ACIP BRIEFING MATERIALS FOR PUBLIC POSTING

The Safety of Hepatitis B Vaccines administered within 24 hrs of birth and within 30 days of birth: A Rapid Systematic Review

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A. Methods

A.1. Key Question Development

The Key Questions were developed by infectious disease and systematic review methodology subject matter experts using the PICO framework[1] (Population, Intervention, Comparator, and Outcome). The Key Question and PI/ECO(ST) Criteria used to guide the literature review are below and in *Table 1.*

1. What is the safety of the hepatitis B vaccine administered within the first 24 hours of life?
2. What is the safety of the hepatitis B vaccine administered within the first 30 days of life?

Table 1. PI/ECO(ST) Criteria for Key Question

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
	• Administration in the first 24 hours of life:
	  ○ Studies clearly identify vaccination within
	  ▪ the first 24 hours of life or birth,
	  ▪ the first day of life, or
	  ▪ the day of or the day after birth
	• Administration in the first 30 days of life:
	  ○ Studies clearly identify vaccination
	  ▪ in first 30 days of life,
	  ▪ at <0.1 years of age, or
	  ▪ of Neonate (aged 28 days or less)

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

A.2. Literature Search

A CDC informationist (J.T.) developed search strategies from the Key Question and PICO criteria, and performed the search in MEDLINE, EMBASE, CINAHL, and Cochrane Library from the start of each database to July 31, 2025. Search strategies and results are provided in Section D of this document (Search Strategies).

A.3. Study Selection

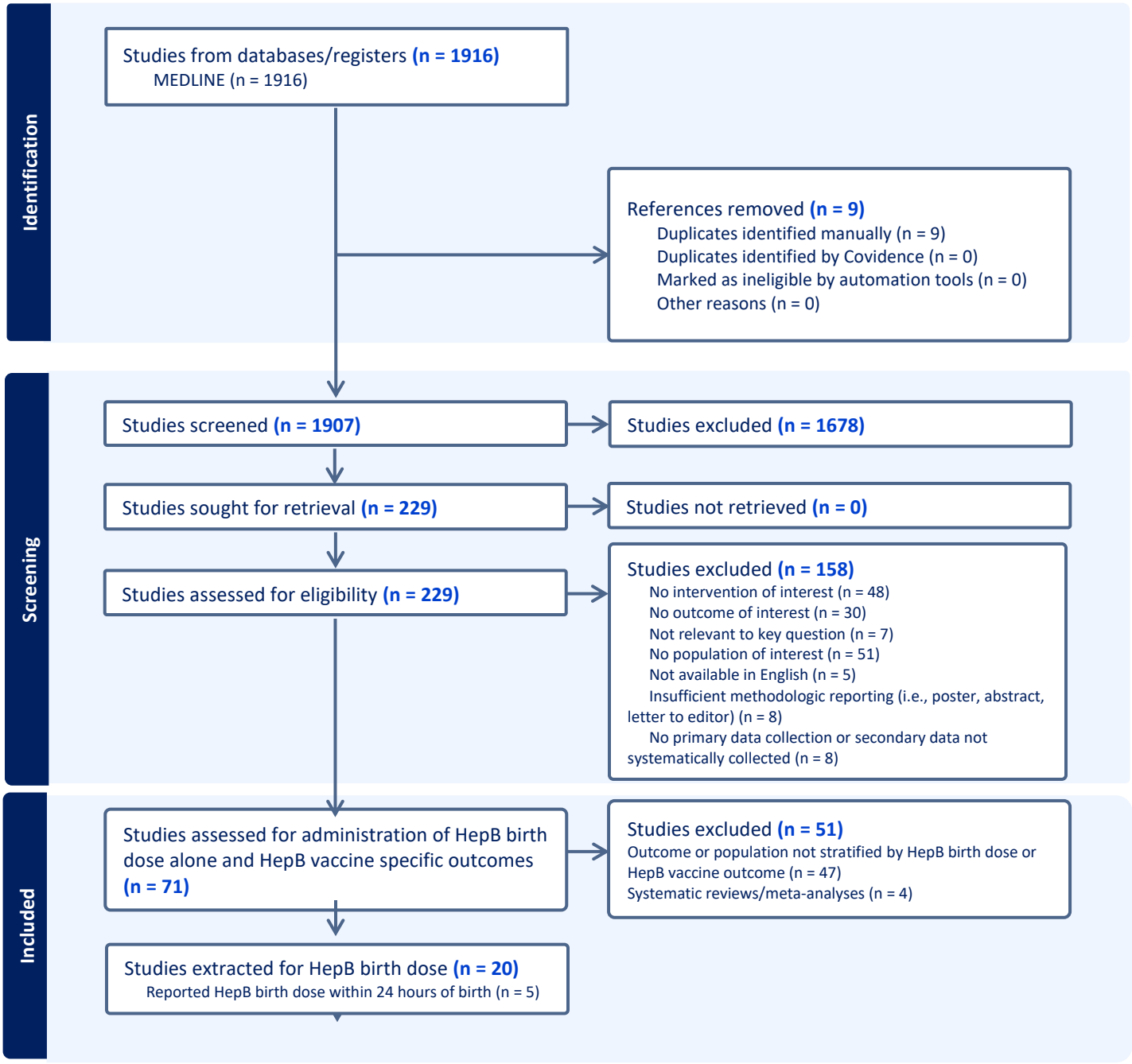
Results of the literature searches were uploaded into EndNote 21 (Clarivate Analytics©, Thomson Reuters, New York, NY, USA), duplicate records were removed, and unique titles and abstracts were uploaded to Covidence (Veritas Health Innovation Ltd., Melbourne, VIC, Australia) where a second round of deduplication was conducted.

Two reviewers (AH, LZ, MM1, MM2, RG, TM) independently screened all titles and abstracts and removed irrelevant references. Relevant full texts were screened independently by two reviewers (AH, LZ, MM1, MM2, RG, TM) and disagreements were resolved by consensus. All studies were screened according to the pre-identified exclusion criteria below, and results of the study selection process are provided in *Figure 1*.

