- **Increased**
- Varies
- Don’t know

7. EtR Domain: Feasibility

Feasibility: Summary of Evidence

- **Implementing the current high-risk adult strategy is challenging.**
  - CDC-funded pilot study found lower vaccine acceptance than anticipated and low series completion (22%)[1]
  - Texas State BRFSS (2018): 50.8 percent of adults who initiated HepB vaccination reported completion of the HepB vaccination series[2]

- **Several studies note that physicians administer HepB vaccination to adults at increased risk, at suboptimal rates.[3,4]**
  - In an urban HIV clinic population, 30% of patients were not offered HepB vaccine.[4]

- **In a meeting sponsored by a vaccine manufacturer, experts suggested that standing orders and consistent recommendations from professional societies and government agencies may address some implementation obstacles.[5]**

- **Electronic provider reminders can be a good tool to achieve series completion of HepB vaccination.**
  - In a California health system, the HepB vaccine initiation rate increased among adults with diabetes by 70-fold compared to a control site.[6]
  - The series completion rate improved 20-fold.

1. Bridges et al. Vaccine. 2019
2. 2018 Texas BRFSS vaccine report
3. Miller et al. Conference abstract. 2016
4. Bailey et al. IJID. 2008
5. Schiff et al. J Appl Res. 2007
6. Hechter et al. Vaccine. 2019

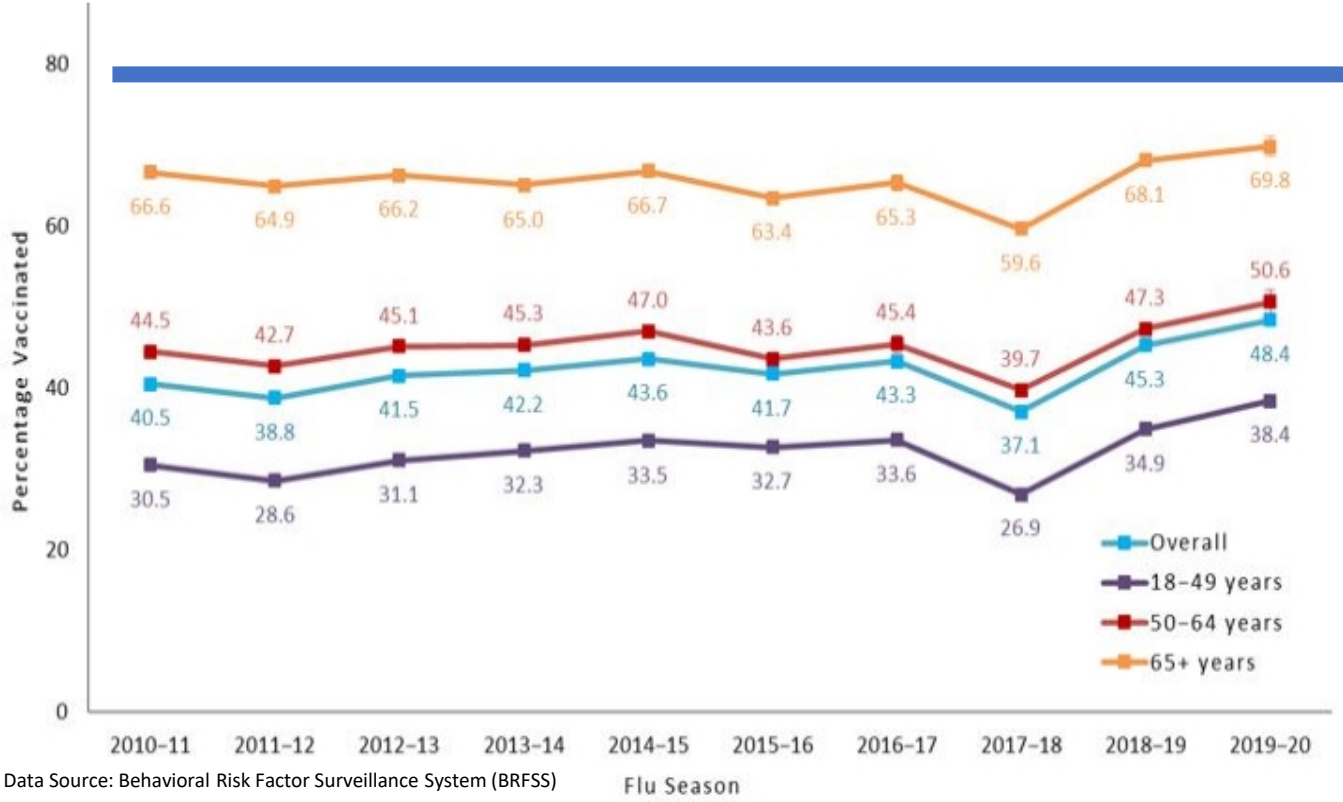
Feasible to increase coverage among older adults

