Safety Review of Hepatitis B Birth Dose Vaccination

CDC Advisory Committee on Immunization Practices meeting

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Safety of the hepatitis B vaccine

- Clinical trials
- Post-licensure safety studies
- IOM and VICP on vaccine-related injuries
- Animal models

Overview of Hepatitis B Vaccine (HBV) Safety:

Safety evidence is limited and often concerning

- There were no randomized placebo-controlled trials in infants; cited trials used short follow up periods of 7 days or less and discounted safety concerns
- CDC/ISO's "rapid systematic review" of post-licensure safety studies reveals concerns but evidence of chronic, late-onset effects was not presented
- IOM Safety of Vaccine reports have highlighted the absence of evidence to assess potential adverse effects in over 30 endpoints
- VICP has processed large numbers of HBV related claims, compensating many
- Mechanisms of injury, especially immune activation, reported in animal models

Clinical trials on infants/children cited for birth dose of Recombivax HB or Engerix-B in 1991 ACIP recommendation

Trial publication	Vaccine	Control group	Sample size and composition	Safety follow up period	Safety findings
Zajac et al, 1986	RecombivaxHB	None	79 children, ages 1-12 years	5 days after each dose	18% "systemic" complaints: "fatigue, weakness, diarrhoea or irritability."
Stevens et al, 1987	Recombivax HB	Plasma vaccine	122 infants 39 plasma/83 recombinant Asian-American HBsAg+/HBeAg+ mothers	7 days after each dose	1 death in recombinant group due to "inoperable congenital malformation"
Andre et al, 1989	Engerix-B	None	1187 neonates	Up to 3 days after each dose	96% "had no reaction to the vaccine." 2.5% mild/moderate fever

“Systemic” clinical complaints in children reported in Zajac et al (1986)

Table II *Percentage of children with a clinical complaint during a 5-day period following vaccination*

Type of complaint	First injection (%) ($n = 79$)	Second injection (%) ($n = 75$)	Third injection (%) ($n = 75$)
Injection site*	3	3	1
Systemic†	18	15	8

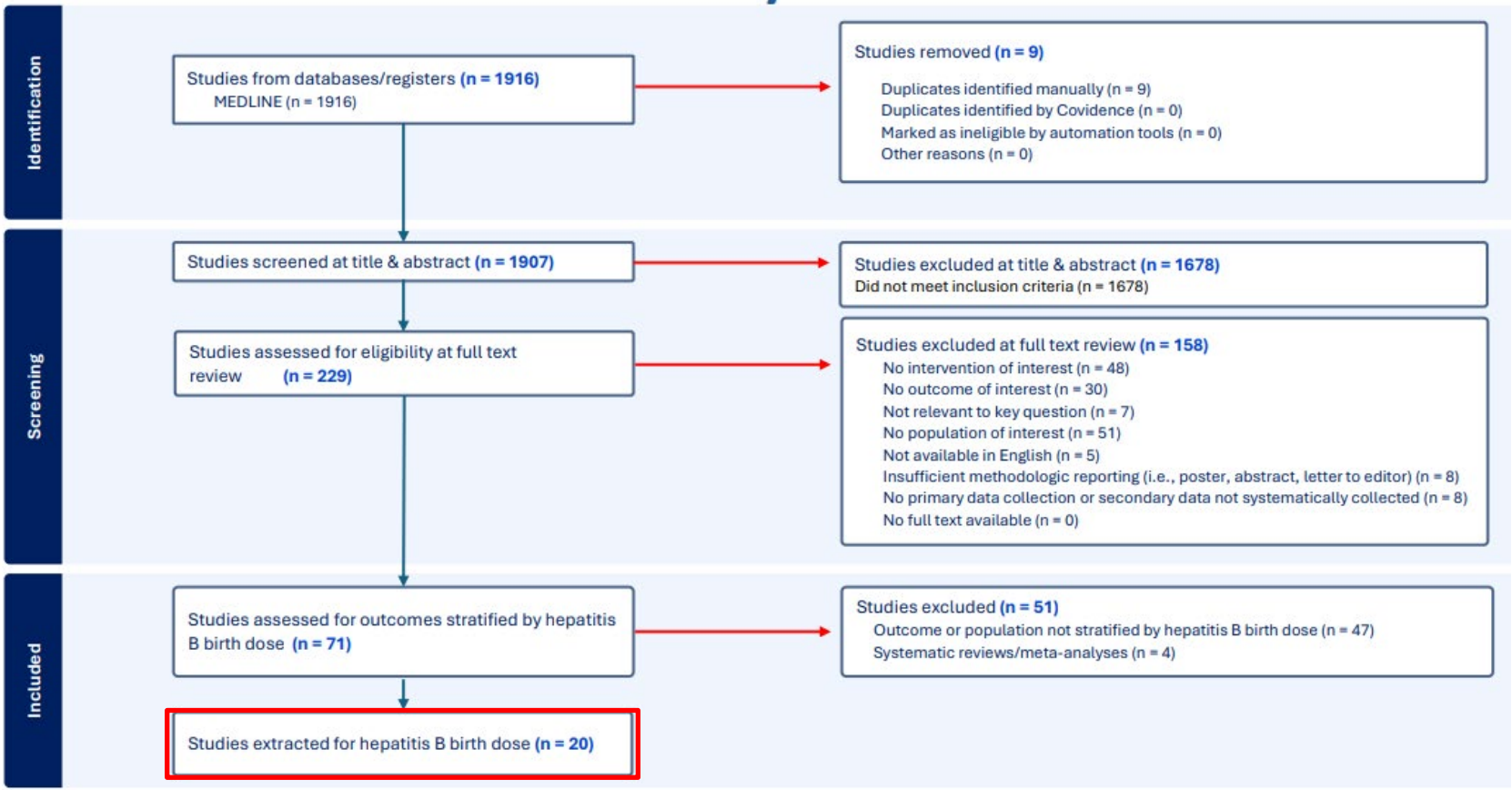
* Soreness.
† Fatigue/weakness, diarrhoea, irritability.