Criteria for excluding studies from the literature review include:

1. No full text available;
2. Not available in English;
3. Not relevant to key question;
4. No population of interest (e.g., no neonates);
5. No intervention of interest (e.g., no hepatitis b vaccine);
6. No outcome of interest (e.g., no adverse event outcomes);
7. No primary data or secondary data not systematically collected (no reproducible methods);
8. Data collected prior to licensure; or
9. Insufficient methodologic reporting (i.e., poster, abstract, letter to editor)

Figure 1. Results of the Study Selection Process



A.4. Data Extraction, Study Assessment, and Synthesis

Data from studies meeting inclusion criteria were independently extracted by two reviewers using a standardized Microsoft Excel (2021) form, and differences were reconciled by discussion. Extracted data included study characteristics, population characteristics (e.g., case and control definitions), outcome definitions, and results (presented in *Section C*). Outcome data were extracted as presented in the studies or calculated using data provided. For the purposes of this review, statistical significance was defined as $p \leq 0.05$. The risk of bias for each study was assessed according to study type using standardized risk of bias tools appropriate to the identified study type. Tools were modified to specify birthweight, age at administration, prematurity, and maternal hepatitis b status as confounding factors and to include an assessment of conflict-of-interest disclosures. The Newcastle-Ottawa Scale was used for cohort and case control studies, R.O.B2. for randomized controlled trials (RCTs), and JBI tools were used to assess the risk of bias for Case Series and Systematic Reviews[2-4]. The signaling questions used to assess study conduct and risk of bias and results are presented in *Section C.3.* The evidence was narratively synthesized for each outcome domain, and for specific outcomes where definitions aligned.

A.5. GRADE-ing and Recommendation Development

The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach was used to assess the risk of bias, imprecision, inconsistency, and indirectness, and final confidence for the body of evidence foreach outcome using.[5] The Summary of findings and confidence in the evidence are found in *Section B*.

B. Summary of Evidence

B.1. GRADE-ed Summary of Findings for Hepatitis B vaccine administered in the first 24 hours of life

Key Question: *Among children, what is the safety of the hepatitis B vaccine administered in the first 24 hours of life?*

Table 2. GRADE Table: Allergic Reaction or Atopy Outcomes and the Administration of the Hepatitis B Vaccine in the first 24 hours of life

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
Summary Events	**The evidence from one cohort study suggests there is no difference in the risk of an allergic reaction and the receipt hepatitis B vaccination in the first 24 hours of life.**	**1 Cohort[6] (N = 5,655)**	**No concerns**	**No concerns**	**No concerns**	**No concerns**	**Low confidence**
Allergic reaction	One cohort[6] of normal birthweight, full term, U.S. infants in the VSD (NCK) reported no difference in the risk of an allergic reaction among infants with a record of Hepatitis B vaccination on the first day of life or the day after compared with infants with no record of Hepatitis B vaccination within the first 21 days of life. [RR: 0.87; (95%CI: 0.05-13.8); p=0.99; 1/2,718 vs 1/2,353].	1 Cohort[6] (N = 5,655)	No concerns	No concerns	No concerns	No concerns	Low confidence

Table 3. GRADE Table: All-cause Mortality Outcomes and the Administration of the Hepatitis B Vaccine in the first 24 hours of life

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
Summary Events	**The evidence from one Cohort[7] suggests no difference in the risk of all-cause mortality among those who did and did not and receive a hepatitis B vaccination in the first 24 hours of life.**	**1 Cohort[7] (N = 818)**	**No concerns**	**No concerns**	**No concerns**	**No concerns**	**Low confidence**
All-cause mortality	One cohort[7] of extremely preterm infants (<29 wks gestation) in Australia's Surveillance of Adverse Events Following Immunization in the Community suggested there is no difference in risk of death during the first 3 months of life when comparing infants with a record of receiving Hepatitis B vaccine within 24 hours of birth to infants with no record in the first 24 hours [aRR: 1.13; (95%CI: 0.42-2.81); 7/306 vs 14/512].	1 Cohort[7] (N = 818)	No concerns	No concerns	No concerns	No concerns	Low confidence

Table 4. GRADE Table: Infection or Infection-related Outcomes and the Administration of the Hepatitis B Vaccine in the first 24 hours of life

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
Infections	**The evidence from one cohort study suggests there is a reduction in the risk of an invasive diagnostic procedure including blood and CSF cultures, and a reduction in positive cultures, among infants who received a hepatitis B vaccination in the first 24 hours of life, compared to those who did not.**	**1 Cohort[6] (N = 5,655)**	**No concerns**	**No concerns**	**No concerns**	**No concerns**	**Low confidence**
Blood or CSF culture performed	One cohort[6] of normal birthweight, full term U.S. infants in the VSD (NCK) reported a reduction in the age-stratified risk of having a blood or CSF culture performed in the first three weeks of life when comparing infants with a record of receiving thimerosal-containing Hepatitis B vaccine on the day of birth or the day after compared to infants with no record of Hepatitis B vaccination [RR: 0.71; (95%CI: 0.63-0.80); p <0.001; 126/2,718 vs 203/2,353].	1 Cohort[6] (N = 5,655)	No concerns	No concerns	No concerns	No concerns	Low Confidence
Blood or CSF culture positive	One cohort[6] of normal birthweight, full term U.S. infants in the VSD (NCK) reported a reduction in the age-stratified risk of having a positive blood or CSF culture in the first three weeks of life when comparing infants with a record of receiving thimerosal-containing Hepatitis B vaccine on the day of birth or the day after compared to infants with no record of Hepatitis B vaccination [RR: 0.57; (95%CI: 0.35-0.94); p <0.027; 7/2,718 vs 16/2,353].	1 Cohort[6] (N = 5,655)	No concerns	No concerns	No concerns	No concerns	Low Confidence

Table 5. GRADE Table: Local Injection Site Reaction Outcomes and the Administration of the Hepatitis B Vaccine in the first 24 hours of life

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
Local Injection Site Reactions	**Two RCTs suggest no difference in local side effects, pain or soreness, redness, or swelling at the injection site within 1 week of vaccination or less when comparing infants who received a dose of a Hepatitis B Vaccine within the first 24 hours, compared to those who were vaccinated never or later.**	**2 RCT[8,9] (N = 741)**	**Serious concerns[a]**	**No concerns**	**No concerns**	**No concerns**	**Low confidence**
Local side effects	One RCT of Egyptian infants[8], compared the outcome of local side effects (e.g., local soreness, or temporary redness/induration at the injection site) 1 week after vaccination among infants randomized to administration of the first of dose of Recombivax immediately after delivery, at	1 RCT[8] (N = 536)	Serious concerns[a]	No concerns	No concerns	No concerns	Low confidence