Age Group	No Risk Factors*			1+ Risk Factors*		
	Sample size	%	95% CI	Sample size	%	95% CI
19-29	1,671	41.1	(37.9-44.4)	1,220	57.1	(53.7-60.4)
30-39	1,697	32.1	(28.9-35.4)	1,661	48.3	(45.3-51.3)
40-49	1,545	25.1	(22.5-27.9)	1,668	38.2	(35.2-41.2)
50-59	1,946	20.2	(17.9-22.8)	1,792	30.1	(27.6-32.8)
60+	4,751	12.3	(11.2-13.6)	4,044	19.5	(18.0-21.1)

*Not diabetic, did not have chronic liver disease, AND did not travel to HBV endemic country

- **Lower HepB vaccination coverage among adults aged ≥50 years compared with those aged 18–49 years, likely due to universal HepB vaccine recommendations for children and adolescents[1]**

*** p<0.05 by t–test for comparisons between adults aged 19-59 years with diabetes and ≥60 years with diabetes. (CDC unpublished, NHIS 2018[2])



Data Source: Behavioral Risk Factor Surveillance System (BRFSS)

Adult Flu Vaccination Coverage by Age Group, 2010 – 2020[3]

1. Yue et al. Vaccine. 2018
2. Vaccination Coverage Among US Adults, NHIS, 2018 | CDC
3. Flu Vaccination Coverage. United States. 2019–20 Influenza

Feasibility: Summary of Evidence

- **Evidence supports that either 2-dose or 3-dose vaccine schedules are effective, but the 2-dose vaccine may be of higher value in the populations with certain risk factors.[1, 2]**
  - The two-dose vaccine would lead to higher series completion rates.
  - Among 10,888 adults vaccinated in a CA health system, rates of series completion at 270 days were 57.9% for Heplisav-B and 28.0% for Engerix-B.[1]

- **The Affordable Care Act requires insurance coverage of routinely recommend vaccines, with no cost sharing.**
  - Does not apply to transitional/grandfathered plans, Medicare, and state Medicaid plans. Medicare does covers hepatitis B vaccines for people at increased risk of infection
  - Limited funding for adult vaccination is also available as part of the Section 317 program

- **Implementation will require integration with the HBV testing guidelines, which are concurrently being developed by a parallel CDC process.**

1. Bruxvoort et al. JAMA Netw Open. 2020
2. Rosenthal et al. Vaccine. 2020

Feasibility: Work Group Interpretation

Is the universal vaccination strategy feasible to implement?

- No
- Probably no
- Probably yes
- **Yes**
- Varies
- Don’t know

Summary

Domain	Question	Work Group Judgments
Public Health Problem	Is the problem of public health importance?	**Yes**
Benefits and Harms	How substantial are the desirable anticipated effects?	**Large**
	How substantial are the undesirable anticipated effects?	**Minimal**
	Do the desirable effects outweigh the undesirable effects?	**Favors intervention**
	What is the overall certainty of evidence for the critical outcomes?	**Probably not important uncertainty**
Values	Does the target population feel the desirable effects are large relative to the undesirable effects?	**Probably yes**
	Is there important variability in how patients value the outcome?	**Probably not important uncertainty or variability**
Acceptability	Is the universal vaccination strategy acceptable to key stakeholders?	**Probably yes/ Yes**
Resource Use	Is the universal vaccination strategy a reasonable and efficient allocation of resources?	**Yes**
Equity	What would be the impact of the universal vaccination strategy on health equity?	**Increased**
Feasibility	Is the universal vaccination strategy feasible to implement?	**Yes**

Evidence to Recommendations Framework
Summary: Work Group Judgment

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

Policy Options for ACIP Considerations

Is there sufficient information to move forward with a recommendation?