“Symptoms of encephalitis…

*“Encephalitis can be dangerous in infants. Watch for **fever**, lethargy (**weakness** or drowsiness), poor feeding, vomiting, body stiffness, unexplained/unusual **irritability** or crying”*

Source: [Encephalitis | National Institute of Neurological Disorders and Stroke]

Results of rapid systematic review of hepatitis B safety administered in the first 30 days of life



Summary of publications meeting search criteria

- **Total of 20 studies of hepatitis B vaccine administration within 30 days of life included in review**
  - Five studies defined birth dose as hepatitis B vaccine administered within 24 hours of birth
    - VSD: 1 study
  - Four studies used other terms to define hepatitis B vaccine birth dose
    - Terms used: Given at birth, Birth dose, within 120 hours of birth
    - One study stated that 85% received hepatitis B on date of birth, none received the vaccine beyond 8 days of life
    - VSD: 1 study

Study characteristics (N = 20)

Characteristic		# of Studies
Study design	RCT	5
	Cohort	7
	Surveillance report	2
	Case control	4
	Case series	1
	Cross-sectional	1
Vaccine administered	Engerix-B	5
	Recombivax	1
	Hepatitis B product not-specified	14
Timing of administration as noted in the paper	≤ 24 hours	5
	Within 8 days of birth	4
	Within first month of life	11

ISO's "rapid systematic review" of hepatitis B post-licensure safety data (ISO, 9/18/25) included 20 studies—presented findings from 9 of 20

Categories	Unvaccinated or no vaccine as control		Vaccine(s) as control
Birth dose defined as <24 hours			
	Linder et al, 1999 Lewis et al, 2001 (VSD) Morgan et al, 2025		Bassil et al, 1995 Yerushalmi et al, 1997
Birth dose defined as 0-3 days			
	Eriksen et al, 2004 (VSD)		Greenberg et al, 2002 Lopez et al, 2002 Wood et al, 2018
Birth dose defined as <30 days			
	Gallagher & Goodman, 2010 (NHIS, ASD) Geier et al, 2015 (VSD, Tics) Geier et al, 2016 (VSD, Dev Delay) Geier et al, 2017 (VSD, Emot Disturb) Geier et al, 2018 (VSD, prem puberty)	Verstraetenet al, 2003 (VSD) VAERS studies (3) -Niu et al, 1996 -Niu et al, 1999 (death) -Haber et al, 2018	Sapru et al, 2007 Geier et al, 2013 (ASD)

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Early post-licensure study described unexplained fever in neonates in the year after HBV introduction in Israel

