A Review of the Safety of Hepatitis B Birth Dose Vaccination

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Request to CDC from ACIP Chair

Safety data for HepB administration within 24 hours of birth from CDC's Vaccine Safety Datalink and from FDA's Biologics Effectiveness and Safety System. Include (i) mild and serious adverse events; (ii) all cause morbidity and mortality; (iii) short term and long-term safety; (iv) both specific outcomes of pre-determined concern as well as results from data mining where large numbers of potential adverse events are evaluated; and (v) both combined results and results stratified by sex. If some of these types of safety studies are unavailable, please mention that.

Rapid systematic review of hepatitis B post-licensure safety data

- **Key question:**
  - What is the safety of the hepatitis B vaccine administered within the first 30 days of life?

- **Conducted a new rapid systematic review of published literature**
  - Search conducted July 31, 2025 with no date restrictions for publications

- **Electronic databases searched:**
  - MEDLINE
  - EMBASE
  - CINAHL
  - Cochrane

Search Strategy

PI/ECO(ST) ELEMENT*	Description for this Review
Population	Neonates, Newborns, Infants
Intervention or Exposure	Hepatitis B vaccine administration within the first 30 days of birth: HepB, HepB-BD, HBV, Engerix-B, Recombivax HB
Comparator (if applicable)	Any or none
Outcome(s)	Adverse events Adverse outcomes Safety outcomes Side effects Reaction Adverse reaction Adverse effect Serious adverse event
Setting	Any
Time Frame	Any publication years Any duration of follow up

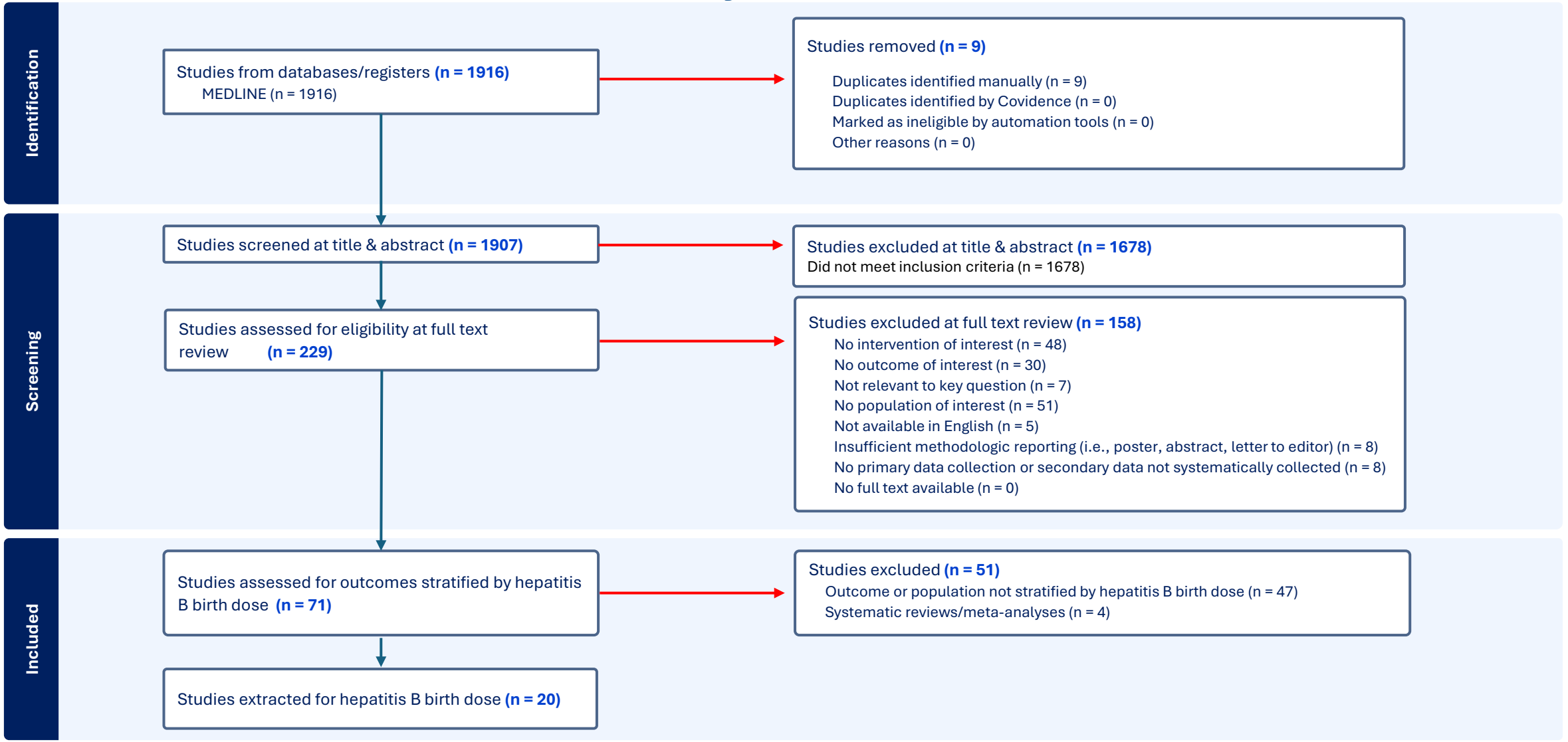
* Population, Intervention, Comparator, and Outcome, Setting, Time framework

