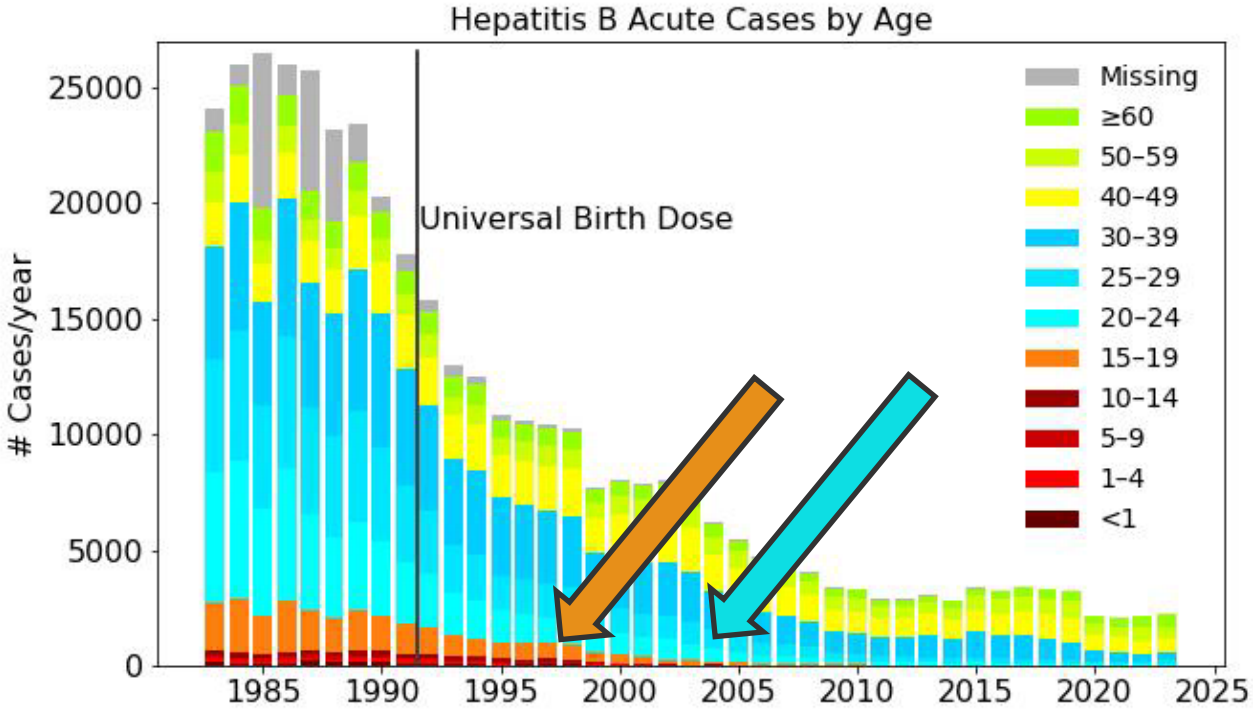
Burden of disease

- Morbidity trends
  - What has the universal birth dose accomplished compared to more targeted measures?
- Vertical (perinatal mother-to-child) transmission
  - Targeted vaccination of at-risk infants vs. the universal birth dose?
- Horizontal transmission in childhood
  - What evidence exists and has the risk to most American children been overstated?

Surveillance data: Acute hepatitis B cases are the longest and most consistently reported metric of morbidity



MMWR 1991,
"… selective vaccination of persons with identified risk factors … has not lowered the incidence hepatitis B."

Data from the National Notifiable Diseases Surveillance System

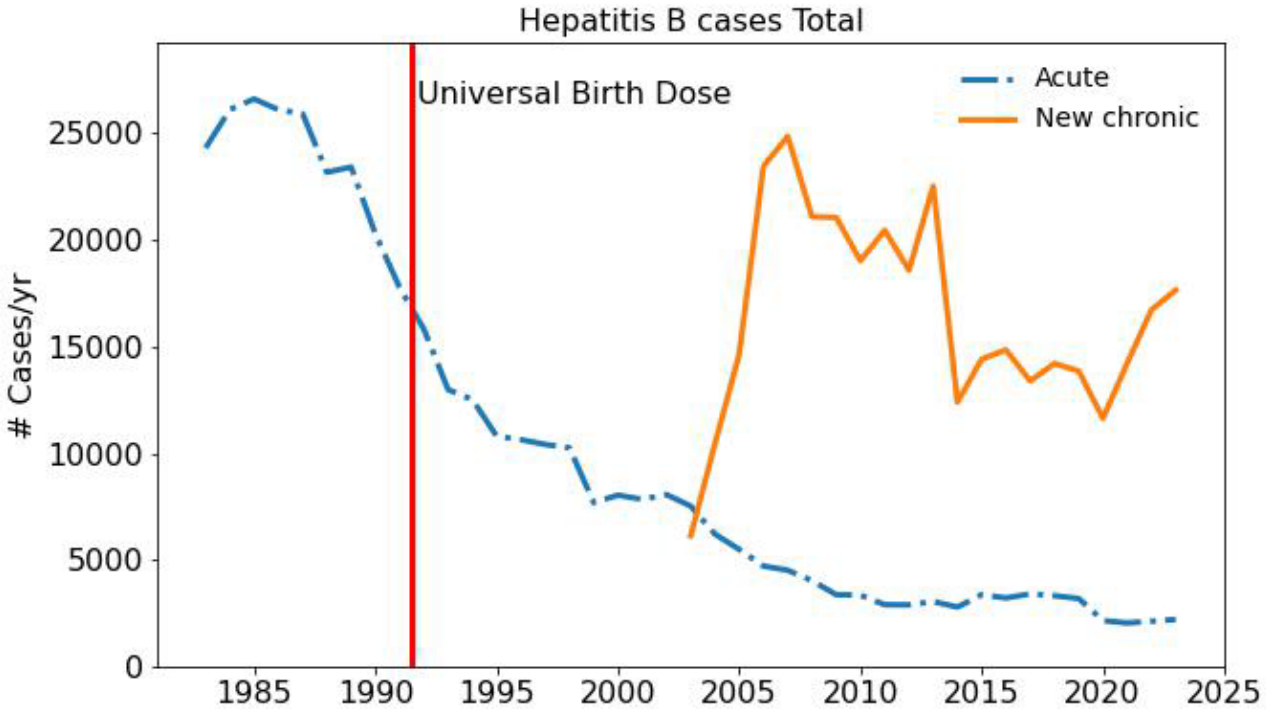
Sources of decline in acute hepatitis B cases