Arch Dis Child Fetal Neonatal Ed 1999;**81**:F206–F207

Unexplained fever in neonates may be associated with hepatitis B vaccine

Nehama Linder, Meirav Raz, Lea Sirota, Brian Reichman, Dan Lubin, Jacob Kuint, Avner Herman Cohen, Asher Barzilai

Table 1 Comparison of infants with neonatal fever before (1991) and after (1992) introduction of routine hepatitis B immunisation

	1991 group	*1992 group*	*p Value*
Total infants	5010	5819	
Neonatal fever above 37.5°C	27	68	0.001
Neonatal fever above 38.0°C	27	50	0.05
Explained neonatal fever	13	15	NS
Unexplained neonatal fever	14	35	0.013

OR= 2.16

"In conclusion, we found that an increased incidence of unexplained neonatal fever, which resulted in evaluation for sepsis, administration of intravenous antibiotics, and prolonged hospital stay, may be associated with vaccination against hepatitis B on the first day of life. "

Post-licensure safety studies with unvaccinated group and negative/protective findings show healthy vaccinee effect (HVE)

Study	Condition(s) examined	Finding	HVE effects in sample selection
Included in 9/2025 ACIP safety review			
1. Lewis et al, 2001 (VSD)	Fever, sepsis, allergies, seizures Testing frequency	No differences 0.73 OR for tests	Exclusions of preterm, LBW Unexplained testing frequency
2. Ericksen et al, 2004 (VSD)	Death	Lower death rate in exposed	Unvaccinated sample mean birth wgt <44% of vaccinated
3. Morgan et al 2025 (Australia)	Bronchopulmonary dysplasia in preterm	0.83 RR	"it is not known how clinician perception of the stability of the newborn affects the decision to vaccinate or not"

TABLE 2. Maternal and Perinatal Risk Factors for Neonatal Mortality by HBV Status

Risk Factor	HBV-Vaccinated Neonates	HBV-Unvaccinated Neonates*
Perinatal factors		
Median birth wt (g)	3100†	1358†
Median gestational age (wk)	39†	28†
Median Apgar score		
1 min	8.0†	5.0†
5 min	9.0†	7.0†
% delivered by cesarean section	34.7	46.4
Mean no. of labor/delivery complications	2.0†	2.7†
% non-Caucasian	30.6	32.7
Median birth plurality (1 = single, 2 = twin, etc.)	1.0	1.0
% HBsAg-positive	3 (n = 2)	0.5 (n = 1)
Total no. of deaths (n = 268)	72	196

*Excludes 83 ELBW neonates.

†Denotes a significant ($P < 0.05$) difference between vaccinated and unvaccinated neonates.

Eriksen et al, 2004 (VSD)

HVE effect: unvaccinated vs. vaccinated neonates

- **<44% of median birth weight**
- **11 weeks lower median gestational age**
- **Only 5% of 1993-98 cohort deaths were in vaccinated infants, 72 of 1363**

Eriksen et al, 2004: death assessment method

Study design

(1) identified all neonatal deaths in NCK and SCK from 1993-98

(2) determined cases that had been vaccinated with HBV

(3) selected 2–4 matched HBV-unvaccinated controls for each HBV-vaccinated neonatal death

- ***Matching based on "days of life" category (0-1, 2-5 and 6-28), birth year, sex and HMO***

(4) determined pre-existing illness and the causes of death

(5) Categorized deaths as "expected" or "unexpected" in a blinded review

(6) assessed the clinical plausibility that HBV contributed to death

(7) assessed SIDS rates, searched for unvaccinated SIDS cases beyond matched sample

(8) Compared maternal and perinatal factors in both groups

Eriksen et al, 2004: Death assessment in matched samples

Primary cause of death	Vaccinated	Unvaccinated
Total deaths	72	196
"Expected"	50 (69%)	128 (65%)
"Unexpected"	22 (31%)	68 (35%)
SIDS	8	0
Sepsis after birth	7	4
Necrotizing enterocolitis (NEC)	3	29
Insufficient information	2	
CNS hemorrhage	1	15
Laryngeal edema	1	
Pulmonary/other hemorrhage	0	5
Other	-	15