Rapid systematic review: Inclusion/exclusion criteria

Inclusion Criteria	Exclusion Criteria
• Newborn infants receiving a hepatitis B vaccine at birth (i.e., ≤30 days old at dose 1)	• Non-English language articles • Animal studies
• Randomized control trial (RCT) • Observational studies • Case series ≥ 10 • Data from surveillance systems	• Any population that did not receive hepatitis B vaccine at ≤30 days old at dose 1 • N < 10
Outcomes include any of the following: • Safety • Adverse events • Serious adverse events • Side effects	• Clinical trial protocols • (e.g., clinicaltrials.gov, trialsearch.gov identified in the citation) • Conference abstracts/ posters • Conference proceedings in title or journal title • Title starts with a number • Poster

Results

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

Studies evaluating local reactions: Pain

Hepatitis B vaccination within 24 hours of birth (n = 1 study)
In one RCT, pain was reported for 7.7% of infants in the 5 days after Engerix-B vaccination.

Study	Study Type	Outcome	Outcome Window	Comparison groups	Local reactions	
					Intervention Results % (N)	Comparison Results % (N)
Yerushalmi 1997	RCT	Pain with movement	Within 5 days of vaccination	Engerix-B vs BioHepB*	7.7 (4)	2.6 (4)
Yerushalmi 1997	RCT	Pain with pressure	Within 5 days of vaccination	Engerix-B vs BioHepB*	7.7 (4)	1.3 (2)

Hepatitis B vaccination within 0-5 days of birth (n = 3 studies)^
Pain or soreness within the 4 days after Engerix-B was reported for <10% of newborns; few were severe.

Study	Study Type	Outcome	Outcome Window	Comparison groups	Local reactions	
					Intervention Results % (N)	Comparison Results % (N)
Greenberg 2002	RCT	Pain or soreness	Within 3 days of vaccination	Engerix-B vs DTaP-HepB, OPV, and Hib at 2 months of age	8.1 (NR); 0 (0) severe**	35.7 (NR); 1.6 (NR) severe**,†
Lopez 2002	Cohort	Pain or soreness	Within 4 days of vaccination	Engerix-B only (no comparison group)	6.0 (7); 4.3 (5) severe§	NA
Wood 2018	RCT	Pain or soreness	Within 2 days of vaccination	Engerix-B alone vs Engerix-B + investigational acellular Pertussis vaccine	9.3 (14); 0 (0) severe¶	19.7 (41); 0.5 (1) severe¶

NA = not applicable; NR = not reported
*The hepatitis B vaccine BioHepB is not approved for use in the United States
^Studies indicated hepatitis B administration at birth, within 120 hours of birth
**Severe: soreness that caused crying when limb moved; †Severe reported for any injection site; §Severe: not defined; ¶Severe: crying when limb moved/spontaneously painful or prevents daily activities

Studies evaluating local reactions: Redness or erythema

Hepatitis B vaccination within 24 hours of birth (n = 1 study)
In one RCT, redness or erythema was not reported in either comparison arm.

