# Hepatitis B Vaccination:
## Update on Adult Recommendations

**LCDR Mark K. Weng, MD, MSc**
**CDC/ NCHHSTP**

Indian Country ECHO Grand Rounds
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# Updated Hepatitis B Recommendations (as of Nov 2021)

The Advisory Committee on Immunization Practices (ACIP) recommends the following groups **should** receive hepatitis B vaccines:

- Adults aged 19 through 59 years
- Adults aged 60 years and older with risk factors for hepatitis B

The ACIP recommends the following groups **may** receive hepatitis B vaccines:

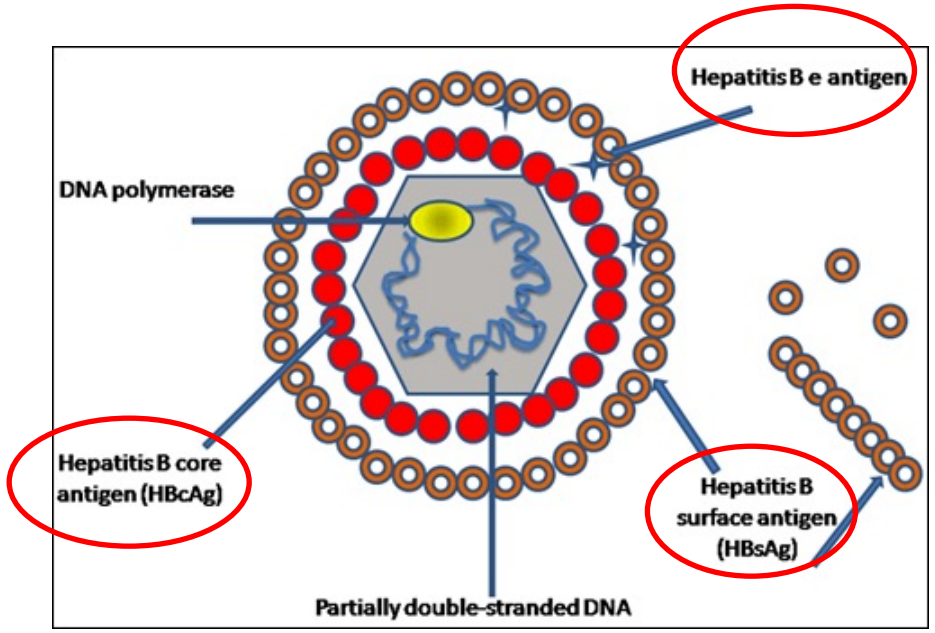
- Adults aged 60 years and older without known risk factors for hepatitis B

# Outline Hepatitis B

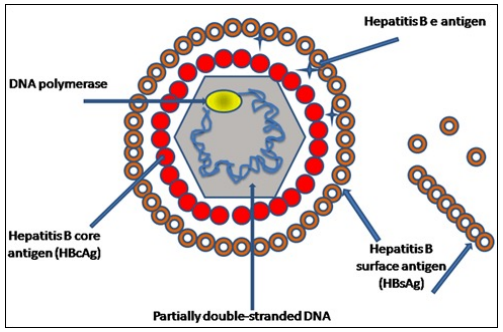
- Background
- Rationale for updating adult HepB recommendations
  - Epidemiology, Equity, and Economics
- HepB Vaccine
- Summary

# Pathogen

- HBV is a 42-nm double-stranded enveloped DNA virus of the *Hepadnaviridae* family
- Composed of:
  - Viral envelope containing the surface antigen (HBsAg)
  - Nucleocapsid core (HBcAg)
  - Hepatitis B e antigen (HBe)
- Eight genotypes (A-H);
  2 provisional genotypes (I,J)
  - Varying regional prevalence
  - Possible differences in disease severity