[a] Inadequate randomization, unclear allocation concealment and blinding

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
	two months of age, or at 18 months of age, and reported a higher proportion of local side effects among those who received the vaccine at birth (2.8% (5/178) at birth, vs 7.2% (12/167), vs. 1.6% (3/191) at 18 months]. No relationship was found between side effects and weight or prematurity.						
Pain	In a RCT of Israeli infants[9], 4/52 (7.7%) infants who received Engerix-B within 24 hours of birth and 4/153 (2.6%) who received BioHepB within 24 hours of birth experienced pain with movement within 5 days of vaccination. Additionally, 4/52 (7.7%) infants who received Engerix-B within 24 hours of birth and 2/153 (1.3%) who received BioHepB within 24 hours of birth experienced pain with pressure within 5 days of vaccination. The HepB vaccine BioHepB is not approved for use in the United States.	1 RCT[9] (N = 205)	Serious concerns[b]	Some concerns[c]	No concerns	No concerns	Very low confidence
Redness or erythema	One RCT of Israeli infants[9] reported no redness or erythema within 5 days of vaccination among infants randomized to receipt of Engerix-B or BioHepB within 24 hours of birth (0/52 vs. 0/153). The HepB vaccine BioHepB is not approved for use in the United States.	1 RCT[9] (N = 205)	Serious concerns[d]	Some concerns[d]	No concerns	No concerns	Very low confidence
Swelling	One randomized control trial of Israeli infants[9] reported a higher proportion of swelling at the injection site within five days of vaccination among infants who received thimerosal-containing Engerix-B within 24 hours of birth compared with those who received BioHepB within 24 hours of birth [4/52 (7.7%) vs. 3/153 (2.0%)] The HepB vaccine BioHepB is not approved for use in the United States.	1 RCT[9] (N = 205)	Serious concerns[e]	Some concerns[d]	No concerns	No concerns	Very low confidence

[b] Unclear allocation concealment; absence of statistical analyses and reporting on protocol deviations
[c] Small sample size
[d] Unclear allocation concealment; absence of statistical analyses and reporting on protocol deviations
[e] Unclear allocation concealment; absence of statistical analyses and reporting on protocol deviations

Table 6. GRADE Table: Systemic Reaction Outcomes and the Administration of the Hepatitis B Vaccine in the first 24 hours of life

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
Systemic Reactions	**2 RCTs and 2 cohorts suggested no difference in fever when comparing infants who were vaccinated in the first 24h with a Hep B Vaccine to those who were vaccinated later, not at all, or with a different vaccine.** **One RCT[9] of Israeli infants suggested no difference in anorexia/ decreased appetite, diarrhea or vomiting, however, it did suggest an increase in irritability or fussiness when comparing infants who received hepatitis B vaccine in the first 24 hours after birth with infants who received the BioHepB (not approved in U.S.) vaccine in the first 24 hours.**	**2 RCTs[8,9] (N = 741)** **2 cohort[6,10] (N = 16,484)**	**Serious concerns[f]** **Some concerns[g]**	**Some concerns[h]** **No concerns**	**No concerns** **No concerns**	**No concerns** **No concerns**	**Very low confidence** **Very low confidence**
Anorexia/Decreased appetite	In a RCT of Israeli infants[9], 0/52 infants who received Engerix-B within 24 hours of birth and 3/153 (2.0%) who received BioHepB within 24 hours of birth experienced anorexia within 5 days of vaccination. The HepB vaccine BioHepB is not approved for use in the United States.	1 RCT[9] (N = 205)	Serious concerns[i]	Some concerns[j]	No concerns	No concerns	Very low confidence
Diarrhea or vomiting	In a RCT of Israeli infants[9], 0/52 infants who received Engerix-B within 24 hours of birth and 1/153 (0.64%) who received BioHepB within 24 hours of birth experienced diarrhea or vomiting within 5 days of vaccination. The HepB vaccine BioHepB is not approved for use in the United States.	1 RCT [9] (N = 205)	Serious concerns[k]	Some concerns[l]	No concerns	No concerns	Very low confidence
Fever	Two RCTs reported no difference in fever among infants who received Hepatitis B vaccination within 24 hours of birth whether compared to the same vaccine at 2 months and at 18 months of age, or a combination vaccine delivered at birth.						Very low confidence

[f] Inadequate randomization, unclear allocation concealment and blinding; absence of statistical analyses and reporting on protocol deviations
[g] One study compared groups with different birth years, and did not adjust or age stratify the results.
[h] One study had a small sample size in one group.
[i] Unclear allocation concealment; absence of statistical analyses and reporting on protocol deviations
[j] Small sample size
[k] Unclear allocation concealment; absence of statistical analyses and reporting on protocol deviations
[l] One study had a small sample size in one group.

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
	• One RCT of Egyptian infants[8], compared the outcome of local side effects 1 week after vaccination among infants randomized to administration of the first of dose of Recombivax immediately after delivery (n=178), or at 18 months of age (n=191). There was no difference in the proportion who experienced fever among those who received the vaccine immediately after delivery (5.6%) compared to at 2 months (7.2%) or at 18 months (2.1%). • In a RCT of Israeli infants[9], 0/52 infants who received Engerix-B within 24 hours of birth and 2/153 (1.3%) who received BioHepB within 24 hours of birth experienced a temperature ≥38°C within 5 days of vaccination. The HepB vaccine BioHepB is not approved for use in the United States.	2 RCTs[8,9] (N = 741)	Serious concerns[m]	Some concerns[o]	No concerns	No concerns	
	Two cohorts reported inconsistent results on the proportion fever among infants who did and did not receive a dose of Hepatitis B vaccine in the first day of life, with the stronger study reporting no difference when adjusting for age at birth and year of vaccination; however, the study that compared different birth years and did not adjust or age-stratify the results reported a higher proportion of fever among those who received the Hep B vaccine in the first day of life. • One cohort[6] of normal birthweight, full term, U.S. infants in the Vaccine Safety Datalink (NCK) reported no difference in the risk of a fever in the first three weeks of life when comparing infants with a record of receiving thimerosal-containing Hepatitis B vaccine on the day of birth or day after birth with infants with no record of Hepatitis B vaccination within the first 21 days of life [RR: 0.85; (95%CI: 0.6-1.1); p=0.28; 21/2,718 vs 25/2,353]. • In a cohort study of full-term Israeli infants[10], 68/5,819 (1.2%) full-term infants receiving hepatitis	2 cohort[6,10] (N = 16,484)	Some concerns[n]	No concerns	No concerns	No concerns	Very low confidence

[m] Inadequate randomization, unclear allocation concealment and blinding; absence of statistical analyses and reporting on protocol deviations

[n] One study compared groups with different birth years and did not adjust, or age stratify the results.