Study	Study Type	Outcome	Outcome Window	Comparison groups	Local reactions	
					Intervention Results % (N)	Comparison Results % (N)
Yerushalmi 1997	RCT	Redness or erythema	Within 5 days of vaccination	Engerix-B vs BioHepB*	0 (0)	0 (0)

Hepatitis B vaccination within 0-5 days of birth (n = 3 studies)^
Redness or erythema within 4 days after Engerix-B was reported for 8-20% of newborns; none were severe.

Study	Study Type	Outcome	Outcome Window	Comparison groups	Local reactions	
					Intervention Results % (N)	Comparison Results % (N)
Greenberg 2002	RCT	Redness or erythema	Within 3 days of vaccination	Engerix-B within 4 days of birth vs DTaP-HepB, OPV, and Hib at 2 months of age	8.8 (NR); 0 (0) severe**	11.6 (NR); 0 (0) severe**,†
Lopez 2002	Cohort	Redness or erythema	Within 4 days of vaccination	Engerix-B only (no comparison group)	11.1 (13); 0 (0) severe**	NA
Wood 2018	RCT	Redness or erythema	Within 2 days of vaccination	Engerix-B alone vs Engerix-B with an investigational acellular Pertussis vaccine	20.0 (30); 0 (0) severe§	27.4 (57); 0 (0) severe§

NA = not applicable; NR = not reported
*The hepatitis B vaccine BioHepB is not approved for use in the United States
^Studies indicated hepatitis B administration at birth, within 120 hours of birth
**Severe: diameter >20 mm; †Severe reported for any injection site; §Severe: diameter ≥30 mm

Studies evaluating local reactions: Swelling

Hepatitis B vaccination within 24 hours of birth (n = 1 study)

In one RCT, swelling was reported for 7.7% of newborns in the days after they received Engerix-B.

Study	Study Type	Outcome	Outcome Window	Comparison groups	Local reactions	
					Intervention Results % (N)	Comparison Results % (N)
Yerushalmi 1997	RCT	Swelling	Within 5 days of vaccination	Engerix-B vs BioHepB*	7.7 (4)	2.0 (3)

Hepatitis B vaccination within 0-5 days of birth (n = 3 studies)^

Swelling within 4 days was reported in 0-4% for newborns who received Engerix-B; there were no severe reports.

Study	Study Type	Outcome	Outcome Window	Comparison groups	Local reactions	
					Intervention Results % (N)	Comparison Results % (N)
Greenberg 2002	RCT	Swelling	Within 3 days of vaccination	Engerix-B vs DTaP-HepB, OPV, and Hib at 2 months of age	0 (0); 0 (0) severe**	16.3 (NR); 3.1 (NR) severe**,†
Lopez 2002	Cohort	Swelling	Within 4 days of vaccination	Engerix-B only (no comparison group)	4.3 (5); 0 (0) severe**	NA
Wood 2018	RCT	Swelling	Within 2 days of vaccination	Engerix-B alone vs Engerix-B + investigational acellular Pertussis vaccine	4.0 (6); 0 (0) severe§	12.5 (26); 0 (0) severe§

NA = not applicable; NR = not reported

*The hepatitis B vaccine BioHepB is not approved for use in the United States

^Studies indicated hepatitis B administration at birth, within 120 hours of birth

**Severe: diameter >20 mm; †Severe reported for any injection site; §Severe: diameter ≥30 mm

Studies evaluating any local reactions

Hepatitis B vaccination within 0-5 days of birth (n = 1 study)

In one RCT, any local reaction* during the week of Recombivax was reported for 2.8% of newborns

Study	Study Type	Outcome	Outcome Window	Comparison groups	Local reactions	
					Intervention Results % (N)	Comparison Results % (N)
Bassily 1995	RCT	Local side effects	Within 1 week of vaccination	Recombivax at birth vs Recombivax at 18 months	2.8 (5)	1.6 (3)

*Local reaction: local soreness, temporary redness/induration at the injection site

Studies evaluating systemic reactions: Fever

Hepatitis B vaccination within 24 hours of birth (n = 4 studies)