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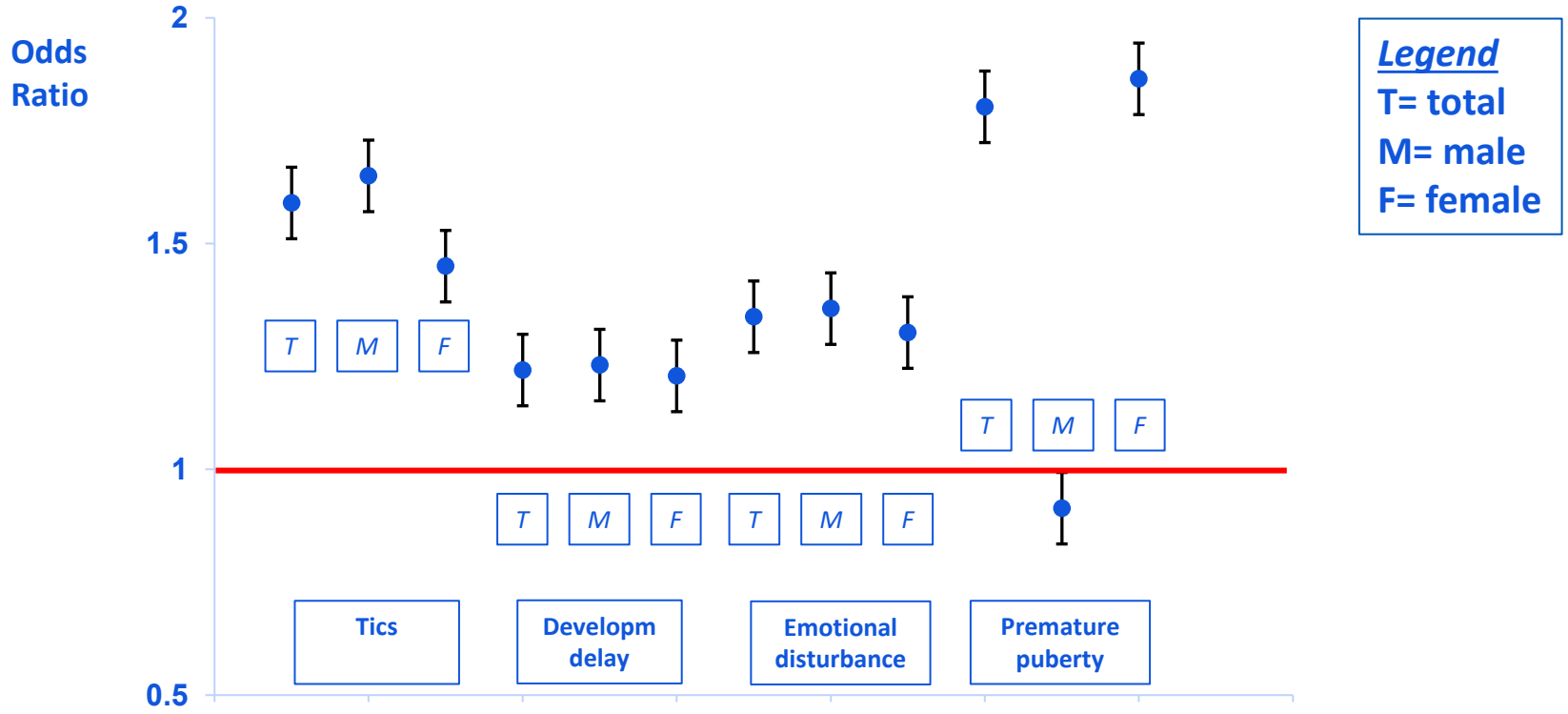
Additional studies with unvaccinated comparisons listed—but not presented—in 9/2025 ACIP safety review presentation

Study	Condition(s) examined	Finding	Comments
1. Verstraetenet al, 2003	Neurodevelopmental disorders (VSD)	No significant associations	Hg/HBV exposure within 1st month
2. Gallagher & Goodman, 2010	Autism (NHIS)	3.002 OR in males	Vaccinated w/in 1st month
3. Geier et al, 2015	Tics (VSD)	1.59 OR total • 1.65 OR in males	Hg/HBV exposure within 1st month
4. Geier et al, 2016	Developmental delay (VSD)	1.22 RR	Hg/HBV exposure within 1st month
5. Geier et al, 2017	Emotional disturbance (VSD)	1.34 OR • 1.36 OR in males	Hg/HBV exposure within 1st month
6. Geier et al 2018	Premature puberty (VSD)	1.80 OR • 1.87 OR in females	Hg/HBV exposure within 1st month
7. Niu et al, 1996	VAERS reports: 1/1991-5/1995 "neonates" <1 month and "infants" < 1 year	"No unexpected adverse events in neonates and infants"	Neonates: 13 of 24 SAEs were fever, 4 seizures 3 of 6 deaths were SIDS
8. Niu et al, 1999	VAERS reports: 1/1991-10/1998	No "clear increase in neonatal deaths"	18 death reports within 1st month 12 SIDS cases, 3 initially SIDS
9. Haber et al 2017	VAERS reports, inc. infants: 2005	No "new or unexpected safety concerns"	27 deaths, 64 SAEs in 1st month, 197 SIDS cases