[o] One study had a small sample size in one group.

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
	B vaccination and 27/5,010 (0.54%) full-term infants not receiving hepatitis B vaccine had a birth hospitalization discharge diagnosis of "neonatal fever" above 37.5°C (p<0.001). Fevers above 38°C were noted in 50 (0.9%) of vaccinated infants and 27 (0.54%) of unvaccinated infants (p<0.05). Identifiable causes of fever (e.g., sepsis, dehydration, maternal fever, respiratory distress) were noted among 15 vaccinated infants (0.3%) and 13 unvaccinated infants (0.3%). Unexplained fevers were noted among 35 (0.6%) vaccinated infants and 14 (0.3%) unvaccinated infants (p=0.013).						
Irritability or fussiness	In a RCT of Israeli infants[9], 6/52 (11.5%) infants who received Engerix-B within 24 hours of birth and 5/153 (3.3%) who received BioHepB within 24 hours of birth experienced irritability within 5 days of vaccination. The HepB vaccine BioHepB is not approved for use in the United States	1 RCT[9] (N = 205)	Serious concerns[p]	Some concerns[q]	No concerns	No concerns	Very low confidence

Table 7. GRADE Table: Cardiopulmonary Outcomes and the Administration of the Hepatitis B Vaccine in the first 24 hours of life

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
Cardiopulmonary	**The evidence from one cohort study of extremely preterm infants suggests a reduction in the adjusted risk of bronchopulmonary dysplasia among infants with a record of receiving Hepatitis B vaccine in the first 24 hours of life compared to infants with no record in the first 24h**	**1 Cohort[7] (N = 818)**	**No concerns**	**No concerns**	**No concerns**	**No concerns**	**Low confidence**
Bronchopulmonary dysplasia	One cohort[7] of extremely preterm infants (<29 wks gestation) in Australia's Surveillance of Adverse Events Following Immunization in the Community suggested there is a reduction in risk of bronchopulmonary dysplasia when comparing infants with a record of receiving Hepatitis B vaccine within 24 hours of birth to infants with no record when adjusting for maternal age, maternal smoking, Apgar	1 Cohort[7] (N = 818)	No concerns	No concerns	No concerns	No concerns	Low confidence

[p] Unclear allocation concealment; absence of statistical analyses and reporting on protocol deviations

[q] Small sample size

	score and congenital heart disease status [aRR: 0.83; (95%CI: 0.68-1.0); 155/306 vs 317/512].						

Table 8. GRADE Table: Neurological Outcomes and the Administration of the Hepatitis B Vaccine in the first 24 hours of life

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
Neurological	**The evidence from one cohort of normal birthweight, full term infants in the U.S.VSD suggested there is no difference in the risk of seizures or Neurologic disease other than seizures when comparing infants who received Hepatitis B vaccine on the day of birth or the day after birth to infants with no record of vaccination in the first 24 hours of life.**	**1 Cohort[6] (N = 5,655)**	**No concerns**	**No concerns**	**No concerns**	**No concerns**	**Low confidence**
Seizure	One cohort[6] of normal birthweight, full term U.S. infants in the VSD (NCK) suggested there is no difference in the risk of seizures in the first three weeks of life when comparing infants with a record of receiving thimerosal-containing Hepatitis B vaccine on the day of birth or day after birth with infants with no record of Hepatitis B vaccination within the first 21 days of life [RR: 0.22; (95%CI: 0.02-1.9); p=0.19; 1/2,718 vs 4/2,353].	1 Cohort[6] (N = 5,655)	No concerns	No concerns	No concerns	No concerns	Low confidence
Neurologic disease, other than seizure	One cohort[6] of normal birthweight, full term U.S. infants in the VSD (NCK) suggested there is no difference in the risk of neurologic disease in the first three weeks of life when comparing infants with a record of receiving thimerosal-containing Hepatitis B vaccine on the day of birth or day after birth with infants with no record of Hepatitis B vaccination within the first 21 days of life [RR: 1.7; (95%CI: 0.3-9.4); p=0.69; 4/2,718 vs 2/2,353].	1 Cohort[6] (N = 5,655)	No concerns	No concerns	No concerns	No concerns	Low confidence

B.2. GRADE-ed Summary of Findings for Hepatitis B vaccine administered in the first 30 days of life

Key Question: *Among children, what is the safety of the hepatitis B vaccine administered in the first 30 days of life?*

Table 9. GRADE Table: Adverse event following immunization (AEFI) outcomes and administration of the Hepatitis B Vaccine in the first 30 days of life