- Increased blood screening for HBsAg
- Sharp declines in post transfusion hepatitis (PTH)
- Cleaner practices in dialysis
- Widespread adoption of safer sexual practices
- Needle exchange
- Screening and case management for HBsAg+ mothers

Universal birth dose contribution to acute case decline is likely very small.

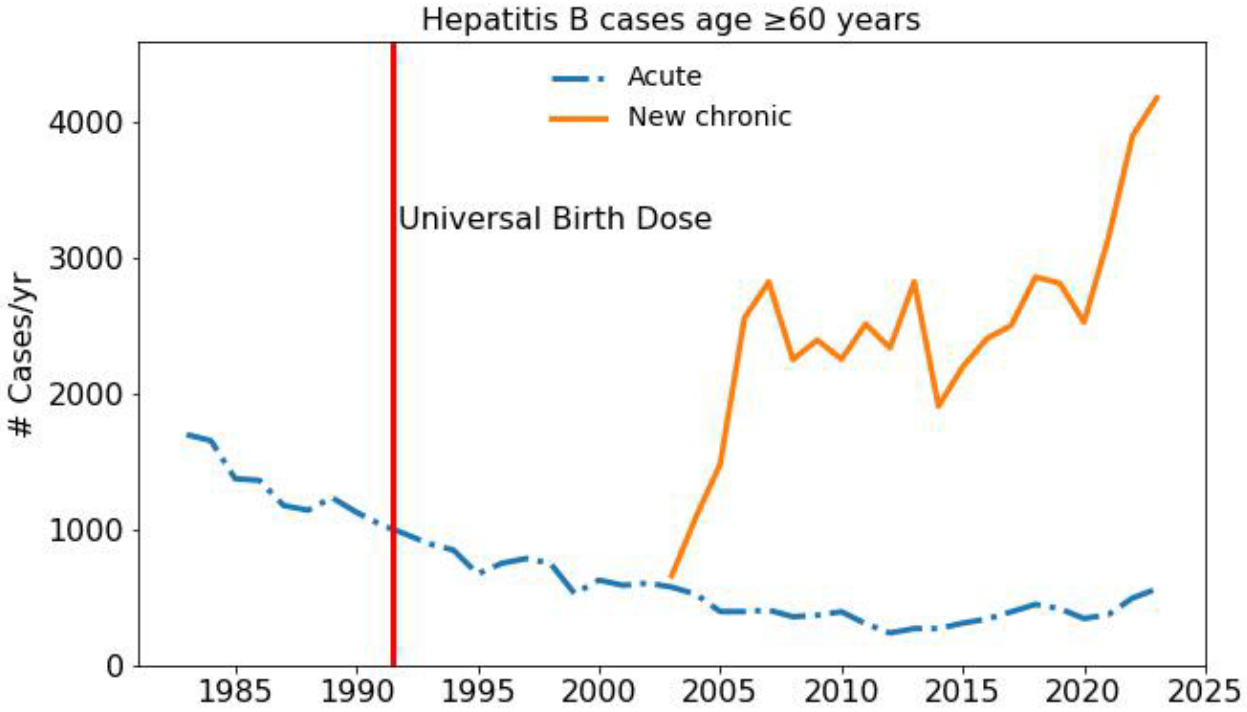
Chronic case data raise new questions

NNDSS began collecting new chronic case data in 2003



NNDSS = National Notifiable Diseases Surveillance System

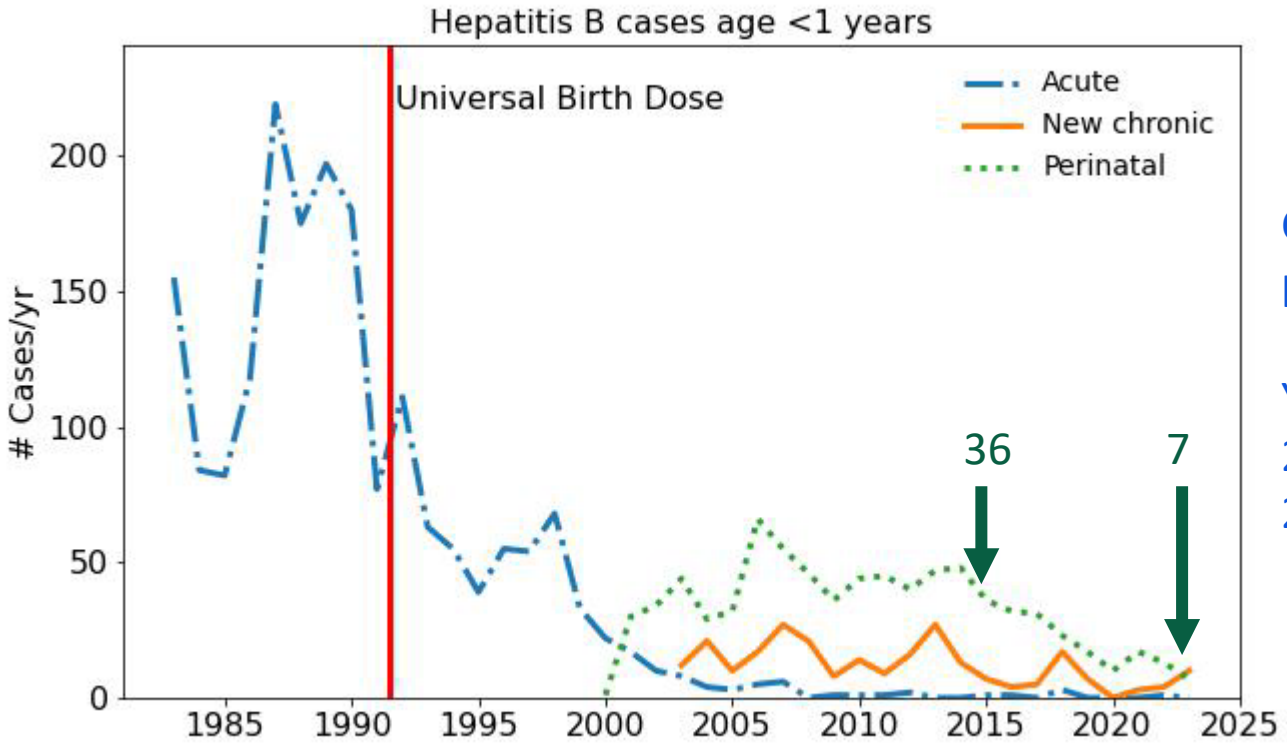
Increasing new chronic cases of hepatitis B in older adults after 2020



Upticks after 2020 also seen in adults 30-39, 40-49, and 50-59 years old.

Data from National Notifiable Diseases Surveillance System