Yes ○ No ○

Policy options for ACIP consideration	ACIP does not recommend the intervention* *Intervention may be used within FDA licensed indications ○	ACIP recommends the intervention for individuals based on shared clinical decision-making ○	ACIP recommends the intervention ●
Draft recommendation (text)	**All adults previously unvaccinated for hepatitis B should receive hepatitis B vaccination**		
Additional considerations (optional)	none		

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.

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Erin Conners
Mona Doshani
Penina Haber
Megan Hofmeister
Mohammed Khan
Lakshmi Panagiotakapoulos
Noele Nelson
Priti Patel
Sarah Schillie
Tom Shimabukuro
Phil Spradling
Carolyn Wester

Hepatitis Work Group Members

ACIP Voting Members

Kevin Ault (Chair)

Sybil Cineas

Liaison Representatives

Elizabeth Barnett (AAP)

Marci Drees (SHEA)

Sharon McMullen (ACHA)

Brenna Hughes (ACOG)

Susan Lett (CSTE)

Pamela Rockwell (AAFP)

Matthew Zahn (NACCHO)

Ex Officio Members

Marian Major (FDA)

Darcie Everett (FDA)

Rajen Koshy (NIAID/NIH)

Consultants

Sharon Frey (SLU)

Robert Frenck (CCHMC)

Prabhu Gounder (LA-DPH)

Kathleen Harriman (CDPH)

Brian McMahon (ANTHC)

Kelly Moore (IAC)

David Nace (AMDA)

Jennifer Rosen (NYC-DOH)

Ann Thomas (OR-DHS/OHA)

Jennifer Zipprich (MDPH)

CDC Lead

Mark Weng

(CDC/Division of Viral Hepatitis)

Appendix- GRADE assessment

Grading of Recommendations, Assessment, Development and Evaluation (GRADE): Should all HepB-unvaccinated adults receive hepatitis B vaccination?

Mohammed Khan, PhD, MSPH

Mona Doshani, MD, MPH

LCDR Mark Weng, MD, MSc

September 2021

PICO Question

Population: Previously unvaccinated adults age ≥ 18 years

Intervention: Universal vaccination strategy (2- and 3-dose schedules)

Comparison: Current risk-based vaccination strategy (2- and 3-dose schedules)

Outcomes of interest

1. Incidence of hepatitis B
2. Morbidity related to hepatitis B
3. Mortality related to hepatitis B
4. Serious adverse events associated with the 2-dose vaccine*

* This outcome is solely aimed at assessing the 2-dose HEPLISAV-B (approved in 2017). The 3-dose HepB vaccines have already been evaluated for their adverse events profiles and recommended by ACIP based on their safety records.

Outcomes

Outcomes	Importance
▪ Incidence of hepatitis B ▪ Morbidity related to hepatitis B ▪ Mortality related to hepatitis B	Important
▪ Serious adverse events associated with the 2-dose HepB vaccine*	Critical

* This outcome is solely aimed at assessing the 2-dose HepB-CpG (HEPLISAV-B, FDA-approved in 2017), for which a standard postmarketing surveillance study is to be presented prior to any votes on the proposed policy question. The 3-dose HepB vaccines have already been evaluated for their adverse events profiles and recommended by ACIP based on their safety records.

Outcomes

Outcomes	Importance
▪ Incidence of hepatitis B ▪ Morbidity related to hepatitis B ▪ Mortality related to hepatitis B	Important
▪ Serious adverse events associated with the 2-dose HepB vaccine*	Critical

* This outcome is solely aimed at assessing the 2-dose HepB-CpG (HEPLISAV-B, FDA-approved in 2017), for which a standard postmarketing surveillance study is to be presented prior to any votes on the proposed policy question. The 3-dose HepB vaccines have already been evaluated for their adverse events profiles and recommended by ACIP based on their safety records.