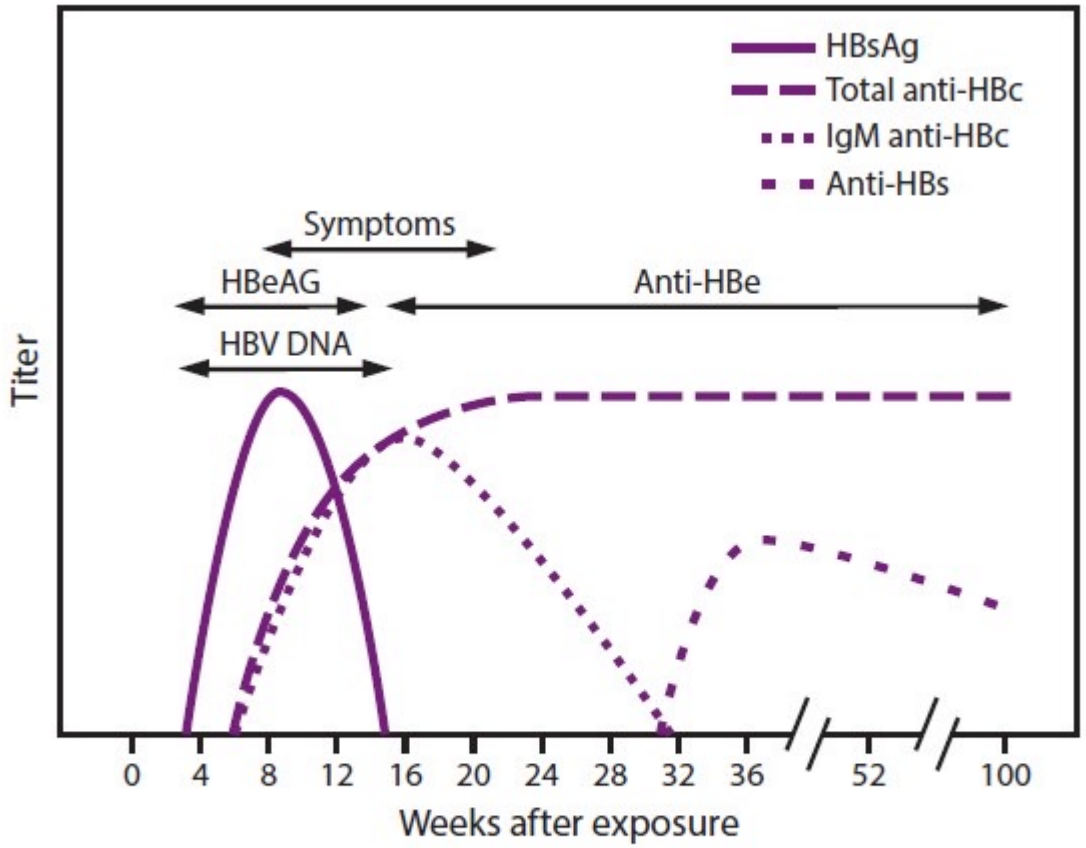


# Hepatitis B Serology Overview

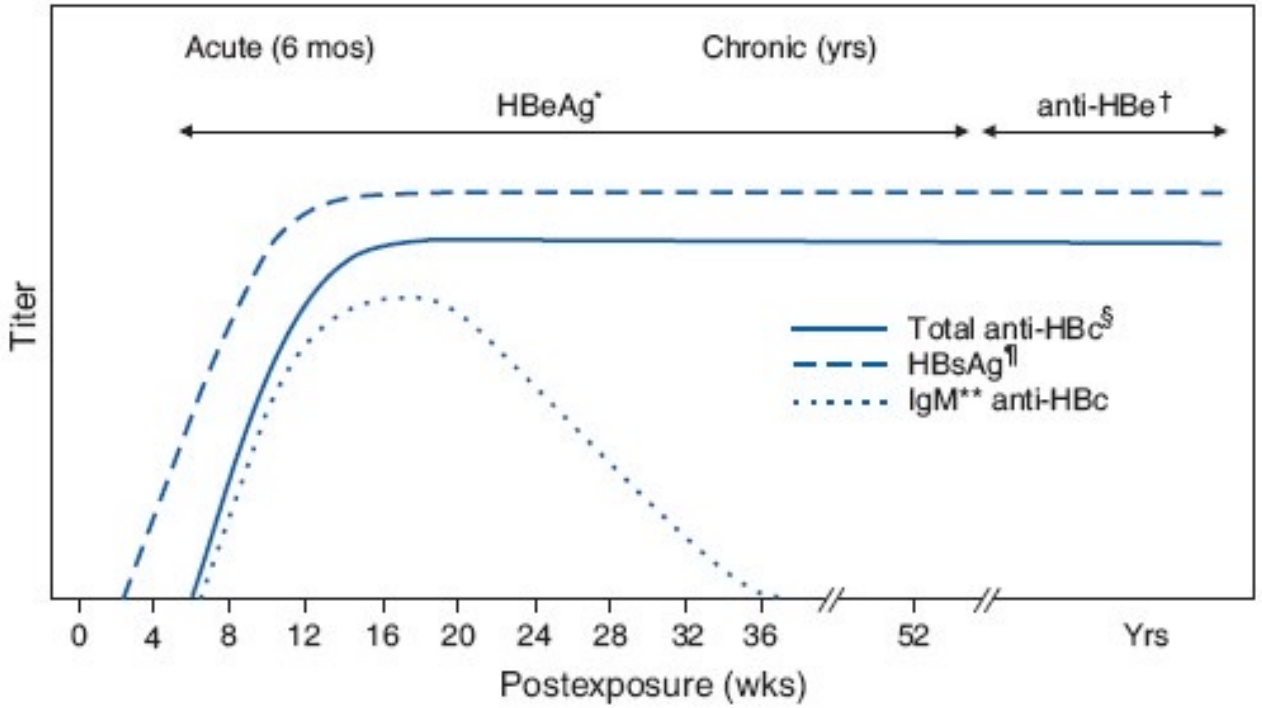



- **HBsAg**: Hepatitis B surface antigen, marker used to screen for HBV infection (acute or chronic) and to estimate chronic HBV prevalence
- **HBeAg**: Hepatitis B e antigen, marker of viral replication and infectivity
- **IgG and IgM anti-HBc**: Total antibody to hepatitis B core antigen, indicates previous or ongoing infection; IgG anti-HBc persists for life
- **Anti-HBs**: Antibody to HBsAg, indicates immunity following either infection or vaccination

# Acute and Chronic Hepatitis B Serology




**Abbreviations:** anti-HBc = antibody to hepatitis B core antigen; anti-HBe = antibody to hepatitis B e antigen; anti-HBs = antibody to hepatitis B surface antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV DNA = hepatitis B virus deoxyribonucleic acid; IgM = immunoglobulin class M.




* Hepatitis B e antigen.
† Antibody to HBeAg.
§ Antibody to hepatitis B core antigen.
¶ Hepatitis B surface antigen.
** Immunoglobulin M.