4 VSD studies with consistent methodologies found increased risk of injury for chronic, late-onset conditions from HBV in 1st month



IOM studies of causal relationships with HBV (1)

Condition	1994	2002	2012
Death			
Death following anaphylaxis	Y		
SIDS			
All other causes			
Arthritis			
Acute Arthropathy			
Chronic Arthropathy			
Psoriatic, onset or exacerbation			
Reactive, onset or exacerbation			
Rheumatoid, onset or exacerbation			
Juvenile Idiopathic, onset or exacerbation			
Anaphylaxis	Y		Y
Brachial Neuritis			
Erythema Nodosum			
Systemic Lupus Erythematosus, Onset or Exacerbation			
Vasculitis, onset or exacerbation			
Polyarteritis Nodusa, onset or exacerbation			
Diabetes, Type 1			
Fibromyalgia			

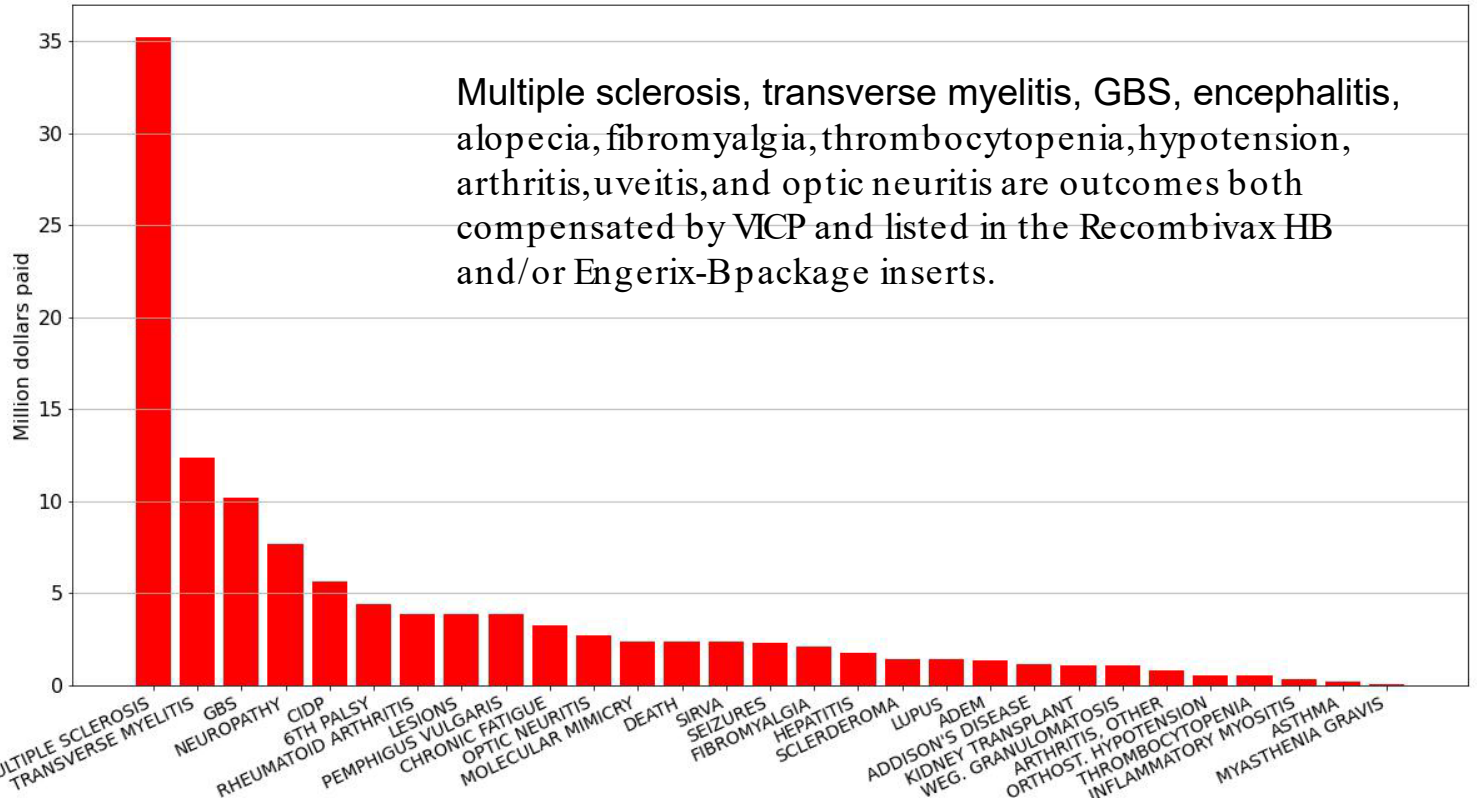
Evidence is:
insufficient to accept or reject,
establishes (Y), or
favors rejection of (N)
causality