Evidence retrieval

- Systematic review of data for Hepatitis B vaccination risk based versus routine universal including a search of PubMed, Medline and EMBASE from January 1, 2006 through September 10, 2020
- Included articles in English from any country

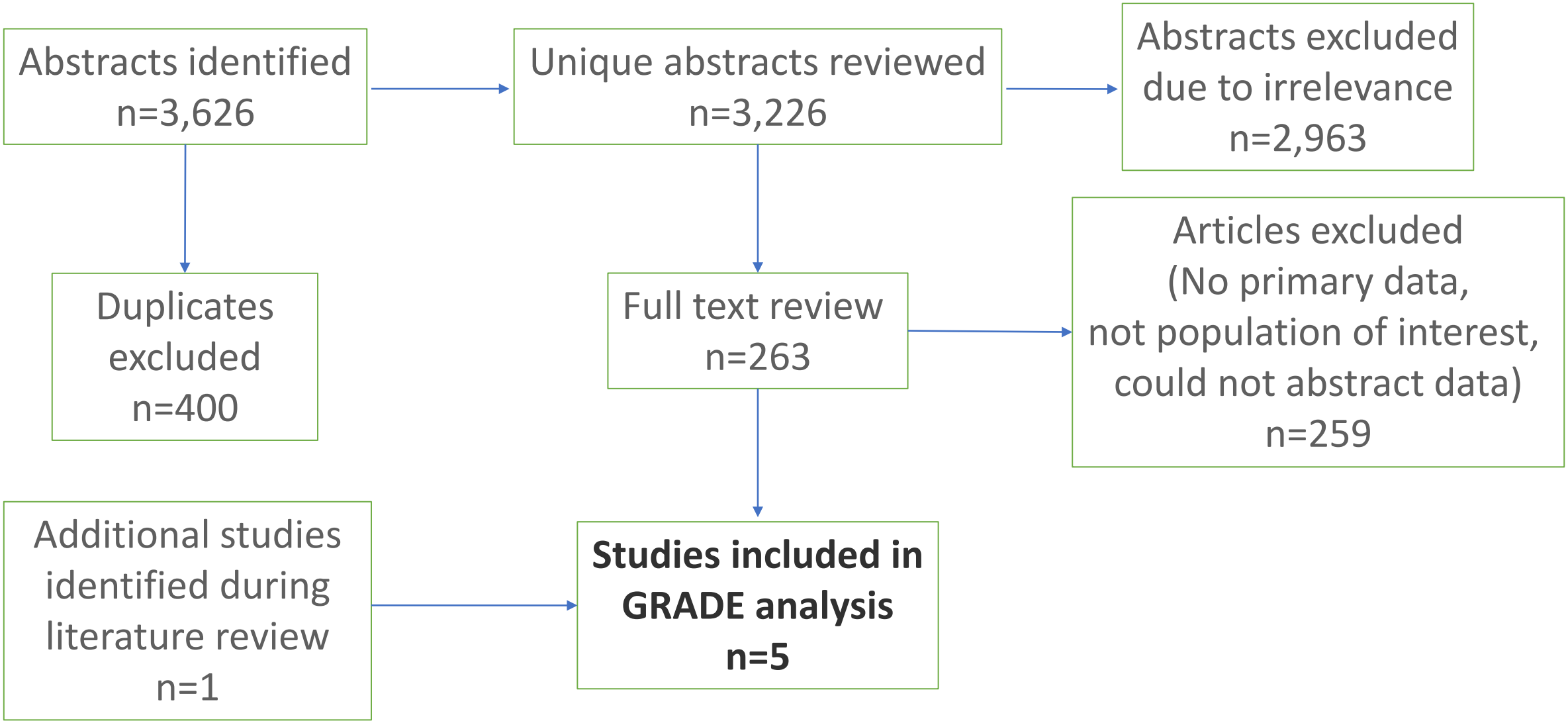
SEARCH TERMS INCLUDED:

hepatitis b vaccines/ OR ((hepatitis B ADJ5 vaccin*) OR (HBV ADJ5 vaccin*) OR recombivax hb OR engerix-b OR heplisav-b OR Twinrix).ti,ab. **AND** Exp Adult/ OR (adult* OR elder* OR senior*).ti,ab. **AND** Ae.fs OR ad.fs OR mo.fs OR review.pt OR (dose* OR dosage* OR administration OR schedule* OR routine OR universal OR adverse OR efficacy OR effective* OR evidence OR safe* OR strateg* OR risk* OR guideline* OR recommendation* OR mortality OR death).ti,ab. **AND**
Meta analys* OR metaanalys* OR systematic review* OR cohort* OR incidence OR incident OR population stud* OR randomized OR randomised OR rct* OR trial* OR clinical stud* OR surveillance OR evidence-based
hepatitis b vaccines/ OR ((hepatitis B ADJ5 vaccin*) OR (HBV ADJ5 vaccin*) OR recombivax hb OR engerix-b OR heplisav-b OR Twinrix).ti,ab.
AND Exp Adult/ OR (adult* OR elder* OR senior*).ti,ab.
AND Ae.fs OR ad.fs OR mo.fs OR review.pt OR (dose* OR dosage* OR administration OR schedule* OR routine OR universal OR adverse OR efficacy OR effective* OR evidence OR safe* OR strateg* OR risk* OR guideline* OR recommendation* OR mortality OR death).ti,ab. **AND**
Meta analys* OR metaanalys* OR systematic review* OR cohort* OR incidence OR incident OR population stud* OR randomized OR randomised OR rct* OR trial* OR clinical stud* OR surveillance OR evidence-based