MMWR, January 12, 2018, Vol 67,(1);1-31
https://www.cdc.gov/mmwr/volumes/67/rr/rr6701a1.htm

MMWR, September 19, 2008, Vol 57(RR08);1-20
https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5708a1.htm

# Transmission

- HBV is highly infectious
- Remains viable on environmental surfaces for at least 7 days
- Routes: percutaneous or mucosal exposure to infectious blood and body fluids

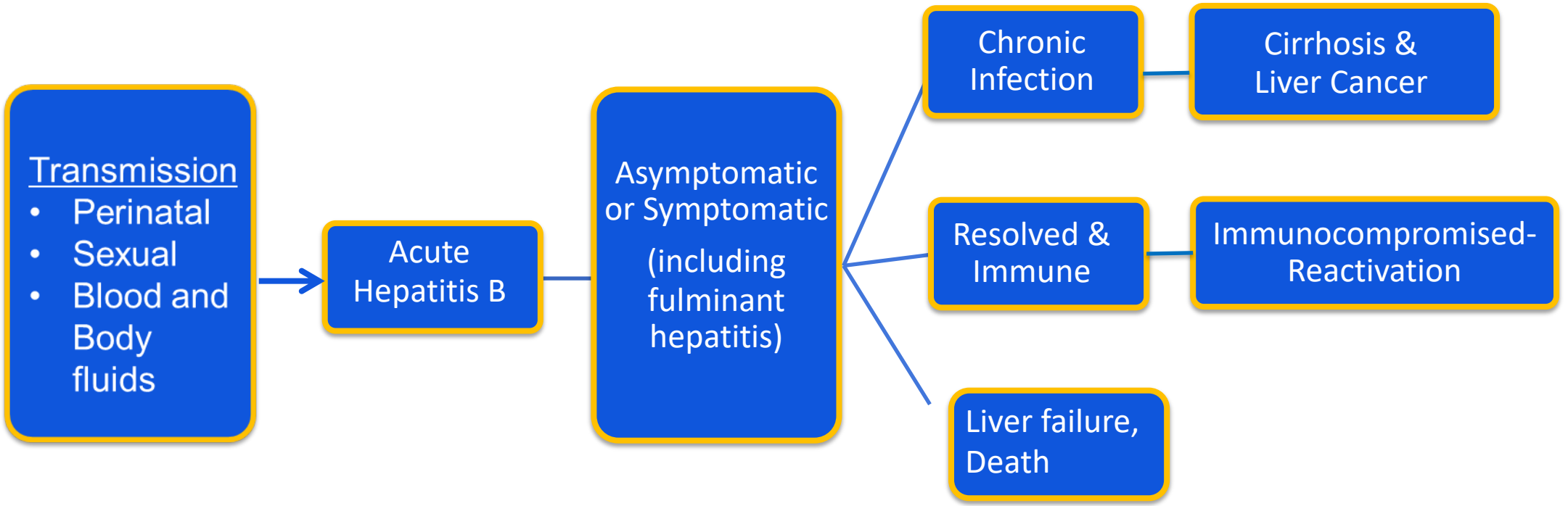
Van Damme P, et al., *Hepatitis B Vaccines*, in *Vaccines*, O. Plotkin SA, WA, and Offit PA, Editor. 2012, Saunders: China. p. 183-204.

# Clinical Features of Symptomatic Acute Hepatitis B

- Nausea, vomiting, anorexia, low grade fever, myalgias, fatigue
  - Similar for other types of acute hepatitis (i.e., A, E)
- Most acute and chronic HBV infections are asymptomatic
- Fulminant hepatitis occurs in ≤1% of acute infections, including perinatal infections*
  - Can result in irreversible liver failure and death

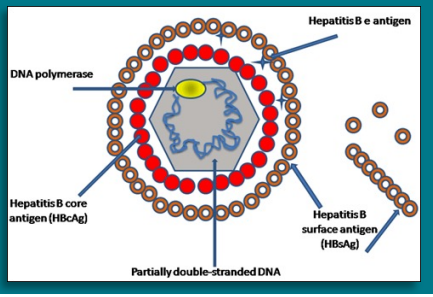
*Chang MH. Hepatitis B virus infection. Semin Fetal Neonatal Med 2007; 12:160–7.

# Natural History of Hepatitis B Virus (HBV) Infection




Chronic Infection
90% of infants
30-50% of children <5 years
5-10% of adults
Up to 50% in some chronic illnesses

# Hepatitis B in the United States

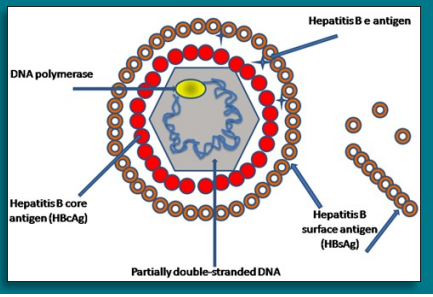



- **20,700 estimated acute hepatitis B virus (HBV) infections each year** (95% CI: 11,800–50,800)[1]

- **> $1 billion spent on hepatitis B-related hospitalizations each year** (not including indirect costs)[2]

[1] https://www.cdc.gov/hepatitis/statistics/2019surveillance/HepB.htm
[2] Corte, et al. J Gastroenterol Hepatol. 2014.