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
All Adverse events following immunization (AEFI)	**The evidence from two single group studies suggesting that serious adverse events can occur following the administration of a thimerosal-containing Hepatitis B vaccine in the first 30 days of life in neonates in Columbia and the U.S. The three serious adverse events in the U.S. occurred in the context of the administration of 12 million doses among infants less than 1 year of age.**	**2 DES[11,12] (N = 177)**	**Some concerns[r]**	**Some concerns[s]**	**No concerns**	**No concerns**	**Very low confidence**
Cerebral venous thrombosis/intraventricular hemorrhage	One case series examined VAERS reports of U.S. neonates <0.1 years of age who received a thimerosal-containing Hepatitis B vaccine between 1991 – 1994[12] and identified one serious report of cerebral venous thrombosis/intraventricular hemorrhage [1.7% (1/60)].	1 DES[12] (N = 60)	Some concerns[t]	No concerns	No concerns	No concerns	Very Low confidence
Disseminated intravascular coagulation	One case series[12] examined VAERS reports of U.S. neonates <0.1 years of age who received a thimerosal-containing Hepatitis B vaccine between 1991 – 1994 and identified one (1.7%) serious report of disseminated intravascular coagulation [1.7% (1/60)].	1 DES[12] (N = 60)	Some concerns[a]	No concerns	No concerns	No concerns	Very Low confidence
Necrotizing enterocolitis	One case series[12] examined VAERS reports of U.S. neonates <0.1 years of age who received a thimerosal-containing Hepatitis B vaccine between 1991 – 1994 and identified one serious report of necrotizing enterocolitis [1.7% (1/60)].	1 DES[12] (N = 60)	Some concerns[a]	No concerns	No concerns	No concerns	Very Low confidence
Serious adverse events	A single group cohort[11] of 117 healthy neonates in Colombia who received an Engerix-B Hepatitis B vaccine dose at birth, reported one adverse event (cough requiring hospitalization) 37 days after vaccination deemed serious, but unrelated to vaccine by study investigators [0.9% (1/117)].	1 DES[11] (N = 117)	Some concerns[u]	Some concerns[v]	No concerns	No concerns	Very low confidence

[r] Measurement bias: -1 for retrospective reporting and unclear temporality

[s] Small sample size

[t] Measurement bias: -1 for retrospective reporting and unclear temporality

[u] Measurement & misclassification: -1 for unclear day of dosing; -1 for no comparator group

[v] Small sample size

Table 10. GRADE Table: Allergic reaction and atopy outcomes and administration of the Hepatitis B Vaccine in the first 30 days of life

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
All Allergic reactions and Atopy	**One RCT[13] and one Cohort[6] suggest a low rate of occurrence of allergic reactions and atopy among infants vaccinated with Hepatitis-B vaccines in the first 30 days of life, and no difference in the occurrence or risk of allergic reactions and atopy when comparing those who did receive the vaccine in the first 30 days compared to those who did not receive the vaccine, or compared to those receiving a Hepatitis-B vaccine that is not approved in the United States (U.S.).**	**1 RCT[13] (N = 360)** **1 Cohort[6] (N = 5,655)**	**Some concerns[w]**	**No concerns**	**No concerns**	**No concerns**	**Moderate confidence**
Allergic reaction	One cohort[6] of normal birthweight, full term, U.S. infants in the VSD (NCK) reported no difference in the risk of an allergic reaction in the first three weeks of life when comparing infants with a record of receiving thimerosal-containing Hepatitis B vaccine in the first 21 days of life to infants with no record of Hepatitis B vaccination during the same time [RR: 0.71 (95%CI: 0.04-11.4); p=0.99; 1/3,302 vs 1/2,353]. This remained consistent in a sub-analysis restricting the infants with a record of Hepatitis B vaccination on the day of birth or day after birth with infants with no record of Hepatitis B vaccination in the first 21 days of life [RR: 0.87; (95%CI: 0.05-13.8); p=0.99; 1/2,718 vs 1/2,353].	1 Cohort[6] (N = 5,655)	Some concerns[1]	No concerns	No concerns	No concerns	Low confidence
Eczema	One RCT of healthy infants in India[13] reported no cases of eczema in infants vaccinated with Engerix-B in the first 2 weeks of life or in infants vaccinated with HepB Gene Vac-B within first 2 weeks of life (0/130 vs. 0/1320, p=NR). The HepB Gene Vac-B is not approved for use in the United States.	1 RCT[13] (N = 360)	No concerns	No concerns	No concerns	No concerns	High confidence

[w] Measurement & misclassification: -1 for unclear duration of follow up.

Table 11. GRADE Table: Mortality outcomes and administration of the Hepatitis B Vaccine in the first 30 days of life

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
All Death Outcomes	**The evidence from 1 RCT[14] and 2 cohort studies[7,15] suggests no difference in the proportion of deaths among infants vaccinated with any Hepatitis B Vaccine at birth compared to those who were not vaccinated at birth.** **The evidence from one cohort study[15] suggests no difference in expected, or unexpected deaths or deaths due to sudden infant death syndrome (SIDS).**	1 RCT[14] (N = 280) 2 Cohorts[7,15] (N =1,086)	Some concerns[x]	No concerns	No concerns	No concerns	Low Confidence
All-cause mortality	One RCT[14] of unvaccinated, healthy infants in the U.S. reported no deaths (N=208) at 7 months follow up among infants who received different timing of the first lifetime dose and the subsequent series of any HBV Vaccine, specifically DTaP-HepB vaccines at 2, 4 and 6 months of age, and infants who received HepB vaccine at birth, 1 month and 6 months of age and DTaP at 2, 4 and 6 months of age.	1 RCT[14] (N = 265)	Some concerns[e]	No concerns	No concerns	No concerns	Low confidence
	One cohort[7] of extremely preterm infants (<29 wks gestation) in Australia's Surveillance of Adverse Events Following Immunization in the Community suggested there is no difference in risk of death during the first 3 months of life when comparing infants with a record of receiving hepatitis b vaccine within 24 hours of birth to infants with no record in the first 24 hours [aRR: 1.13; (95%CI: 0.42-2.81); 7/306 vs 14/512].	1 Cohort[7] (N = 818)	No concerns	No concerns	No concerns	No concerns	Low confidence
	Three case series summarizing VAERS data[16] for infants <1 month of age, reported 18 neonatal death reports were submitted between 2005-2015[16] and 27 reports of death between 1991-1998[12,17] • One case series[16] of reports following single antigen thimerosal containing Hepatitis B vaccine in U.S. infants aged <1 month in the VAERS between 2005 - 2015 reported on Hepatitis B vaccine, 27/240 (11.3%) reports of death, including one due to sepsis. • There were two case series of VAERS reports in neonates following vaccination with a thimerosal-	3 DES[12,16,17] (N = 2,011)	Some concerns[q]	No concerns	No concerns	No concerns	Low confidence

[x] Unanalyzed loss to follow up.