Fever in the days to weeks after hepatitis B vaccination was reported for 0-5.6% of newborns

Study	Study Type	Outcome	Outcome Window	Comparison groups	Systemic reactions		Measure of Association
					Intervention Results % (N)	Comparison Results % (N)	
Bassily 1995	RCT	Fever	Within 1 week of vaccination	Recombivax at birth vs Recombivax at 18 months	5.6 (10)	2.1 (4)	NR
Linder 1999	Cohort	Fever, >37.5°C	Within birth hospitalization	Hepatitis B vaccine vs No Hepatitis B vaccine	1.2 (68)	0.5 (27)	p = 0.001
					0.9 (50) >38°C	0.5 (27) >38°C	p = 0.05
Lewis 2001	Cohort	Fever	Within first 21 days of life	Hepatitis B vaccine vs. No Hepatitis B Vaccine	0.8 (21)	1.1 (25)	aRR§: 0.85 (95%CI: 0.6-1.1); p=0.28
Yerushalmi 1997	RCT	Fever, ≥38°C	Within 5 days of vaccination	Engerix-B vs BioHepB*	0 (0)	1.3 (2)	NR

Hepatitis B vaccination within 0-5 days of birth (n = 3 studies)^

Fever within 4 days after Engerix-B vaccination was reported for 0-5.9% of newborns; few were severe.

Study	Study Type	Outcome	Outcome Window	Comparison groups	Systemic reactions		Measure of Association
					Intervention Results % (N)	Comparison Results % (N)	
Greenberg 2002	RCT	Fever, ≥38.0°C	Within 3 days of vaccination	Engerix-B vs DTaP-HepB, OPV, and Hib at 2 months of age	5.9 (NR); 0 (NR) >39.5°C	14.7 (NR); 0.8 (NR) >39.5°C	NR
Wood 2018	RCT	Fever, ≥38.0°C	Within 2 days of vaccination	Engerix-B alone vs Engerix-B + investigational acellular Pertussis vaccine	0.7 (1); 0 (0) ≥39.0°C	0 (0); 0 (0) ≥39.0°C	NR
Lopez 2002	Cohort	Fever, ≥38.0°C	Within 4 days of vaccination	Engerix-B only (no comparison group)	0.9 (1); 0.9 (1) >39.0°C axillary or >39.5°C rectal	NA	NA

NA = not applicable; NR = not reported. *The hepatitis B vaccine BioHepB is not approved for use in the United States.; ^Studies indicated hepatitis B administration at birth, within 120 hours of birth
§ Adjusted relative risk; Adjusted for maternal age, low Apgar at 1 minute, low Apgar at 5 minutes, maternal smoking, gestation period and congenital heart disease status

Studies evaluating systemic reactions: anorexia or decreased appetite

Hepatitis B vaccination within 24 hours of birth (n = 1 study)

In one RCT, anorexia or decreased appetite was not reported for newborns who received Engerix-B.

Study	Study Type	Outcome	Outcome Window	Comparison groups	Systemic reactions	
					Intervention Results % (N)	Comparison Results % (N)
Yerushalmi 1997	RCT	Anorexia/ decreased appetite	Within 5 days of vaccination	Engerix-B vs BioHepB*	0 (0)	2.0 (3)

Hepatitis B vaccination within 0-5 days of birth (n= 3 studies)^

Anorexia or decreased appetite was reported for 2.6-16.5% of newborns after Engerix-B vaccination; there were few severe reports.

Study	Study Type	Outcome	Outcome Window	Comparison groups	Systemic reactions	
					Intervention Results % (N)	Comparison Results % (N)
Greenberg 2002	RCT	Anorexia/Decreased appetite	Within 3 days of vaccination	Engerix-B vs DTaP-HepB, OPV, and Hib at 2 months of age	14.0 (NR); 1.5 (NR) severe**	25.6 (NR); 0.8 (NR) severe**
Lopez 2002	Cohort	Anorexia/Decreased appetite	Within 4 days of vaccination	Engerix-B only (no comparison group)	2.6 (3); 1.7 (2) severe†	NA
Wood 2018	RCT	Feeding issues/Decreased appetite	Within 2 days of vaccination	Engerix-B alone vs Engerix-B + investigational acellular Pertussis vaccine	16.5 (17); 1.0 (1) severe§	12.7 (28); 0 (0) severe§