# Hepatitis B in the United States

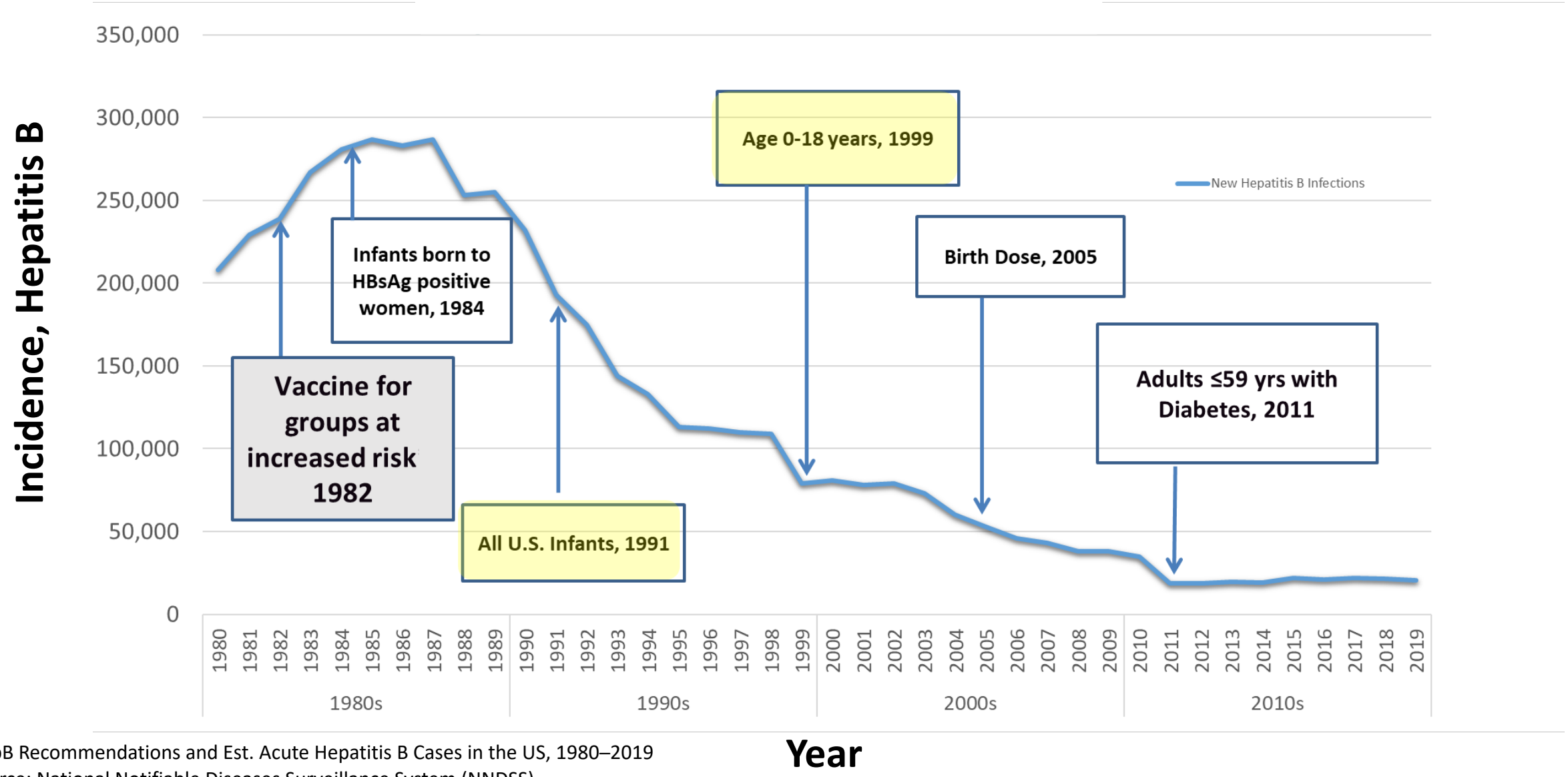



- **1.89 million persons living with chronic HBV** (modeled estimate; range, 1.49–2.40 million)[1]

- **15-25% risk of premature death from cirrhosis or liver cancer among people living with chronic HBV infection**[2]

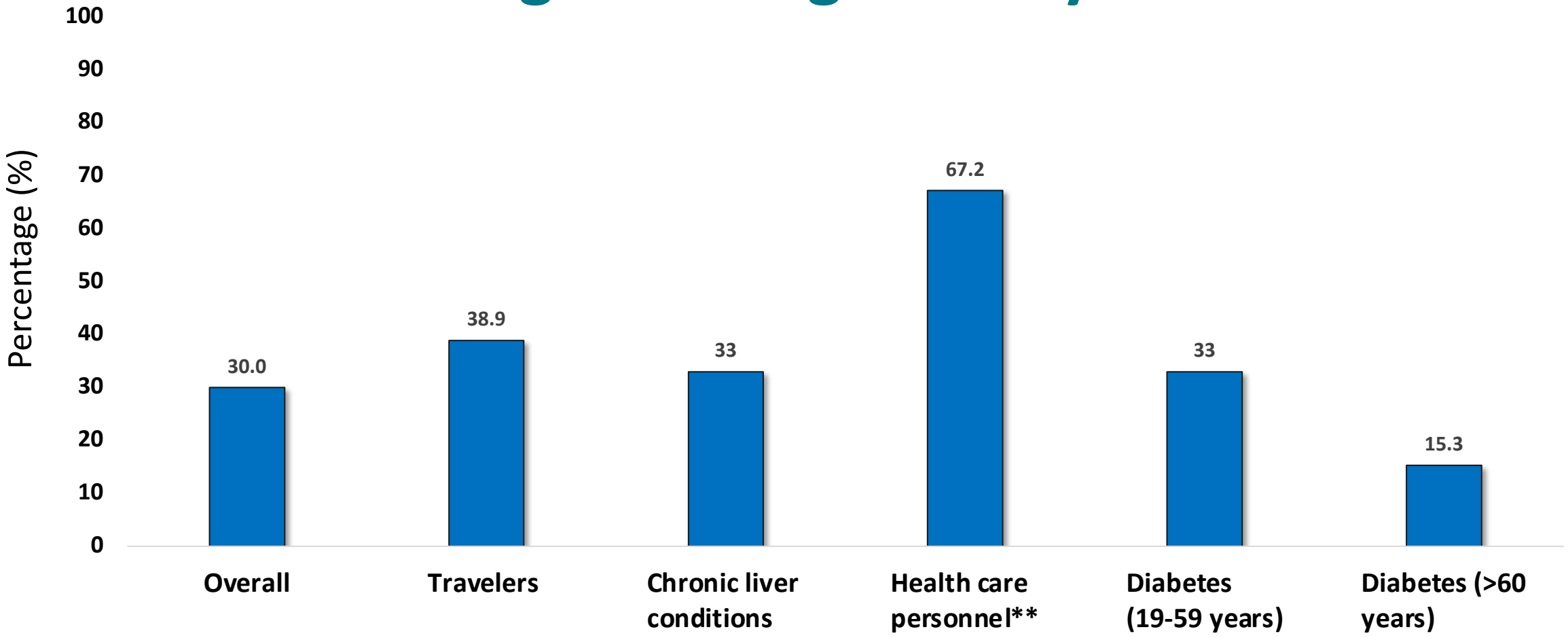
[1] Wong, et al. Am J Med. 2021.
[2] https://www.cdc.gov/std/treatment-guidelines/hbv.htm