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
	containing Hepatitis B vaccine during overlapping study periods 1991 - 1995[12] and 1991 – 1998[17]. The study examining a longer window of time for neonates aged <28d, reported 18 deaths among 1,771 VAERS reports.[17] Causes of death included accidental suffocation (1), congenital heart disease (1), infection (3), intracerebral hemorrhage (1), and SIDS (12).						
Expected neonatal death	One cohort study[15] of neonates in the VSD (NCK, SCK) suggested no difference in the proportion of deaths during the first 29 days of life from expected causes when comparing neonates who received Hepatitis B vaccine during the first 29 days of life to neonates who did not [50/72 (69%) vs. 128/196 (65%0; p=0.6].	1 Cohort[15] (N = 268)	No concerns	No concerns	No concerns	No concerns	Low Confidence
Unexpected neonatal death	One cohort study[15] of neonates in the VSD (NCK, SCK) suggested no difference in the proportion of deaths during the first 29 days of life from unexpected causes when comparing neonates who received Hepatitis B vaccine during the first 29 days of life to neonates who did not [22/72 (31%) vs. 68/196 (35%); p=0.6].	1 Cohort[15] (N = 268)	No concerns	No concerns	No concerns	No concerns	Low Confidence
Unexpected neonatal death from SIDS	One cohort study[15] of neonates in the VSD (NCK, SCK) suggested no difference in the death rate from SIDS when comparing neonates who received Hepatitis B vaccine during the first 29 days of life to neonates who did not [8/240,717 (3.3 deaths per 10^5 births) vs. 4/120,979 (3.3 deaths per 10^5 births); p=0.99].	1 Cohort[15] (N = 361,696)	Serious concerns[y]	No concerns	No concerns	No concerns	Very low Confidence

Table 12. GRADE Table: Infection outcomes and administration of the Hepatitis B Vaccine in the first 30 days of life

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
All Infection outcomes	**Evidence from 1 cohort[6] suggests a reduction in risk of having a blood or CSF culture performed to evaluate a fever, and a suggested reduction in positive blood or CSF cultures, among infants who received a thimerosal-containing Hepatitis B vaccine in the first 21 days of life when stratifying by age in days. This study also reported no difference in the incidence of fever due to infectious reasons. These results were**	**2 studies 1 Cohort[6] (N = 5,655) 1 DES[16]**	**No concerns**	**No concerns**	**No concerns**	**No concerns**	**Low confidence**

[y] No adjustment for confounding by age at administration, maternal or perinatal risk factors, or years of study.

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
	consistent in a sub analysis of infants who received the Hepatitis B vaccine on the day of birth or day after birth. **1 case series[16] summarizing reports in neonates following thimerosal-containing Hepatitis B vaccine immunization in VAERS reported 11 reports coded using the Medical Dictionary for Regulatory Activities as "infection and infestation" in 10 years (2005 – 2015).**	**(N = 240)**	**Some concerns[z]**	**No concerns**	**No concerns**	**No concerns**	**Very low confidence**
Blood or CSF culture performed	One cohort[6] of normal birthweight, full term U.S. infants in the VSD (NCK) suggested there is a reduction in the age-stratified risk of having a blood or CSF culture performed in the first three weeks of life when comparing infants with a record of receiving thimerosal-containing Hepatitis B vaccine in the first 21 days of life to infants with no record of Hepatitis B vaccination [RR: 0.73 (95%CI: 0.65-0.82); p <0.001; 133/3,302 vs 203/2,353]. This reduction in risk remained consistent in a sub-analysis restricting the infants with a record of Hepatitis B vaccination on the day of birth or day after birth with infants with no record of Hepatitis B vaccination. [RR: 0.71; (95%CI: 0.63-0.80); p <0.001; 126/2,718 vs 203/2,353].	1 Cohort[6] (N = 5,655)	No concerns	No concerns	No concerns	No concerns	Low Confidence
Blood or CSF culture positive	One cohort[6] of normal birthweight, full term U.S. infants in the VSD (NCK) suggested there is a reduction in the age-stratified risk of having a positive blood or CSF culture in the first three weeks of life when comparing infants with a record of receiving thimerosal-containing Hepatitis B vaccine in the first 21 days of life to infants with no record of Hepatitis B vaccination [RR: 0.60 (95%CI: 0.38-0.95); p=0.030; 8/3,302 vs 16/2,353]. This reduction in risk remained consistent in a sub-analysis restricting the infants with a record of Hepatitis B vaccination on the day of birth or day after birth with no record of Hepatitis B vaccination. [RR: 0.57; (95%CI: 0.35-0.94); p <0.027; 7/2,718 vs 16/2,353].	1 Cohort[6] (N = 5,655)	No concerns	No concerns	No concerns	No concerns	Low Confidence
Fever due to infectious reasons	One cohort[6] of normal birthweight, full term, U.S. infants in the Vaccine Safety Datalink (NCK) reported no difference in the risk of a fever due to infectious reasons in the first three weeks of life when comparing infants with a record of receiving thimerosal-containing Hepatitis B vaccine in the first 21 days of life to infants with no record of Hepatitis B vaccination during the same time when adjusting by age in days [aRR: 0.92 (95%CI: 0.7-1.2); p=0.51; 26/3,302 vs 25/2,353]. This remained	1 Cohort[6] (N = 5,655)	No concerns	No concerns	No concerns	No concerns	Low Confidence

[z] Descriptive study, no comparison

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
	consistent in a sub-analysis restricting the infants with a record of Hepatitis B vaccination on the day of birth or day after birth with infants with no record of Hepatitis B vaccination. [RR: 0.85; (95%CI: 0.6-1.1); p=0.28; 21/2,718 vs 25/2,353].						
Infections and infestations	One case series[16] (Haber 2018) of reports following single antigen thimerosal-containing Hepatitis B vaccine in U.S. infants aged <1 month in VAERS between 2005 - 2015 reported 4.6% (11/240) non-death serious reports coded using the Medical Dictionary for Regulatory Activities as**Error! Bookmark not defined.** "infections and infestations".	1 DES[16] (Haber 2018) (N = 240)	Some concerns[aa]	No concerns	No concerns	No concerns	Very low confidence

Table 13. GRADE Table: Local injection site outcomes and administration of the Hepatitis B Vaccine in the first 30 days of life