Infant morbidity



CDC model of perinatal infections:

Year	# of Cases	
2015:	952	(Ko et al. 2016)
2023:	601	(CDC staff)

Data from the National Notifiable Diseases Surveillance System

Summary of hepatitis B morbidity trends

- **Acute cases have declined sharply from peak in 1985 for multiple reasons.**
- **New chronic cases have been increasing among older adults after 2020.**
- **Perinatal cases are down to 36 and 7 in 2015 and 2023, respectively, but CDC model predicts many more cases.**

Modeling perinatal infections

Estimate begins by tabulating how many mothers are HBsAg+, i.e., chronic carriers of hepatitis B virus

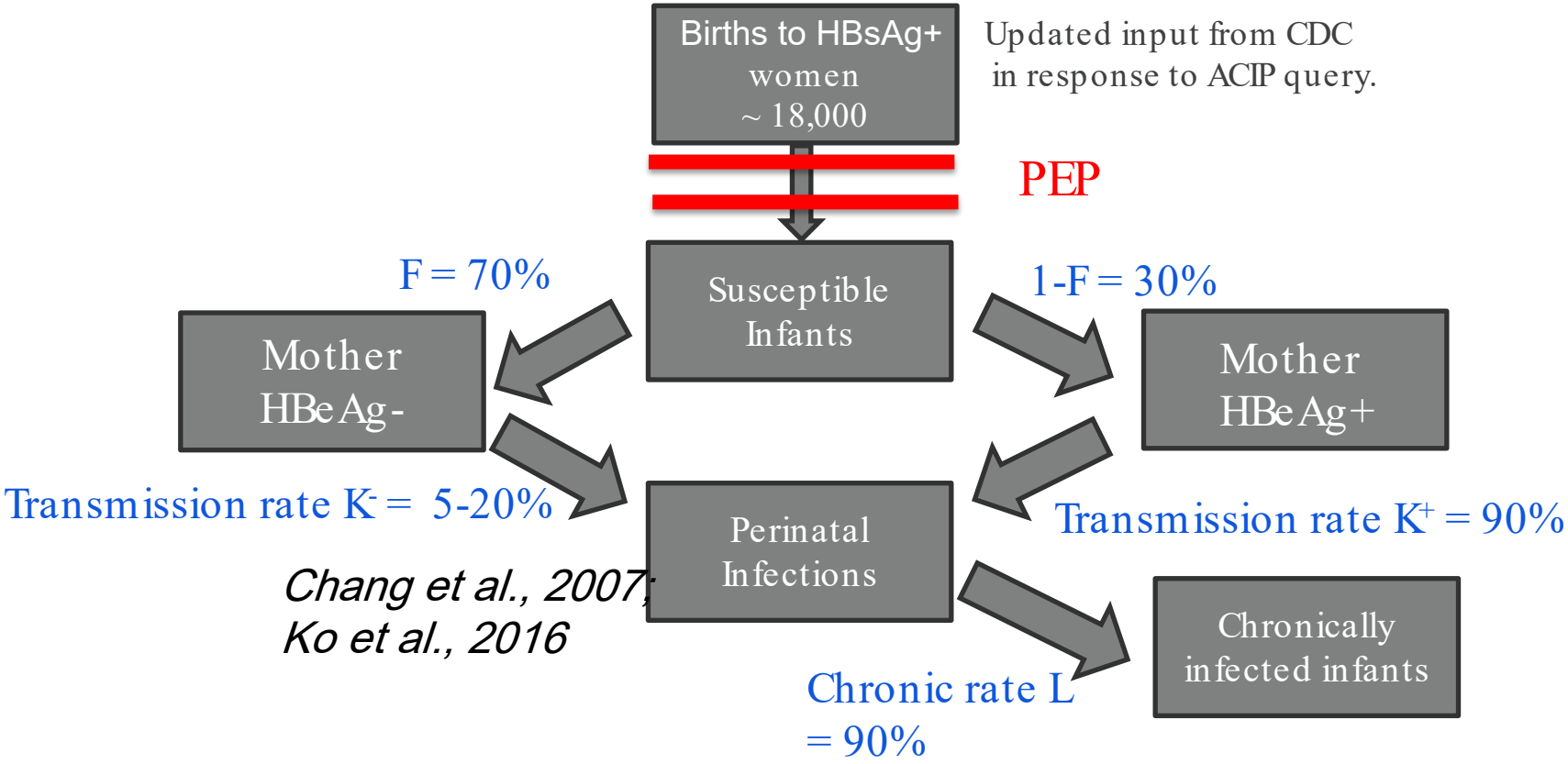
Majority of HBsAg+ mothers in US are foreign-born