NA = not applicable; NR = not reported

*The hepatitis B vaccine BioHepB is not approved for use in the United States

^Studies indicated hepatitis B administration at birth, within 120 hours of birth

**Severe: prevents normal daily activities; †Severe: not defined; §Severe: prevents normal daily activities or requires significant medical intervention

Studies evaluating systemics reactions: Gastrointestinal (GI) symptoms

Hepatitis B vaccination within 24 hours of birth (n = 1 study)
In one RCT, diarrhea or vomiting was not reported for newborns who received Engerix-B

Study	Study Type	Outcome	Outcome Window	Comparison groups	Systemic reactions	
					Intervention Results % (N)	Comparison Results % (N)
Yerushalmi 1997	RCT	Diarrhea or vomiting	Within 5 days of vaccination	Engerix-B vs BioHepB*	0 (0)	0.6 (1)

Hepatitis B vaccination within 0-5 days of birth (n = 2 studies)^
GI symptoms were reported for 0-22% of newborns who received Engerix-B; there were no reports.

Study	Study Type	Outcome	Outcome Window	Comparison groups	Systemic reactions	
					Intervention Results % (N)	Comparison Results % (N)
Greenberg 2002	RCT	Diarrhea	Within 3 days of vaccination	Engerix-B vs DTaP-HepB, OPV, and Hib at 2 months of age	8.1 (NR); 0.7 (NR) severe**	10.1 (NR); 0 (0) severe**
Wood 2018	RCT	Diarrhea	Within 2 days of vaccination	Engerix-B alone vs Engerix-B + investigational acellular Pertussis vaccine	11.7 (12); 0 (0) severe†	17.2 (38); 0 (0) severe†
Greenberg 2002	RCT	Vomiting	Within 3 days of vaccination	Engerix-B vs DTaP-HepB, OPV, and Hib at 2 months of age	4.4 (NR); 0 (0) severe**	7.8 (NR); 0 (0) severe**
Wood 2018	RCT	Vomiting	Within 2 days of vaccination	Engerix-B alone vs Engerix-B + investigational acellular Pertussis vaccine	22.3 (23); 0 (0) severe†	20.4 (45); 0 (0) severe†

NR = not reported
*The hepatitis B vaccine BioHepB is not approved for use in the United States
^Studies indicated hepatitis B administration at birth, within 120 hours of birth
**Severe: prevents normal daily activities; †Severe: prevents normal daily activities or requires significant medical intervention

Studies evaluating systemic reactions: Irritability or fussiness or crying

Hepatitis B vaccination within 24 hours of birth (n = 1 study)

In one RCT, irritability or fussiness was reported for 11.5% of infants in the days after Engerix-B vaccination.

Study	Study Type	Outcome	Outcome Window	Comparison groups	Systemic reactions	
					Intervention Results % (N)	Comparison Results % (N)
Yerushalmi 1997	RCT	Irritability or fussiness	Within 5 days of vaccination	Engerix-B vs BioHepB*	11.5 (6)	3.3 (5)

Hepatitis B vaccination within 0-5 days of birth (n = 3 studies)^

Irritability, fussiness, or crying was reported for 1.5-22.1% of newborns who received Engerix-B; there were few severe reports.

Study	Study Type	Outcome	Outcome Window	Comparison groups	Systemic reactions	
					Intervention Results % (N)	Comparison Results % (N)
Greenberg 2002	RCT	Irritability or fussiness	Within 3 days of vaccination	Engerix-B vs DTaP-HepB, OPV, and Hib at 2 months of age	22.1 (NR) 0.7 (NR) severe**	54.3 (NR); 3.9 (NR) severe**
Wood 2018	RCT	Irritability or fussiness	Within 2 days of vaccination	Engerix-B alone vs Engerix-B + investigational acellular Pertussis vaccine	20.4 (21); 1.0 (1) severe†	24.4 (54); 0.9 (2) severe†
Lopez 2002	Cohort	Irritability or fussiness	Within 4 days of vaccination	Engerix-B only (no comparison group)	2.6 (3); 1.7 (2) severe§	NA
Greenberg 2002	RCT	Unusual crying	Within 3 days of vaccination	Engerix-B vs DTaP-HepB, OPV, and Hib at 2 months of age	1.5 (NR); 0 (0) severe**	3.1 (NR); 0.8 (NR) severe**