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
All Local injection site reactions	**Evidence from five RCTs suggests no difference in parent reported local injection site reactions including pain or soreness, swelling, or redness or erythema in the first 5 days post-vaccination among infants vaccinated with Engerix-B in the first five days of birth compared with combination vaccines or other Hepatitis B vaccines that were administered at birth or later. One RCT[8] suggested an increase in local side effects when comparing doses of Recombivax administered at 2 months of age compared with birth or 18 months.**	**5 RCT[8,9,13,14,18] (N = 1,626)**	**Some concerns[n]**	**No concerns**	**No concerns**	**No concerns**	**Moderate confidence**
Local side effects	One RCT[8] of Egyptian infants, compared the outcome of local side effects (e.g., local soreness, or temporary redness/induration at the injection site) 1 week after vaccination among infants randomized to administration of the first of dose of Recombivax immediately after delivery, at two months of age, or at 18 months of age, and reported a higher proportion of local side effects among those who received the vaccine at two months of age (2.8% (5/178) at birth, vs 7.2% (12/167) at two months, vs. 1.6% (3/191) at 18 months]. No relationship was found between side effects and weight or prematurity.	1 RCT[8] (N = 536)	Serious concerns[bb]	No concerns	No concerns	No concerns	Low confidence

[aa] No comparison group

[bb] Inadequate randomization, unclear allocation concealment and blinding

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
Pain with movement or pressure	One RCT[9] of healthy Israeli infants, reported no difference in parent reports of pain with movement and pain with pressure within 5 days of vaccination among infants who received thimerosal-containing Engerix-B within 24 hours of birth compared with those who received thimerosal-containing BioHepB within 24 hours of birth [4/52 (7.7%) vs. 4/153 (2.6%)] and [4/52 (7.7%) vs. 2/153 (1.3%)]. The HepB vaccine BioHepB is not approved for use in the United States.	1 RCT[9] (N = 205)	Serious concerns[cc]	Some concerns[dd]	No concerns	No concerns	Very low confidence
Pain or soreness	Two RCT reported a lower proportion of infants with soreness or pain with the administration of Hepatitis B vaccine alone at birth compared to the combination vaccines at any age. • One RCT[18] of healthy, full term Australian infants aged five days or less reported a higher proportion of parent identified pain at the injection site among those who received co-administration of thimerosal-containing Energix-B vaccine and an investigational acellular pertussis vaccine compared with thimerosal-containing Energix-B vaccine alone within 120 hours of birth [41/208 (20%) vs. 14/150 (9%)]. One grade 3 reaction, defined as crying when the limb was moved or pain that prevents daily activities, was reported in the co-administration group. • One RCT of healthy U.S. infants[14] reported a higher proportion parent reports of soreness at the injection site within three days of vaccination with the first lifetime dose of a HBV Vaccine among infants who received Engerix-B alone within 4 days of birth compared with those who received DTaP-HepB or DT, at 2 months of age compared with those (8.1% vs. 35.7%). One single group cohort[11] of 117 healthy neonates in Colombia who received the thimerosal-containing Engerix-B Hepatitis B vaccine at birth reported 7 (6%) infants experienced pain and 5 (4.3%) experienced severe pain that resolved during the 4 days following vaccination.	2 RCT[14,18] (N = 623) 1 Cohort[11] (N = 117)	Some concerns[ee] Some concerns[ff]	No concerns Some concerns[h]	No concerns No concerns	No concerns No concerns	Low confidence Very low confidence
Redness or erythema	Three RCTs suggest no difference in redness or erythema at the injection site when comparing thimerosal-containing Energix-B vaccine at birth with thimerosal-containing Energix-B at one month.	3 RCT[9,14,18] (N = 841)	Some concerns[gg]	No concerns	No concerns	No concerns	Low confidence

[cc] Unclear allocation concealment; absence of statistical analyses and reporting on protocol deviations

[dd] Small sample size

[ee] Unclear allocation concealment and no blinding, unanalyzed loss to follow up

[ff] Measurement & misclassification: -1 for unclear day of dosing; -1 for no comparator group

[gg] Unclear allocation concealment and no blinding

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
	• One RCT[14] reported no difference in the proportion of parent reports of redness at the vaccination site within 3 days of vaccination with the first lifetime dose of HBV vaccine among infants who received Engerix-B within 4 days of birth or among those who received DTaP-HepB vaccines at 2 months of age (8.8% vs 11.6%); no grade 3 reactions were reported. • One RCT of Israeli infants[9] reported no redness or erythema within 5 days of vaccination among infants randomized to receipt of Engerix-B or BioHepB within 24 hours of birth (0/52 vs. 0/153). The HepB vaccine BioHepB is not approved for use in the United States. • One RCT[18] of Australian infants, 57/208 (27%) infants who were co-administered an acellular pertussis vaccine and Engerix-B within 120 hours of birth and 30/150 (20%) infants who received Engerix-B alone within 120 hours of birth experienced injection site erythema within 2 days of vaccination. No grade 3 reactions were reported. In one single group cohort[11] of 117 Columbian neonates who received a thimerosal-containing Engerix-B Hepatitis B birth dose, 13 (11.1%) experienced redness during the 4 days following vaccination; there were no reports of severe redness.	1 DES[11] (N = 117)	Serious concerns[hh]	Some concerns	No concerns	No concerns	Very low confidence
Swelling	Four RCTs reported no difference in the proportion of parent reported swelling for infants who received Engerix-B within 5 days of birth compared with a combination vaccine or a novel vaccine administered in the same timeframe. • In a randomized non-blinded clinical trial[18] of Australian infants, 26/208 (12.5%) infants who received an investigational acellular pertussis vaccine and Engerix-B within 120 hours of birth and 6/150 (4%) infants who received Engerix-B within 120 hours of birth experienced injection site swelling within 2 days of vaccination. No grade 3 reactions were reported. • One RCT[14] of healthy U.S. infants reported a lower proportion of parent reports of swelling at the injection site within three days of the first lifetime dose of a HBV	4 RCT[9,13,14,18] (N = 1,090)	Some concerns[n]	No concerns	No concerns	No concerns	Moderate confidence

[hh] No blinding, unclear sequence allocation, unanalyzed loss to follow up.