Koneru et al., 2019, Table 2 excerpts; estimated for 2015

Maternal country of birth	Total Births	HBsAg+ prevalence (%)	Estimated births to HBsAg+ women
Total	3,978,500		**20,678** (15,625-30,640)
US-born total	3,070,700	**0.17** (0.07-0.39)	**8,296** (4,031-17,100)
Non-US-born			
Total	857,105		**11,981** (11,395-12,762)
Africa	64,228	**3.42** (3.27-3.96)	**2,197** (2,100-2,543)
Asia			
East Asia	66,384	**8.73** (8.52-8.93)	**5,795** (5656-5928)
Southeast Asia	62,044	**3.92** (3.76-4.08)	**2,432** (2,333-2531)

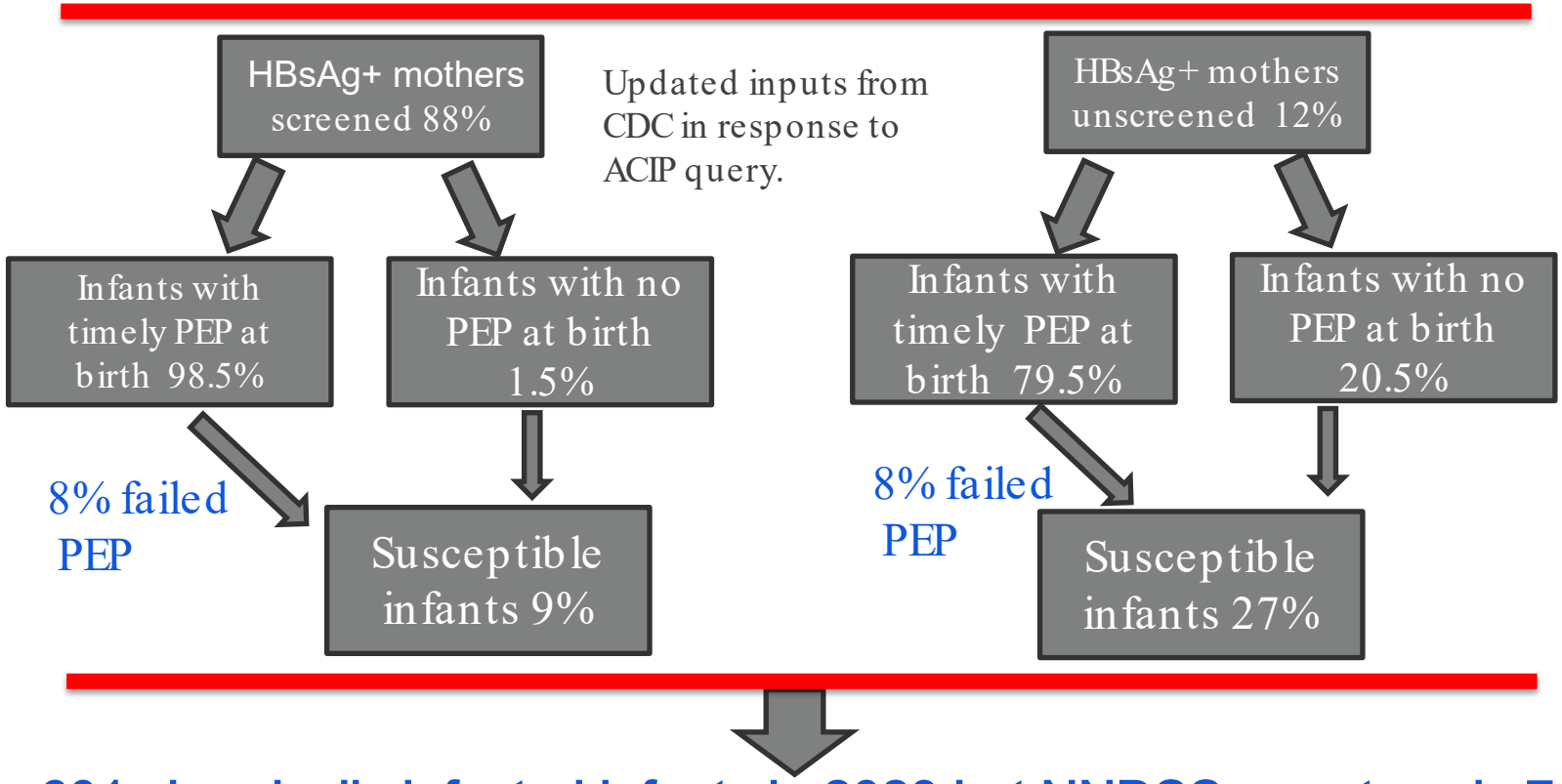
Modeling perinatal cases

based on Ko et al., 2016 model



PEP (post exposure prophylaxis)