Evidence retrieval

- Exclusion criteria
  - Articles dated earlier than year 2006
  - Vaccines not licensed in U.S.
  - Articles not addressing the population of interest
  - Articles where data could not be abstracted

Evidence retrieval



GRADE: Serious adverse events associated with the 2-dose vaccine

Summary of Studies Reporting Cardiovascular Events

Study	Population	n/N (%) HBsAg-1018 (Heplisav-B)	n/N (%) HBsAg-Eng (Engerix-B)	Difference (95% CI) Risk ratio (95% CI)	Study limitations (Risk of Bias)
Hyer, 2018	**HBV-10:** 2,415 adults 18–55 years	0/1,810 (0%)	0/605 (0%)	--	Not serious
	HBV-16: 2,449 adults 40–70 years	3/1,968 (0.2%)	2/481 (0.4%)	-0.3% (-0.8%, 0.3%) 0.37 (0.06, 2.19)	Not serious
	HBV-23: 8,368 adults 18–70 years	28/5,587 (0.5%)	6/2,781 (0.2%)	0.3% (0.03%, 0.5%) 2.32 (0.96, 5.60)	Not serious

Summary of Studies Reporting Cardiovascular Events

Study	Population	n/N (%) HBsAg-1018 (Heplisav-B)	n/N (%) HBsAg-Eng (Engerix-B)	Difference (95% CI) Risk ratio (95% CI)	Study limitations (Risk of Bias)
Janssen, 2013	516 adults 18–75 years with chronic kidney disease	10/254 (3.9%)	8/262 (3.1%)	0.9% (-2.3%, 4.1%) 1.29 (0.52, 3.21)	Not serious
Bruxvoort, 2021	69,625 adults routinely vaccinated in a US health system	52/31,183 (0.2%)	71/38,442 (0.2%)	0.0% (-0.1%, 0.0%) HR 0.92 (0.63, 1.39)	Not serious

Summary of Studies Reporting Serious Adverse Events

Study	Population	n/N (%) HBsAg-1018 (Heplisav-B)	n/N (%) HBsAg-Eng (Engerix-B)	Difference (95% CI) Risk ratio (95% CI)	Study limitations (Risk of Bias)
Halperin, 2006	99 healthy adults 18–28 years	1/51 (2.0%)	4/48 (8.3%)	-6.4% (-15.1%, 4.4%) 0.24 (0.03, 2.03)	Not serious
Sablan, 2012	412 healthy adults 40–70 years	10/206 (4.9%)	13/206 (6.3%)	-1.5% (-5.9%, 3.0%) 0.77 (0.35, 1.71)	Not serious
Janssen, 2013	516 adults 18–75 years with chronic kidney disease	68/254 (26.8%)	76/262 (29.0%)	-2.2% (-10.0%, 5.5%) 0.92 (0.70, 1.22)	Not serious

Summary of Studies Reporting Serious Adverse Events

Study	Population	n/N (%) HBsAg-1018 (Heplisav-B)	n/N (%) HBsAg-Eng (Engerix-B)	Difference (95% CI) Risk ratio (95% CI)	Study limitations (Risk of Bias)
Hyer, 2018	**HBV-10:** 2,415 adults 18–55 years	28/1,810 (1.5%)	13/605 (2.1%)	-0.6% (-1.9%, 0.7%) 0.72 (0.38, 1.38)	Not serious
	HBV-16: 2,449 adults 40–70 years	76/1,968 (3.9%)	23/481 (4.8%)	-0.9% (-3.0%, 1.2%) 0.81 (0.51, 1.27)	Not serious
	HBV-23: 8,368 adults 18–70 years	345/5,587 (6.2%)	148/2,781 (5.3%)	0.9% (-0.2%, 1.9%) 1.16 (0.96, 1.40)	Not serious

GRADE Summary

GRADE Evidence Type

- Type 1 (high certainty): We are very confident that the true effect lies close to that of the estimate of the effect.
- Type 2 (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.
- Type 3 (low certainty): Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- Type 4 (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.