IOM studies of causal relationships with HBV (2)

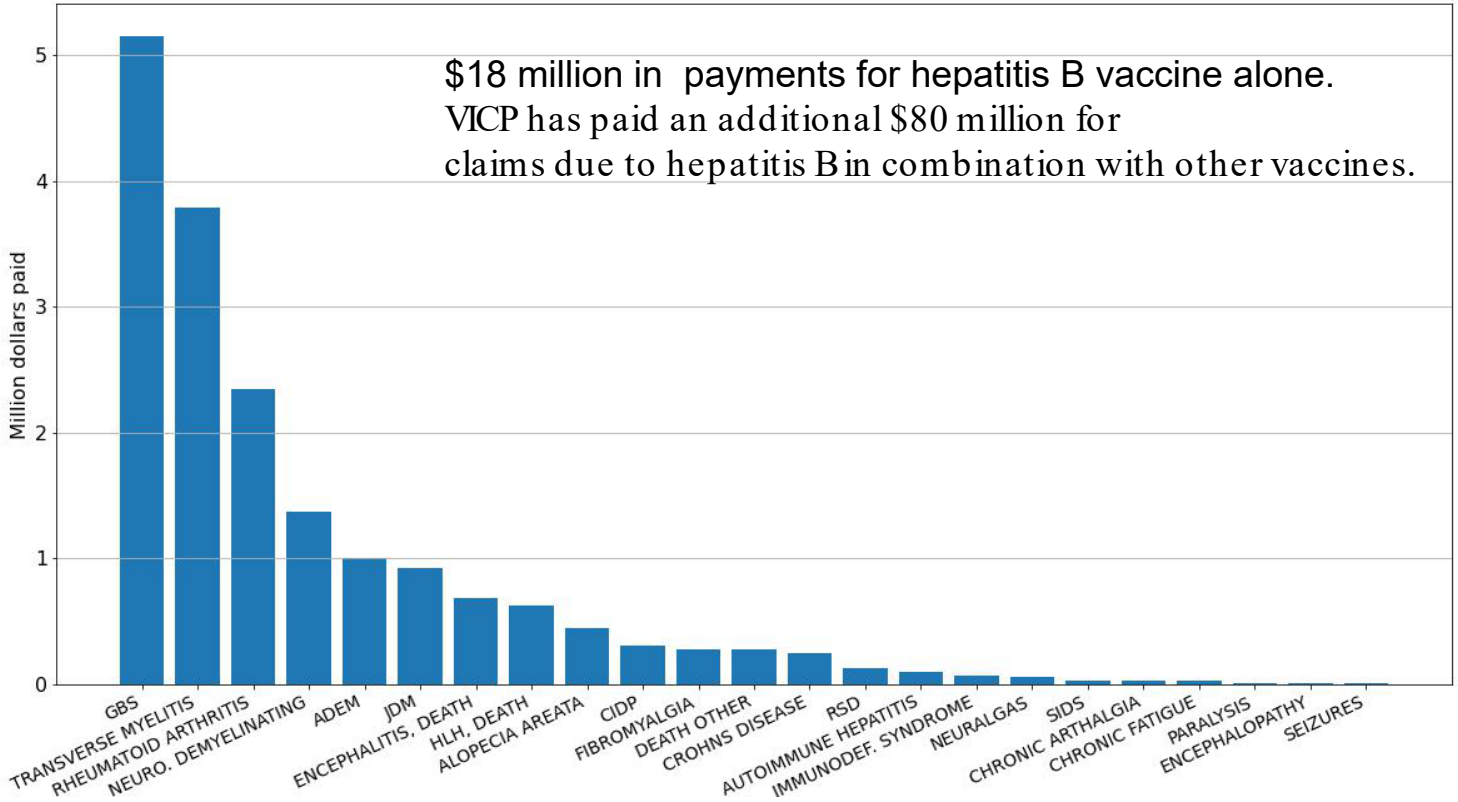
Condition	1994	2002	2012
Encephalitis			
Encephalopathy			
Seizures			
Guillain-Barre Syndrome			
Encephalomyelitis, Acute Disseminated			
Demyelinating Disorder, Central Nervous System, 1st episode			
Demyelinating Event, first episode, ADULTS			
Demyelinating Event, first episode, CHILDREN			
Optic Neuritis			
Multiple Sclerosis			
Multiple sclerosis, incident/onset, ADULTS		N	
Multiple sclerosis, incident/onset, CHILDREN			
Multiple sclerosis relapse, ADULTS		N	
Multiple sclerosis relapse, CHILDREN			
Transverse Myelitis			
Neuromyelitis Optica			
Chronic Inflammatory Disseminated Polyneuropathy			