PEP includes hepatitis B vaccine and HBIG at birth



601 chronically infected infants in 2023 but NNDSS reports only 7 !

Perinatal (mother-to-child) transmission summary

- Risk is isolated to ~0.5% of pregnancies, mainly immigrants from high endemicity countries.
  - Add hep B to immigrant medical examination.

- Improve screening measures in prenatal care and delivery. PEP is effective in preventing transmission!

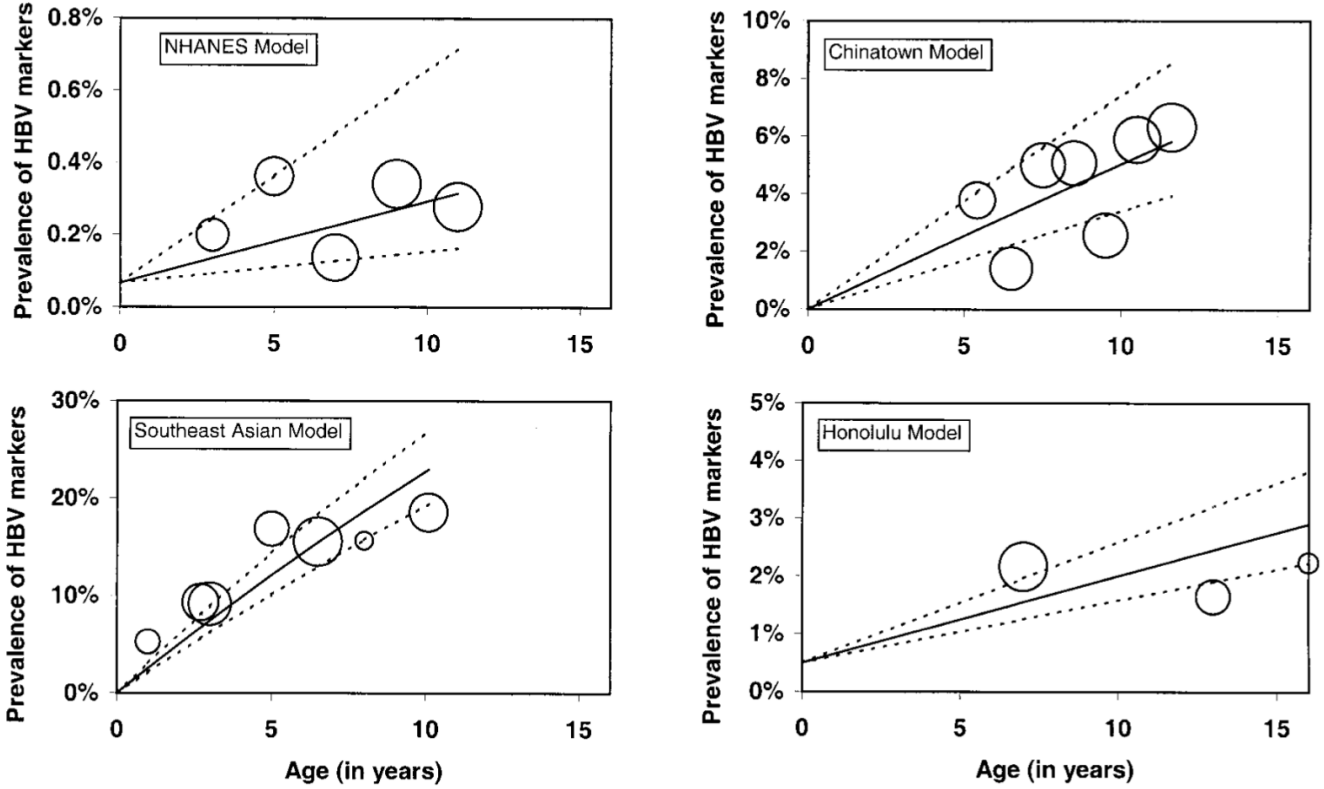
- CDC's Ko et al. model may overestimate perinatal cases.
  - U.S. infants are not all equally at risk- many mothers intentionally decline birth dose.
  - Other inputs (screening rate, PEP failure rate) may be too pessimistic.