NA = not applicable; NR = not reported

*The hepatitis B vaccine BioHepB is not approved for use in the United States

^Studies indicated hepatitis B administration at birth, within 120 hours of birth

**Severe: prevents normal daily activities; †Severe: prevents normal daily activities or requires significant medical intervention ; §Severe: not defined

Studies evaluating systemic reactions: Sleep disturbance

There were no studies evaluating sleep disturbance for children who received hepatitis B vaccine within 24 hours of birth

Hepatitis B vaccination within 0-5 days of birth (n = 3 studies)^
Sleep disturbances were reported for 5.1-32.4% of newborns who received Engerix-B; there were few severe reports.

Study	Study Type	Outcome	Outcome Window	Comparison groups	Systemic reactions	
					Intervention Results % (N)	Comparison Results % (N)
Greenberg 2002	RCT	Drowsiness or sleeping more	Within 3 days of vaccination	Engerix-B vs DTaP-HepB, OPV, and Hib at 2 months of age	32.4 (NR); 2.9 (NR) severe*	40.3 (NR); 0.8 (NR) severe*
Wood 2018	RCT	Drowsiness or sleeping more	Within 2 days of vaccination	Engerix-B alone vs Engerix-B + investigational acellular Pertussis vaccine	27.2 (28); 1.0 (1) severe§	17.6 (39); 0.5 (1) severe§
Lopez 2002	Cohort	Drowsiness or sleeping more	Within 4 days of vaccination	Engerix-B only (no comparison group)	5.1 (6); 0.9 (1) severe†	NA
Greenberg	RCT	Restlessness or sleeping less	Within 3 days of vaccination	Engerix-B vs DTaP-HepB, OPV, and Hib at 2 months of age	16.9 (NR); 1.5 (NR) severe*	26.4 (NR); 0.8 (NR) severe*
Wood 2018	RCT	Restlessness or sleeping less	Within 2 days of vaccination	Engerix-B alone vs Engerix-B +investigational acellular Pertussis vaccine	31.1 (32); 2.9 (3) severe§	22.2 (49); 0.9 (2) severe§

NA = not applicable; NR = not reported
^Studies indicated hepatitis B administration at birth, within 120 hours of birth
*Severe: prevents normal daily activities; †Severe: not defined; §Severe: prevents normal daily activities or requires significant medical intervention

Studies evaluating allergic reaction or atopy

Hepatitis B vaccination within 24 hours of birth (n = 1)

There were no differences between vaccinated and unvaccinated newborns in the proportion of those who received care for an allergic reaction in the first 21 days of life.

Study	Study Type	Outcome	Outcome Window	Comparison groups	Allergic Reaction		Measure of Association
					Intervention Results % (N)	Comparison Results % (N)	
Lewis 2001	Cohort	Allergic reaction	Within 3 weeks of life	Hepatitis B vaccine vs No hepatitis B vaccine	<0.1 (1)	<0.1 (1)	RR†: 0.87 (95% CI: 0.05-13.8); p=0.99

There were no studies evaluating allergic reaction or atopy for newborns who received hepatitis B vaccine within 0-5 days of birth

†Relative risk

Studies evaluating infections

Hepatitis B vaccination within 24 hours of birth (n = 1)

Newborns vaccinated against hepatitis B were less likely to be evaluated for possible sepsis and less likely to have a positive blood or cerebrospinal fluid (CSF) culture.