Dr. Julia Gargano. Moderna COVID-19 Vaccine GRADE presentation. December 19th, 2020.

GRADE Criteria

- Initial evidence type (certainty level) determined by study design
  - Initial evidence type 1 (high certainty): A body of evidence from randomized controlled trials
  - Initial evidence type 3 (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.

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GRADE Summary of Findings Table

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HBsAg-1018	HBsAg-Eng	Relative (95% CI)	Absolute (95% CI)		
Cardiovascular events - RCTs												
4	randomised trials	not serious	serious [a]	not serious	serious [b]	none	41/9619 (0.4%)	16/4129 (0.4%)	RR 1.33 (0.58 to 3.08)	128 more per 100,000 (from 163 fewer to 806 more)	Type 3 LOW	CRITICAL
Cardiovascular events – observational												
1	observational studies	not serious	not serious	not serious	serious [b]	none	52/31183 (0.2%)	71/38442 (0.2%)	HR 0.92 (0.63 to 1.32)	15 fewer per 100,000 (from 68 fewer to 59 more)	Type 4 VERY LOW	CRITICAL
Serious adverse events												
6	randomised trials	not serious	not serious	not serious	not serious	none	528/9876 (5.3%)	277/4383 (6.3%)	RR 0.96 (0.79 to 1.16)	253 fewer per 100,000 (from 1,327 fewer to 1,011 more)	Type 1 HIGH	CRITICAL

CI: Confidence interval; RR: Risk ratio; HR: Hazard Ratio

a. Heterogeneity of estimates across studies. I2 = 43%

b. Few events suggest fragility of the estimate. 95% CI cannot exclude the possibility of meaningful harm.

GRADE Conclusions

- No studies comparing universal and risk-based adult hepatitis B vaccination
- Cardiovascular events were more common in the Heplisav-B arms of RCTs compared to Engerix-B, but this difference was not statistically significant.
  - Estimates were heterogeneous across trials and imprecise.
- A lower rate of cardiovascular events was observed in the Heplisav-B group in an observational study, but this estimate was also imprecise.
- The risk of serious adverse events was significantly lower in the Heplisav-B arms of RCTs.
  - Estimates were heterogeneous across trials.

GRADE References

1. Halperin SA, Dobson S, McNeil S, Langley JM, Smith B, McCall-Sani R, et al. Comparison of the safety and immunogenicity of hepatitis B virus surface antigen co-administered with an immunostimulatory phosphorothioate oligonucleotide and a licensed hepatitis B vaccine in healthy young adults. Vaccine. 2006;24(1):20-6.
2. Sablan BP, Kim DJ, Barzaga NG, Chow WC, Cho M, Ahn SH, et al. Demonstration of safety and enhanced seroprotection against hepatitis B with investigational HBsAg-1018 ISS vaccine compared to a licensed hepatitis B vaccine. Vaccine. 2012;30(16):2689-96.
3. Janssen RS, Mangoo-Karim R, Pergola PE, Girndt M, Namini H, Rahman S, et al. Immunogenicity and safety of an investigational hepatitis B vaccine with a toll-like receptor 9 agonist adjuvant (HBsAg-1018) compared with a licensed hepatitis B vaccine in patients with chronic kidney disease. Vaccine. 2013;31(46):5306-13.
4. Hyer R, McGuire DK, Xing B, Jackson S, Janssen R. Safety of a two-dose investigational hepatitis B vaccine, HBsAg-1018, using a toll-like receptor 9 agonist adjuvant in adults. Vaccine. 2018;36(19):2604-11.
5. Bruxvoort K. Post-licensure safety of an adjuvanted hepatitis B vaccine: Final results of the HEPLISAV-B acute myocardial infarction study. Presentation to ACIP Hepatitis B Working Group, May 19, 2021.