Modeling horizontal transmission in childhood

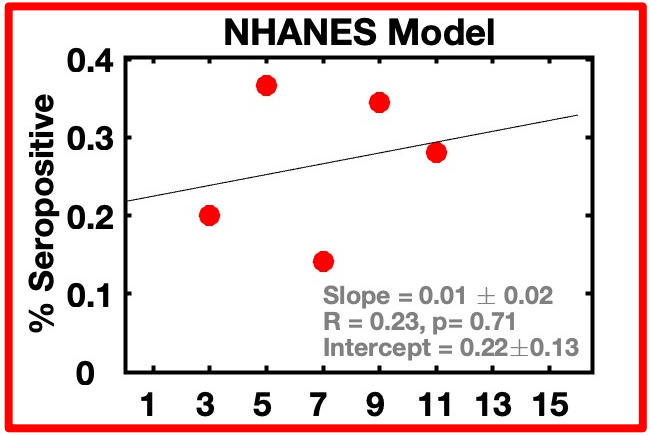
- Little published evidence documenting horizontal transmission.
- A single modeling study, Armstrong et al. [2001], raised concerns that **all young children in the U.S. are at significant risk for horizontal transmission** of hepatitis B**.**
- The model estimated ~ **16,000 cases/yr in children age 0-9 years old** in the pre-vaccine era due to horizontal transmission, half in Asian immigrants, half in the general U.S. population.

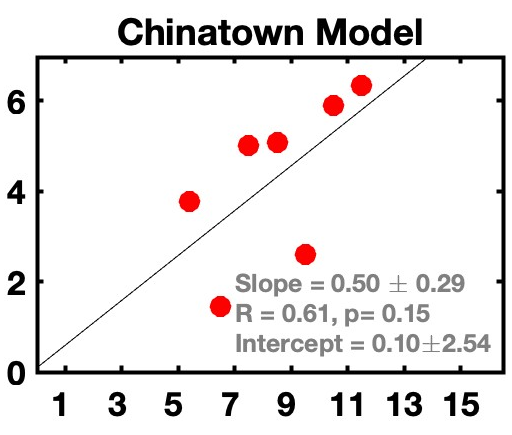
Armstrong G, Mast E, Wojczynski M, Margolis H. 2001. Childhood Hepatitis B Virus Infections in the United States Before Hepatitis B Immunization, Pediatrics 108(5), 1123-1128.

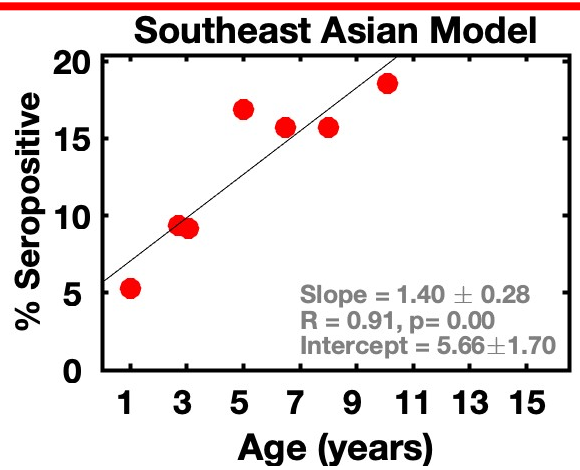
Armstrong 2001 modeled HepB horizontal transmission based on seropositivity v. age in NHANES and among Asian immigrants

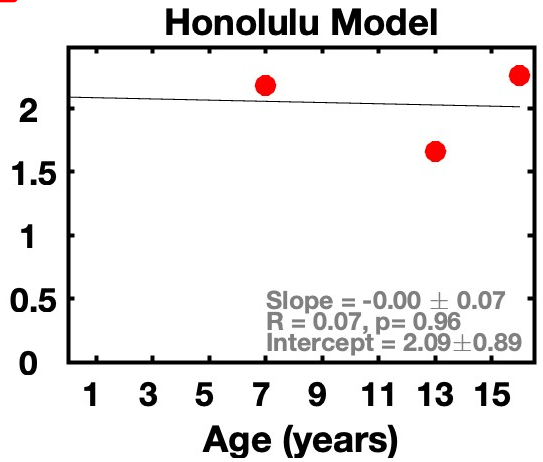


Independent calculation of Armstrong linear fits









Without the assumed perinatal infection (P_o), seropositivity is significantly correlated with age only for the Southeast Asian model.

NHANES seropositivity v. age correlation is statistically insignificant with a natural intercept of 0.22% (perinatal).

Comparison of 2 SE Asian Groups

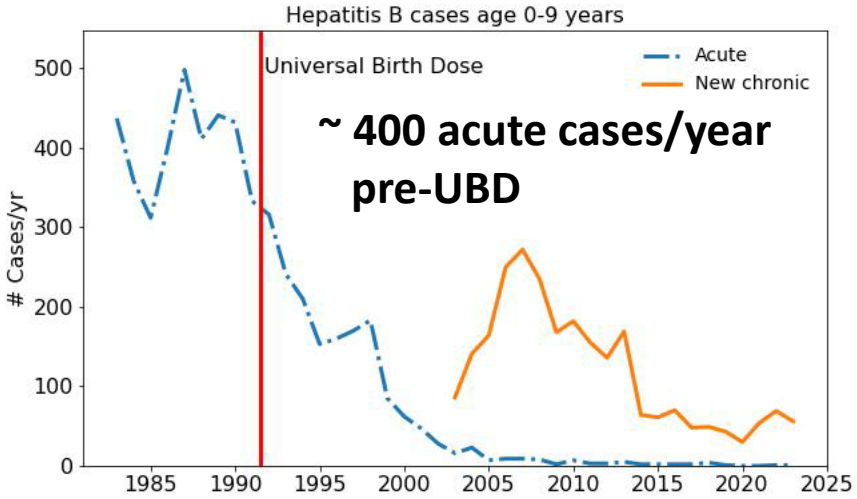
Characteristic	Louisiana (Vietnamese)	Wisconsin (Hmong)
All, families, US-born children	N =1403, 227, 679	N=1183, 161 ,429
HBV markers used, past or present infection	Anti-HBc	Anti-HBc or HBsAg+
HBV markers used, chronic	HBsAg+, anti-HBsIgM-	HBsAg+
US born, % any HBV (% chronic)	16%, (4%)	14% (6%)
Asian-born, % any HBV (% chronic)	59% (11%)* (inferred)	72% (19%)**
% of children with HBsAg+ moms	9% (60/656)	16% (69/429)
Reference	Mahoney et al., 1995	Hurie et al., 1992