# The hepatitis B immunization strategy evolves




HepB Recommendations and Est. Acute Hepatitis B Cases in the US, 1980–2019
Source: National Notifiable Diseases Surveillance System (NNDSS)

# Hepatitis B vaccine coverage (≥3 doses) among adults aged ≥19 years*



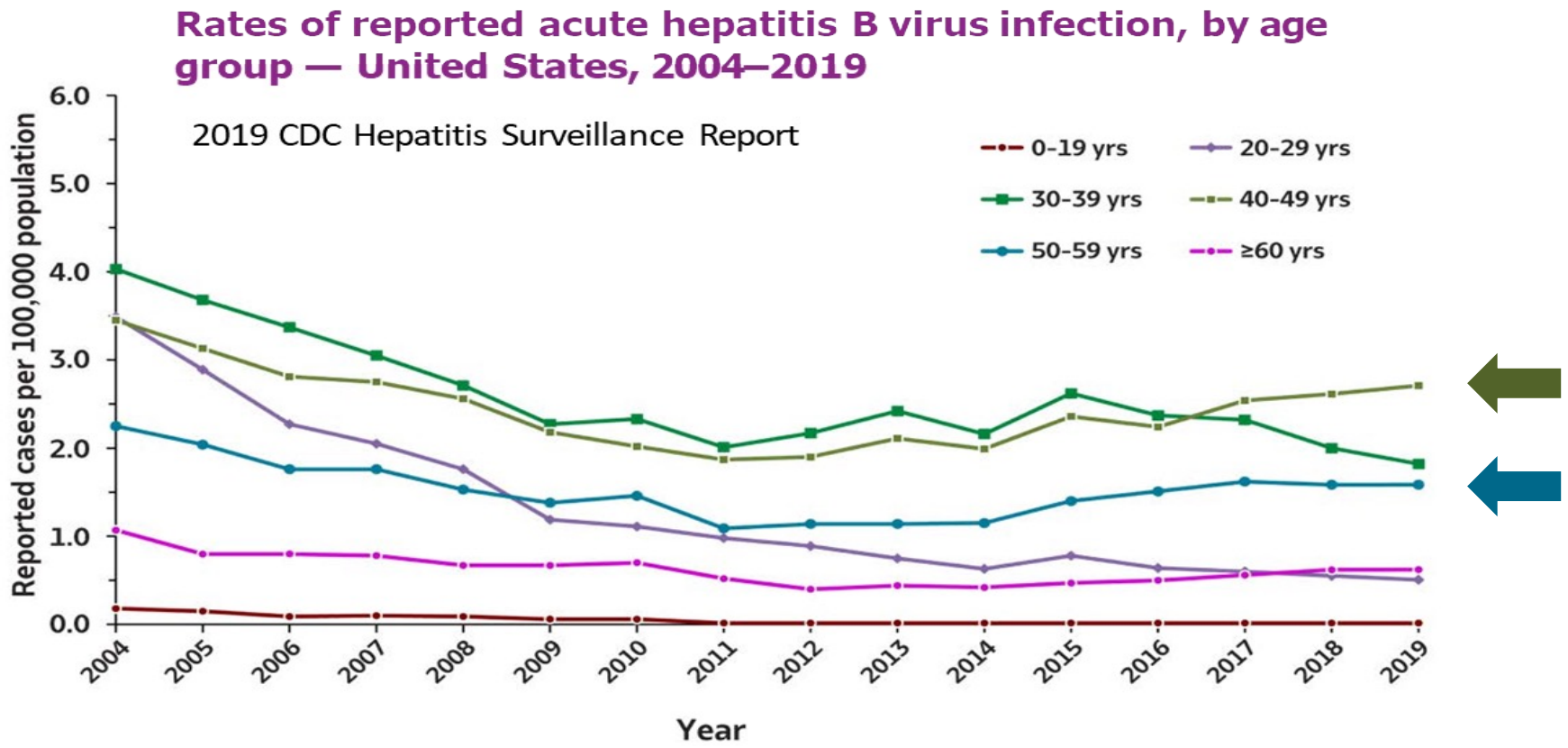

* For adults with diabetes categories: 19-59 years and 60+ years

** Refers to health care personnel (HCP) overall; 75.3% vaccination rate among HCP with direct patient care; 50.9% among HCP without direct patient care

Source: Lu, et al. MMWR, 2018.