Study	Study Type	Outcome	Outcome Window	Comparison groups	Number of cultures		Measure of Association
					Intervention Results % (N)	Comparison Results % (N)	
Lewis 2001	Cohort	Blood or CSF culture performed	Within 3 weeks of life	Hepatitis B vaccine vs no hepatitis B vaccine	4.6 (126)	8.6 (203)	RR: 0.71 (95% CI: 0.63-0.80); p<0.001
Lewis 2001	Cohort	Blood or CSF culture positive	Within 3 weeks of life	Hepatitis B vaccine vs no hepatitis B vaccine	0.3 (7)	0.7 (16)	RR: 0.57 (95% CI: 0.35-0.94); p=0.027

There were no studies evaluating infection for newborns who received hepatitis B vaccine within 0-5 days of birth

[†]Relative risk

Studies evaluating other adverse events

Hepatitis B vaccination within 24 hours of birth (n = 3)

Hepatitis B vaccination does not appear to affect risk of seizures or neurological disorders. It may have a slight protective effect on bronchopulmonary dysplasia (BPD) among preterm infants.

Study	Study Type	Outcome	Outcome Window	Comparison groups	Adverse Event		Measure of Association
					Intervention Results % (N)	Comparison Results % (N)	
Lewis 2001	Cohort	Seizures	Within 3 weeks of life	Hepatitis B vaccine vs no hepatitis B vaccine	0.04 (1)	0.17 (4)	RR[†]: 0.22 (95% CI: 0.02-1.9), p=0.19
Lewis 2001	Cohort	Neurological disorders other than seizures	Within 3 weeks of life	Hepatitis B vaccine vs no hepatitis B vaccine	0.15 (4)	0.08 (2)	RR[†]: 1.7 (95% CI: 0.3-9.4), p=0.69
Morgan 2025*	Cohort	BPD in preterm infants born at <29 gestational weeks	36 weeks postmenstrual age**	Hepatitis B vaccine vs no Hepatitis B vaccine	50.7 (155)	61.9 (317)	aRR[§]: 0.83 (95% CI: 0.68-1.0)

Hepatitis B vaccination within 0-5 days of birth (n =1)

There was one report of cough requiring hospitalization 37 days after Engerix-B birth dose vaccination.

Study	Study Type	Outcome	Outcome Window	Comparison groups	Adverse Event		Measure of Association
					Intervention Results % (N)	Comparison Results % (N)	
Lopez 2002	Cohort	Serious adverse event	Within 30 days of vaccination	Engerix-B only (no comparison)	0.9 (1)	NA	NA

NA = not applicable; *Extremely preterm infants <29 weeks gestation; [†]Relative risk

§ Adjusted relative risk; Adjusted for maternal age, low Apgar at 1 minute, low Apgar at 5 minutes, maternal smoking, gestation period and congenital heart disease status (unadjusted RR: 0.81; 95% CI: 0.67-0.98); ** A diagnosis of BPD was evaluated for all infants once they reached 36 weeks postmenstrual age

Studies evaluating all cause mortality

Hepatitis B vaccination within 24 hours of birth (n = 1)

There were no differences in all cause-mortality within 3 months of life among preterm infants who received hepatitis B vaccine within 24 hours of birth and those who did not.

Study	Study Type	Outcome	Outcome Window	Comparison groups	Deaths		Measure of Association
					Intervention Results % (N)	Comparison Results % (N)	
Morgan 2025*	Cohort	All-cause mortality in preterm infants born at <29 gestational weeks	Within 3 months of life	Hepatitis B Vaccine vs No Hepatitis B Vaccine	2.3 (7) †	2.7 (14)	aRR§: 1.13 (95%CI: 0.42-2.81)

Hepatitis B vaccination within 0-8 days of birth (n = 2 studies)^

One cohort suggested no difference in expected or unexpected deaths, deaths due to SIDS, among newborns who received hepatitis B vaccine and those who did not. There were no deaths reported in one RCT.

Study	Study Type	Outcome	Outcome Window	Comparison groups	Neonatal deaths		Measure of Association
					Intervention Results % (N)	Comparison Results % (N)	
Eriksen 2004	Cohort	Expected neonatal death	Within 29 days of vaccination	Hepatitis B Vaccine vs No Hepatitis B Vaccine	69 (50)	65 (128)	p=0.6
Eriksen 2004	Cohort	Unexpected neonatal death	Within 29 days of vaccination	Hepatitis B Vaccine vs No Hepatitis B Vaccine	31 (22)	35 (68)	p=0.6
Eriksen 2004	Cohort	Unexpected neonatal death from SIDS	Within 29 days of vaccination	Hepatitis B Vaccine vs No Hepatitis B Vaccine	3.3 per 100,000 births	3.3 per 100,000 births	p=0.99
Greenberg 2002	RCT	All-cause mortality	Within 7 months of vaccination	Engerix-B vs DTaP-HepB, OPV, and Hib	0 (0)	0 (0)	NA

NA = not applicable.