* Nguyen and Trevison. 2020. Vietnam a country in transition: BMJ doi:10.1.1136/bmjnph-2020-000069 **does not list hepatitis B among the leading causes of death in Vietnam**.

** In the Asian-born Hmong, 86%-97% of those aged 15 to >40 years had HBV blood markers.

Horizontal transmission in childhood?

- **Horizontal transmission is rare among most U.S. children …**
- **Although it can occur in some high-risk immigrant families**
- **Armstrong et al.'s 16,000 cases/year are not supported by NNDSS data**



NNDSS = National Notifiable Diseases Surveillance System

Horizontal transmission in childhood – final note

The Informed Consent Action Network (ICAN) asked the CDC for **“documentation sufficient to reflect any case(s) of transmission of Hepatitis B in an elementary, middle, or high school setting.”**

The CDC responded, **“A search of our records failed to reveal any documents pertaining to your request.”**

https://icandecide.org/article/cdc-concedes-it-lacks-any-proof-of-hepatitis-b-being-transmitted-in-a-school-setting/

Summary of burden of disease

Mixed trends in hepatitis B morbidity 34 years after the Universal Birth Dose

- Acute cases have declined sharply for multiple reasons.
- New chronic cases are increasing since 2020 in adults over 30.
- Reported perinatal cases are in the single to low double digits thanks to PEP.

Models yield larger estimates than surveillance data - cross checks useful

- Ko et al. model may overstate perinatal chronic cases.
- Horizontal transmission among young children is rare and was strongly overstated by the Armstrong et al. model.

Efficacy and Waning Immunity

Many studies show reduced antibody levels over time following hepatitis B vaccination, especially when vaccination begins in infancy or early childhood.

Native Alaskans vaccinated for hepatitis B between ages 5-19 years had highest titers 30 years later

Age (years) at the time of:		Anti-HBs (mIU/ml) Before booster dose		Anti-HBs (mIU/ml) After booster dose*	
Booster	Primary series	GMC	% with ≥ 10 ($N_{>10}$/N_{total})	GMC	% with ≥ 10 ($N_{>10}$/N_{total})
< 40	< 5	6.8	32% (19/59)	98.2	83% (25/30)
35 to 39	5 to 9	24.9	61% (30/49)	134.2	94% (16/17)
40 to 49	10 to 19	22.8	64% (58/90)	275.7	89% (17/19)
≥ 50	≥ 20	8.5	40% (18/45)	179.4	89% (17/19)

*Booster dose was given to 85 people with titers < 10 mIU/ml as well as an additional N=36 people who were not boosted in the 22-year follow-up.

Bruce et al. 2016. Protection and antibody levels after Hepatitis B vaccine: Results of a 30-year follow-up study and response to a booster dose, JID 214: 16-22. (Tables 1,3)

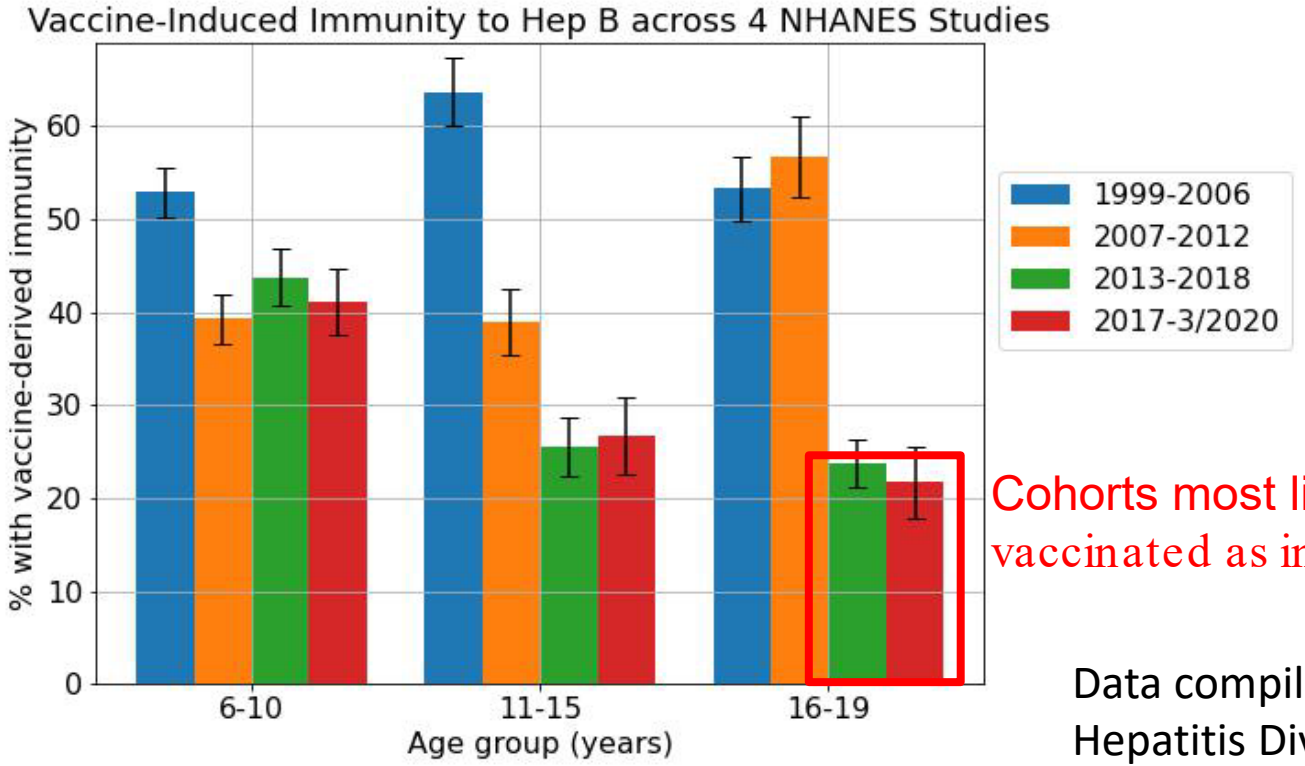
By age 16-19 years, most US children vaccinated as infants had low antibodies, but most responded well to a booster dose