Evidence is: insufficient to accept or reject, establishes (Y), or favors rejection of (N) causality

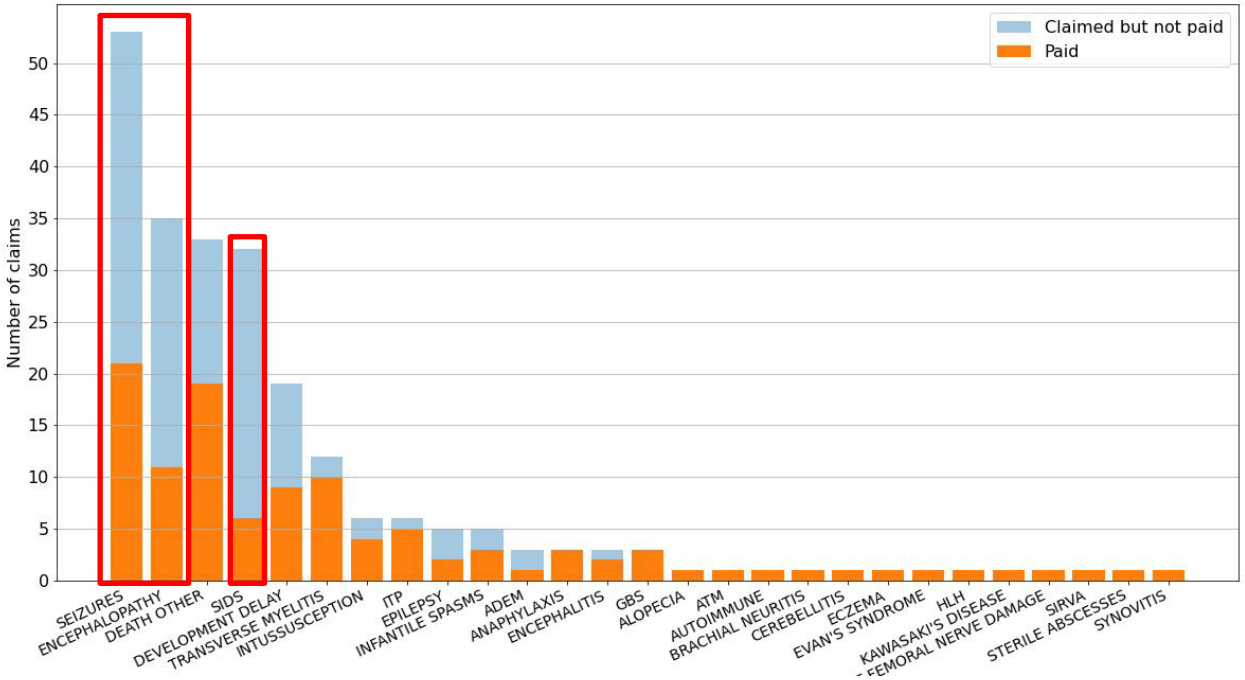
Vaccine Injury Compensation Program (VICP)
Adult compensation claims for hepatitis B vaccine total $92 million



Vaccine Injury Compensation Program (VICP)
Children's compensation claims for hepatitis B vaccine