^ Greenberg indicated hepatitis B administration occurred within 4 days (median 1 day) of birth. Eriksen stated that 85% received HBV on date of birth, none received the vaccine beyond 8 days of life

*Extremely preterm infants <29 weeks gestation. † Infants may have received other vaccines within the 3-month period. The cause of death for most of these infants appeared to be unrelated to the disease and multifactorial in nature, with most deaths probably a result of prematurity or congenital abnormalities (i.e. preceding the HBV vaccination). § Adjusted relative risk; Adjusted for maternal age, low Apgar at 1 minute, low Apgar at 5 minutes, maternal smoking, gestation period and congenital heart disease status (unadjusted RR: 0.83; 95% CI: 0.32–2.00)

Lack of association between hepatitis B birth immunization and neonatal death: A population-based study from the Vaccine Safety Datalink Project

- **Methods:**
  - Birth cohort was defined from Southern and Northern California Kaiser Permanente Health Plans of more than 350,000 live births from 1993 – 1998
  - All deaths were ascertained occurring under 29 days of age
    - Expected deaths:
      - Deaths among extremely low birth weight (ELBW) neonates (defined as birth weight 600 g or extremely preterm 24 weeks of gestation)
      - Death because of lethal congenital anomalies or other genetic conditions
      - Deaths from multiple cardiac or multiple (individually) nonlethal conditions
      - Potentially fatal conditions present at or within several hours of birth, such as neonatal sepsis or severe respiratory distress syndrome.
    - Unexpected deaths: No apparent preexisting medical conditions
  - The proportion of deaths among birth hepatitis b vaccinated and unvaccinated were compared
  - Medical record review conducted
- **Results:**
  - 1,363 neonatal deaths identified during the study period
  - 66% of the entire birth cohort received hepatitis B vaccine at birth
  - Among all deaths, only 5% (72) neonates who died received hepatitis vaccine at birth
  - No significant difference in the proportion of hepatitis B vaccinated to unvaccinated dying of unexpected causes
- **Conclusion: A relationship between hepatitis B and neonatal death was not identified**

Eriksen EM, Perlman JA, Miller A, et al. Lack of association between hepatitis B birth immunization and neonatal death: A population-based study from the Vaccine Safety Datalink Project. *Pediatr Infect Dis J.* July 2004;23(7):656-661. doi:10.1097/01.inf.0000130953.08946.d0

Limitation of rapid systematic review

- Not all papers specified the exact timing of hepatitis B administration
- There were variable approaches to data collection, data analysis, and reporting in the studies
- Primary end points included short-term outcomes (e.g., <30 days) such as reactogenicity and mortality
- Studies that met the inclusion criteria of hepatitis B administration within 24 hours or at birth did not include long-term outcomes
    - Studies that did not meet the inclusion criteria of hepatitis b administration within 24 hours or at birth do include long-term safety outcomes (e.g., > 30 days)

Summary of evidence

- The safety data available for hepatitis B vaccine administered at birth did not identify an increased risk:
  - Allergic reaction
  - All-cause mortality
  - Expected, or unexpected deaths or deaths due to sudden infant death syndrome (SIDS)
  - Seizures or neurologic disease other than seizures

- Compared to those who did not receive a hepatitis B vaccine administered at birth, there was a reduction in risk among those who received hepatitis B vaccine for:
  - An invasive diagnostic procedure (blood and CSF cultures) and a reduction in positive cultures
  - Bronchopulmonary dysplasia

- Reactogenicity within 1 week of vaccination varied by study.

References (1 of 2)

Studies that defined birth dose as hepatitis B vaccine administered within 24 hours of birth

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Questions?

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