# Risk-based hepatitis B immunization among adults: a partial success

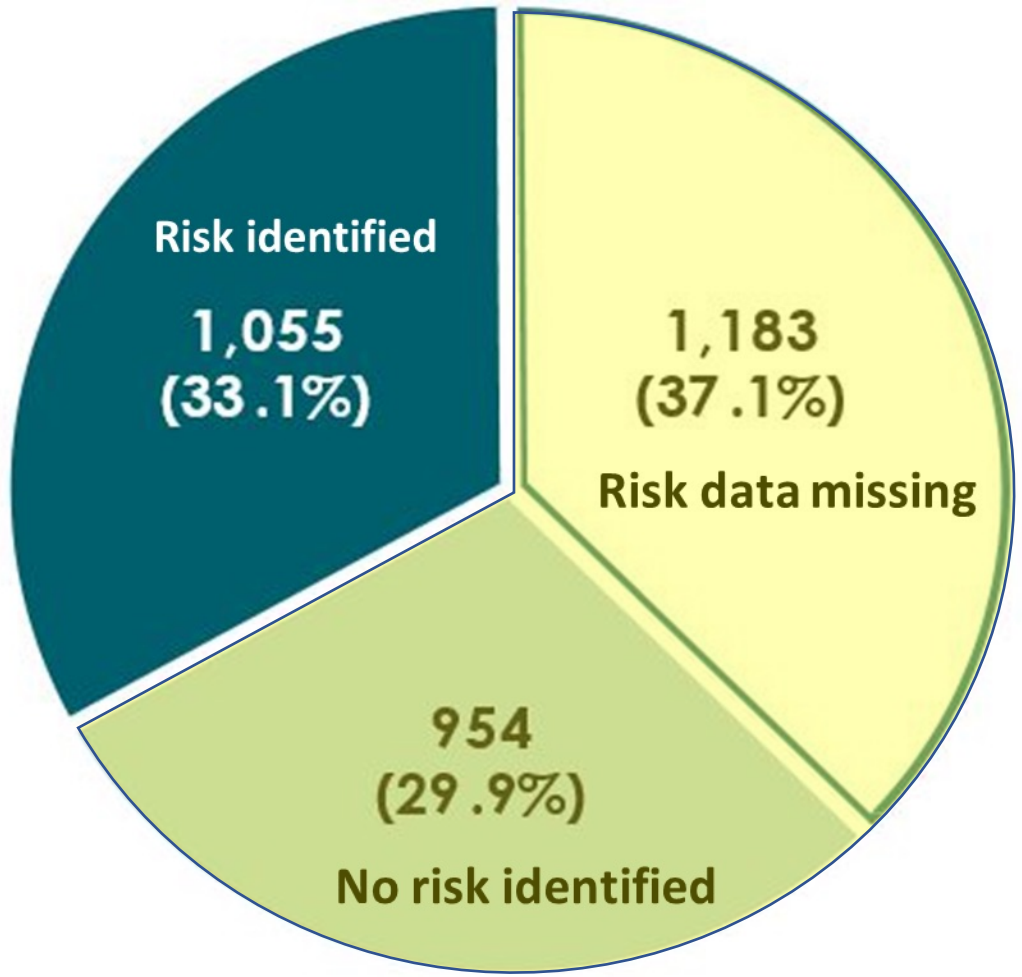
- Initial decreases in new hep B infections plateaued 10 years ago
- Rates are now highest among adults
- Rates have *increased* among adults ≥40 years of age




Source: https://www.cdc.gov/hepatitis/statistics/2019surveillance/pdfs/2019HepSurveillanceRpt.pdf

# Limitations of a risk-based approach

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



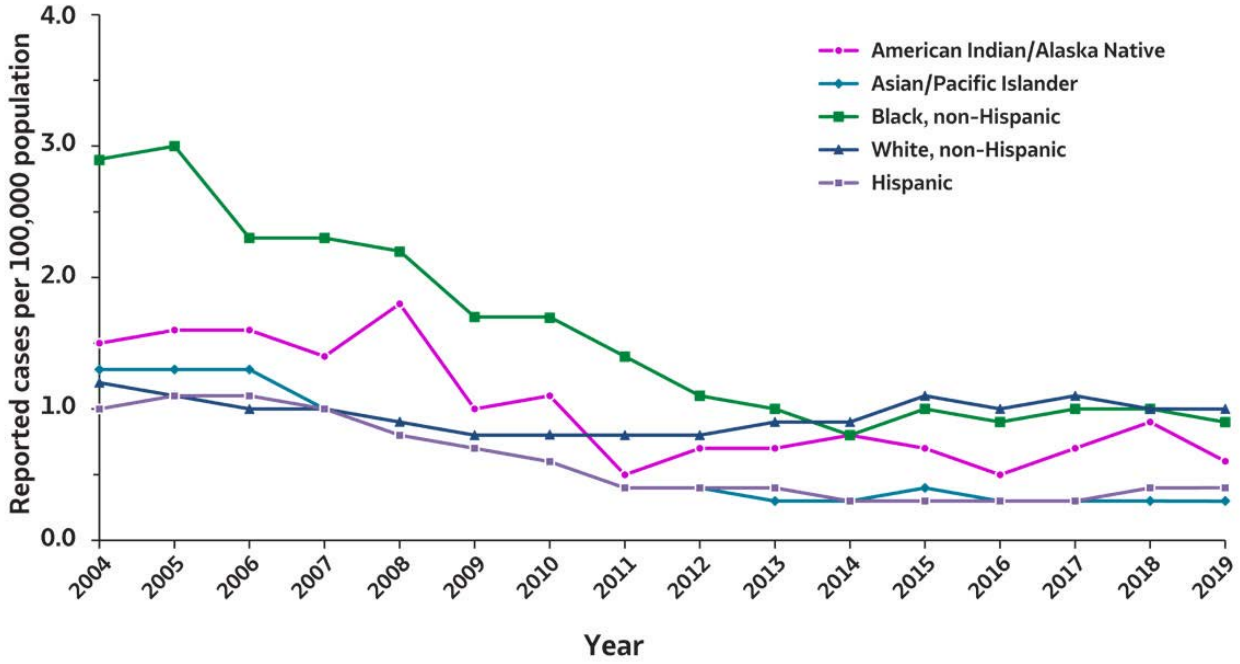

**2/3 of reported cases were either missing risk data or reported no identified risk**

Source: https://www.cdc.gov/hepatitis/statistics/2019surveillance/index.htm

# Health equity: Disparities could be reduced with a universal adult HepB recommendation

- Rates of HBV infection for children and adolescents of all races/ethnicities converged to a lower rate when a universal vaccination strategy was implemented for children ≤18y. [1, 2]
- Current rate among Black American adults is now up to 3x those of Asian/Pacific Islander and Hispanic groups.[1]
- Current rate among American Indian/Alaska Native adults is double that of Asian/Pacific Islander adults.
- Racial/ethnic disparities remain in hepatitis B virus infections