Children's claims for hepatitis B vaccine are more commonly denied than compensated by VICP



Animal models of hepatitis vaccine birth dose

Study	Model	Selected findings		
		Immune	*Brain*	*Behavioral*
Studies finding altered development				
Yang et al, 2016	mice	Th2 bias	↓ hippocampal neurogenesis	↑ anxiety ↓locomotor activity
Wang et al, 2018	mice	↑ IL-4 levels	↑ neuroinflammation	↓ spatial learning & memory
Zhou et al, 2024	mice	CD8+ infiltrate CNS	↓ hippocampal neurogenesis	↑ anxiety
Li et al, 2015	rats	Th2 shift	↓ synaptic plasticity	--
Hewitson et al 2010a	macaques	--	--	Delayed neonatal reflexes
Hewitson et al 2010b	macaques	--	Altered amygdala maturation	--
Studies finding no changes				
Curtis et al 2015	macaques	--	--	No consistent evidence of deficits
Gadadet al 2015	macaques	--	No evidence of neuropathology	No evidence of aberrant behavior

Immune activation after infant birth dose in rodent models leads to neurodevelopmental and behavioral impairments

Study	Immune findings	Immune -> brain	Brain findings	Brain -> behavior	Behavioral findings
Li et al, 2015 (rats)	• Anti-HBs response; Th2 bias at 8 wks • ↑ TNF-α, ↑ IL-6, ↓ IFN-γ, ↓ BDNF, ↓ IGF-1	• Serum & hippocampal cytokines track together • IFN-γ/IL-4 ratio tracks with hippocampal BDNF & IGF-1	Impaired DG LTP • ↓ dendritic spine density, ↓ stubby spines • ↓ synaptophysin, PSD-95, NR2A, NR2B	--	--
Yang et al 2016 (mice)	• Hippocampus (6 wks): ↓ IFN-γ, ↓ BDNF, ↓ IGF-1; ↑ TNF-α, ↑ IL-1β, ↑ IL-6 • Serum Th2 bias (↓ IFN-γ/IL-4) • HEL+alum reproduces phenotype; alum alone does not	• IFN-γ/IL-4 correlates with hippocampal BDNF/IGF-1 & neurogenesis markers	• ↓ BrdU+, ↓ BrdU+/DCX+, ↓ BrdU+/NeuN+ • Impaired CA1 LTP at 8 wks	• Early neurogenesis & cytokine changes precede behavior	• OFT: ↓ distance, ↓ rearing, ↓ center time • EPM: ↓ open-arm activity • MWM: impaired learning & memory (normal swim speed) • Deficits only at 8 wks
Wang et al, 2018 (mice)	• Sustained ↑ IL-4 in serum & hippocampus • Delayed neuroinflammation (↑ TNF-α, IL-1β, IL-6) • Serum IL-4 correlates with hippocampal IL-4	• Neonatal IL-4 reproduces HBV outcome • HBV & IL-4 ↑ BBB permeability to IL-4 • ↓ IL-4R in hippocampus	• Delayed hippocampal neuroinflammation	• Early IL-4 surge → later neuroinflammation → behavior deficits	Delayed spatial cognition
Zhou et al, 2024 (mice)	• HBV induces effector memory CD8+ T-cells • CD8+ T cells: ↑ CXCR6; ↓ Arid5a, Mc1r, Flt3, etc. • ↑ effector-memory CD4+ and CD8+ T cells • ↑ TNF-α+ / IFN-γ+ CD8+ cells	• CD8+ T cells enter CNS via CXCL16/CXCR6 axis • Adoptive transfer of HBV-T cells → ↓ neurogenesis	• ↓ Ki67+ and ↓ DCX+ cells in DG • CXCL16 from glia recruits CD8+ cells	• CD8 infiltration → anxiety-like behavior	• OFT: ↓ center time, ↓ exploration • EPM: ↓ open-arm activity • ↑ anxiety-like behavior

Conclusions

The safety of the universal birth dose (UBD) was not studied, pre-licensure, in randomized, placebo-controlled, extended follow-up trials.

Post-licensure studies have in some cases been confounded by the healthy vaccinee affect; others have found evidence of chronic, late onset adverse effects.

IOM Safety of Vaccine reports have highlighted the absence of evidence to assess potential adverse effects in over 30 endpoints

Animal models provide evidence for risk of immunological activation and neurobehavioral impairment.