Table 2 Levels of Seroprotection (anti-HBs Titer ≥ 10 IU/mL) by Group

	Group 1, %	Group 2, %	Total, %	P value
	1st dose ≤7 days	1st dose ≥ 4 weeks		
Baseline seroprotection	16.7 %	33.9 %	24.1 %	< 0.0001
Postchallenge dose seroprotection	90.4 %	93.9 %	91.9 %	0.2

Middleman et al. 2014. Duration of protection after infant Hepatitis B vaccination series, Pediatrics 133(6).

Waning immunity also seen among teenagers vaccinated as infants in NHANES data



Cohorts most likely vaccinated as infants

Data compiled by CDC Hepatitis Division

Waning immunity summary and concluding thoughts

- **Anti-HBs titers wane the most rapidly in children who begin their primary series as infants, especially as newborns.**

- **While most vaccinees respond well to a booster dose, some of those vaccinated as infants may lack protection when they enter their years of highest risk for acquiring hepatitis B.**

References

Armstrong G, Mast E, Wojczynski M, Margolis H. 2001. Childhood Hepatitis B Virus Infections in the United States Before Hepatitis B Immunization, Pediatrics 108(5), 1123-1128

Bruce et al. 2016. Protection and antibody levels after Hepatitis B vaccine: Results of a 30-year follow-up study and response to a booster dose, The Journal of Infections Diseases, 214(1 July) 16-22

Chang, M-H. 2007. Hepatitis B virus infection. Seminars in Fetal & Neonatal Medicine (2007) 12, 160e167.

Hurie MB, Mast EE, Davis JP. Horizontal transmission of hepatitis B virus infection to United States-born children of Hmong refugees. *Pediatrics*. 1992;89:269–273

Klevens RM, Liu S, Roberts H, Jiles RB, Holmberg SD. 2014. Estimating acute viral hepatitis infections from nationally reported cases. Am J Public Health, 104(3): 482-487

Koneru, A. 2019. Estimating Annual Births to Hepatitis B Surface Antigen–Positive Women in the United States by Using Data on Maternal Country of Birth Public Health Reports 134(3)

Ko SC et al. Estimated Annual Perinatal Hepatitis B Virus Infections in the United States, 2000-2009. J Pediatric Infect Dis Soc. 2016 Jun;5(2):114-21

Mahoney FJ, Lawrence M, Scott C, et al. Continuing risk for hepatitis B virus transmission among Southeast Asian infants in Louisiana. *Pediatrics*. 1995;96:1113–1116

McQuillan GM, Townsend TR, Fields HA, et al. Seroepidemiology of hepatitis B virus infection in the United States. 1976 to 1980. *Am J Med.* 1989:87:5S–10S

McQuillan GM, Coleman PJ, Kruszon-Moran D, et al. Prevalence of hepatitis B virus infection in the United States: the National Health and Nutrition Examination Surveys, 1976 through 1994. *Am J Public Health.*1999; 89:14–18

Middleman et al. 2014. Duration of protection after infant Hepatitis B vaccination series, Pediatrics 133(6)

MMWR 1991. CDC/ACIP, Hepatitis B Virus: A Comprehensive Strategy for Eliminating Transmission in the United States Through Universal Childhood Vaccination: Recommendations of the Immunization Practices Advisory Committee (ACIP), MMWR, November 22, 1991 / 40(RR-13);1-19, https://www.cdc.gov/mmwr/preview/mmwrhtml/00033405.htm

Ott et al. The risk of perinatal hepatitis B virus transmission: hepatitis B e antigen (HBeAg) prevalence estimates for all world regions BMC Infectious Diseases 2012, 12:131 http://www.biomedcentral.com/1471-2334/12/131

Smith E.A. et al., 2012. The national Perinatal Hepatitis B Prevention Program 1994-2008. Pediatrics 129(4). doi:10.1542/peds.2011-2866

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