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





1. https://www.cdc.gov/hepatitis/statistics/2019surveillance/HepB.htm
2. Wasley, et al. MMWR. 2008

# Health equity: Disparities could be reduced with a universal adult HepB recommendation

**Risk-based recommendations favor individuals with:**

- Consistent access to preventive health services
- Trust to disclose potentially stigmatizing risk factor(s)
- Awareness of risk (e.g., infected household contact or sex partner)
- Health literacy

# Simplifying a complex hepatitis B vaccination schedule

## Persons recommended to receive hepatitis B vaccination

### Existing Recommendations

*Schillie, et al., 2018*

- **All infants**
- **Unvaccinated children aged <19 years**
- **Persons at risk for infection by sexual exposure**
  - Sex partners of hepatitis B surface antigen (HBsAg)–positive persons
  - Sexually active persons who are not in a long-term, mutually monogamous relationship (e.g., persons with more than one sex partner during the previous 6 months)
  - Persons seeking evaluation or treatment for a sexually transmitted infection
  - Men who have sex with men
- **Persons at risk for infection by percutaneous or mucosal exposure to blood**
  - Current or recent injection-drug users
  - Household contacts of HBsAg-positive persons
  - Residents and staff of facilities for developmentally disabled persons
  - Health care and public safety personnel with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids
  - Hemodialysis patients and predialysis, peritoneal dialysis, and home dialysis patients
  - Persons with diabetes aged 19–59 years; persons with diabetes aged ≥60 years at the discretion of the treating clinician
- **Others**
  - International travelers to countries with high or intermediate levels of endemic hepatitis B virus (HBV) infection (HBsAg prevalence of ≥2%)
  - Persons with hepatitis C virus infection
  - Persons with chronic liver disease (including, but not limited to, persons with cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, and an alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level greater than twice the upper limit of normal)
  - Persons with HIV infection
  - Incarcerated persons
- **All other persons seeking protection from HBV infection**

### New Recommendations

**The ACIP recommends the following groups <u>should</u> receive hepatitis B vaccines:**

- All infants [No change]
- Unvaccinated children aged <19 years [No change]
- Adults 19 through 59 years of age
- Adults 60 years of age and older with risk factors for hepatitis B infection

**The ACIP recommends the following group <u>may</u> receive hepatitis B vaccines:**

- Adults 60 years of age and older without known risk factors for hepatitis B infection

**Approved by unanimous vote**
**November 3, 2021**

# Can universal recommendations increase vaccine uptake among people with risk factors?

| Vaccine<br>Date of relevant recommendation | Risk-based Cohort | Coverage (95% CI) | "Universal" Cohort | Coverage (95% CI) | |
|---|---|---|---|---|---|
| **Flu**<br>**2010** | 25–64y +high risk conditions[1]<br>2009-10 season | 28.6%<br>(±1.1) | 51.0%<br>(± 1.4) | 18–64 years +high risk conditions[1]<br>2020-21 season |
| **Pneumococcal**<br>**2012** | 19–64y at increased risk[2]<br>2018 | 23.3%<br>(22.0-24.6) | 69.0%<br>(67.5-70.4) | ≥65y[2]<br>2018 |
| **HepB-BD**<br>**2005** | Newborns[3]<br>1/2003 – 6/2005 | 50.1%<br>(±1.1) | 79.6%<br>(78-81) | birth year 2018[4] |

[1]CDC FluVaxView

[2] NHIS 2018. NHIS captures "any" pneumococcal vaccination; risk-based recommendation includes groups with different pneumococcal recommendations.

[3] Allred, NJ et al CDC *MMWR* 2008. Birth Dose, to 3 days from birth

[4] CDC ChildVaxView, HepB Birth Dose by Age 0-3 Days

# Is a universal HepB vaccination recommendation an effective use of resources?

- **ICER (incremental cost-effectiveness ratio): $153,000 per QALY gained[1]**
  - ICER decreases as coverage improves in groups at higher risk*
- **Conservative economic model was presented, estimating health improvements from universal adult HepB vaccination**
  - Reduce acute HBV infections by 24%
  - Reduce HBV-related deaths by 23%

[1]Hall E. et al, JID 2022 (accepted).
*Assumptions*: 3-dose vaccine; base case summary input of **~30% coverage** (based on 35.8% protected, with varying age-group specific coverages among people with risk factors; 50% vaccination coverage in general population)
*With 20% additional coverage in high-risk groups, the $/QALY was $135,000, illustrating the benefits of increased access

# Hepatitis B Vaccine

- Introduced in 1982
  - Safe, immunogenic, effective
- Administered as 3- or 4-dose series, starting at birth; 2, 3- or 4-dose series for adults
- Hepatitis B vaccine induces antibody to hepatitis B surface antigen (anti-HBs)
  - Protection against infection is associated with initial antibody concentration ≥10 mIU/mL after a complete vaccine series

Source: MMWR Recomm Rep. 2018 Jan 12;67(1):1-31.

# Hepatitis B Vaccine Protection

- 90-95% protection against hepatitis B infection among infants born to HBsAg-positive mothers[1,2,3]
- >90% protection among healthy adults who complete the 3-dose series[1,2,3]
- Immunocompetent persons remain protected, even if anti-HBs titers decline to < 10 mIU/mL[4]

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

# Immunogenicity: HepB Vaccine Long-term Protection

- Long-term immunogenicity studies are based on data from Alaska among Alaskan Native populations and conducted by the Alaska Native Tribal Health Consortium
  - Studies conducted among recruited participants in a long-term vaccine demonstration project from 15 villages in a remote region of Alaska where HBV was endemic at the time.
- Based on anti-HBs level ≥10 mIU/mL at 30 years and an 88% booster dose response, it is estimated that ≥90% of participants had evidence of protection 30 years later. [1,2]
- Anti-HBs level antibodies ≥10 mIU/mL are estimated to persist for 35 years or longer [2]


1. Bruce et al. *The Journal of Infectious Diseases*, Volume 214, Issue 1, 1 July 2016, Pages 16–22, https://doi.org/10.1093/infdis/jiv748
2. Bruce et al. Protection and Antibody Levels 35 Years after Primary Series with Hepatitis B Vaccine and Response to a Booster Dose. Hepatology. Accepted 3/2022.

# Available Hepatitis B Vaccines

1. Recombivax-HB (monovalent, aluminum adjuvant)
   - Approved for use at any age
2. Engerix-B (monovalent, aluminum adjuvant)
   - Approved for use at any age
3. Pediarix (combination DTaP-IPV-HepB)
   - Approved for doses administered at 6 weeks to 6 years of age
4. Vaxelis (combination DTaP-IPV-Hib-HepB)
   - Approved for doses administered at 6 weeks through 4 years of age
5. Twinrix (combination HepA-HepB)
   - Approved for use in adults ≥ 18 years
6. Heplisav-B (monovalent, 1018 adjuvant) [2018]
   - Approved for use in adults ≥ 18 years, 2-dose series over 1 month
7. PreHevbrio (monovalent, aluminium adjuvant) [2022]
   - Approved for use in adults ≥ 18 years, 3-dose series over 6 months

# ACIP Policy Statement for PreHevbrio, added February 2022

| 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. |

# Note on Heplisav-B, PreHevbrio

## In Dialysis or Pregnancy

- Safety and effectiveness of Heplisav-B and PreHevbrio have not been established in adults on hemodialysis

- Data on Heplisav-B and PreHevbrio are currently insufficient to inform vaccine-associated risks in pregnancy

- Data are not available to assess the effects of Heplisav-B and PreHevbrio on the breastfed infant or on milk production/excretion

FDA package inserts: Heplisav-B (2017) and PreHevbrio (2021)

# Hepatitis B (HepB) Vaccine Safety

- HepB vaccines are safe with rare side effects/adverse reactions[1]
- Most frequent side effects are pain at injection site and fever[1]
- Evidence supports association between HepB vaccine and anaphylaxis in yeast-sensitive persons[2,3]
  - Estimate incidence 1.1 per million doses administered (95% CI 0.1-3.9)
  - Vaccination is contraindicated for these persons

[1]Lewis et al. Pediatr Infect Dis J. 2001
[2]IOM. 2011
[3]Bohlke et al. Pediatr. 2003

# Adult hepatitis B vaccines

| Adult hepatitis B vaccine[1] | Derivation | Adjuvant | Dose of HBs Antigens | Schedule |
|---|---|---|---|---|
| PreHevbrio[2] | mammalian (Chinese hamster ovary) cell | alum | 10µg | 3 doses at 0, 1, 6 months |
| Engerix-B | yeast | alum | 20µg | 3 doses at 0, 1, 6 months |
| Recombivax HB | yeast | alum | 10µg | 3 doses at 0, 1, 6 months |
| Heplisav-B | yeast | CpG 1018 | 20µg | 2 doses at 0, 1 months |

**Twinrix** (combination HepA-HepB) not shown.

[1] See ACIP Recommended Immunization Schedule for Adults Aged 19 Years or Older — United States, 2022 for dosing details (http://dx.doi.org/10.15585/mmwr.mm7107a1).
[2] ACIP approval February 2022

Summary

# HHS and NASEM[1] have called for viral hepatitis elimination

- **Evidence supports where universal recommendations are preferred over risk-based vaccination approaches**

- **More vaccine tools available than when risk-based policy was first recommended**
  - Two 3-dose monovalent vaccines are available; safe, effective with long-term immunogenicity (>35 y)
  - One 2-dose vaccine is available; safe and effective
  - One 3-dose, 3-antigen vaccine was recently approved

- **Universal hepatitis B vaccination recommendation among adults will provide best chance of achieving HBV elimination goals**

[1] National Academies of Science, Engineering, and Medicine. https://www.nationalacademies.org/our-work/a-national-strategy-for-the-elimination-of-hepatitis-b-and-c

# ACIP Hepatitis Work Group

**ACIP Voting Members**

Kevin Ault (Chair)

Sybil Cineas

**Liaison Representatives**

Elizabeth Barnett (AAP)

Marci Drees (SHEA)

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)

Chinedu Okeke (HHS)

Jessica Deerin (HHS)

**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 Subject Matter Experts**

Erin Conners

Mona Doshani

Brian Edlin

Ruth Gallego

Megan Hofmeister

Neil Murthy

Lakshmi Panagiotakopoulos

Noele Nelson

Priti Patel

Phil Spradling

Mark Weng

Carolyn Wester

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# Thank you

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