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
	Vaccine among those who received Engerix-B alone within 4 days of birth and among infants who received DTaP-HepB vaccines at 2 months of age (0 vs. 16.3%). • One RCT[13] of healthy infants in India, reported no cases of injection site swelling among infants vaccinated with Engerix-B or infants vaccinated with the HepB Gene Vac-B within first 2 wks of life (0/130 vs. 0/132, p=NR). The HepB Gene Vac-B is not approved for use in the United States. • A RCT[9] of Israeli infants reported a higher proportion of swelling at the site within five days of vaccination among infants who received thimerosal-containing Engerix-B within 24 hours of birth compared with those who received BioHepB within 24 hours of birth [4/52 (7.7%) vs. 3/153 (2.0%)] The HepB vaccine BioHepB is not approved for use in the United States. In a single group cohort[11] of 117 neonates in Colombia who received an Engerix-B Hepatitis B birth, there were 5 reports of any swelling (4.3%), and no reports of severe swelling.	1 DES[11] (N = 117)	Serious concerns[ii]	No concerns	No concerns	No concerns	Very low confidence

Table 14. GRADE Table: Neurodevelopmental outcomes and administration of the Hepatitis B Vaccine in the first 30 days of life

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
All Neurodevelopmental outcomes	**The evidence from four studies report inconsistent results on the association between autism or autism spectrum disorder[19-21], Emotional disorders/ Emotional disturbances[19,22] and Tics/ Tic disorders[19,22], and the receipt of an HBV vaccine in the first month of life. The strongest study[19] reported no difference in the adjusted risk of any of these diagnoses among infants in the**	**1 Cohort[19] (N = 110,833)** **4 Case-control[20,22-24] (N = unclear due to**	**No concerns**	**No concerns**	Some concerns[ll]	**No concerns**	**Low confidence**

[ii] Unclear timing of dosing ("at birth") and no comparison group

[ll] Inconsistent results across studies using different inclusion criteria, different analytic approaches, and differences in adjustment for confounding.

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
	U.S. VSD with receipt of Hepatitis B vaccine in the first month of life, while the unadjusted case control studies[22-24] examined the same infants in the U.S. VSD and the cross-sectional study of parent interviews reported an increase in the unadjusted odds or adjusted risk of these diagnoses with exposure to Hepatitis B vaccine in the first month of life. **Results from one cohort[19], suggest no difference in the adjusted risk of attention deficit disorder (ADD), coordination disorder, speech or language delay, eating disorders, emotional disturbances, other childhood psychosis, sleep disorders, or stammering among infants in the U.S. VSD** **Results from one case-control study[24] of children in the U.S. VSD suggests an increase in the risk of diagnoses for specific delays in development among infants who were exposed to a dose of thimerosal-containing Hep B vaccine in the first 30 days of life compared to those who were not**	**overlapping populations)** **1 Cross-sectional[21] (N = 7,381)**	**Serious concerns[jj]** **Serious concerns[kk]**	**No concerns** **No concerns**		**No concerns** **No concerns**	**Very low confidence** **Very low confidence**
Attention deficit disorder (ADD)	One cohort study[19] of U.S. infants at three VSD sites (HMO A-C) reported no difference in the risk of an ADD diagnosis after the first year of life with the receipt of a thimerosal-containing Hepatitis B vaccine within 1 month of age, when stratified by HMO, year of birth, and sex, and adjusted for birth weight (HMO A: aHR: 0.92 (95%CI 0.52-1.59)); adjusted for clinic (HMO B: aHR: 0.90 (95%CI 0.74-1.10)) (HMO C: aHR: 0.88 (95CI% 0.53-1.48)).	1 Cohort[19] (N = 140,887)	No concerns	No concerns	No concerns	No concerns	Low confidence
Autism/Autism Spectrum Disorder	Results from three studies are inconsistent on the relationship between the receipt of HBV vaccine in the first month of life and autism. The largest and strongest study[19] (N = 110,833) suggested no relationship between the adjusted risk of a medical record of an autism diagnosis and HBV vaccine in the first month of life, while one case-control study[20] and one cross sectional study that did not adjust for age of administration, year of administration, or health seeking behaviors, suggested an increase in the odds of HBV vaccination among children with an autism diagnosis[20] (N=25,939) or parent report of an autism diagnosis in boys[21] (N=7,381).	1 Cohort[19] (N = 110,833) 1 Case-control[20] (N = 25,939)	No concerns	No concerns No concerns	Some concerns[oo]	No concerns No concerns	Low confidence Very low confidence

[jj] No adjustment age at administration, birthweight, year of administration, cases and controls taken from different study years.

[kk] No adjustment for birthweight, age at administration, year of administration taken from different study years, outcome is not medically validated.

[oo] Inconsistent results across studies using different inclusion criteria, different analytic approaches, and differences in adjustment for confounding.

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
	• One cohort study[19] of U.S. infants in VSD site HMO B reported no difference in the risk of an autism diagnosis after the first year of life with the receipt of a thimerosal-containing Hep B vaccine within 1 month of age, when stratified by year of birth, and sex, and adjusted for birth weight and clinic (HMO B: aHR: 1.16 (95%CI 0.78-1.71)). Measures of association not assessed for HMOs with <50 cases. • One case-control study[20] of children in the U.S. VSD (KPNW, KPC), suggested the unadjusted odds of an exposure to a dose of thimerosal-containing HepB vaccine within the first month of life was greater among children with an autism spectrum disorder diagnosis compared to children without an autism spectrum diagnosis [OR: 2.18; (95%CI: 1.74-2.73); p<0.00001; 155/302 vs 8161/25632]. A cross-sectional study[21] of U.S. boys aged 3-17 years suggested the odds of a parent report of an autism diagnosis was greater among boys aged 3-17 years of age who received the Hepatitis B vaccine within 1 month of age born before 1999, when compared to late- or never- vaccinated boys when adjusting for race and ethnicity, family structure, and maternal education [aOR: 3.002; (95%CI: 1.109-8.126); p=0.031].	1 Cross-sectional[21] (N = 7,381)	Serious concerns[mm] Serious concerns[nn]	No concerns		No concerns	Very low confidence
Coordination Disorder	One cohort study[19] of U.S. infants in VSD site HMO A suggested a potential increase in the risk of a coordination disorder after the first year of life with the receipt of a thimerosal-containing Hep B vaccine within 1 month of age, when stratified by year of birth, and sex, and adjusted for birth weight (HMO A: aHR: 1.67 (95%CI 0.78-3.57)). Measures of association not assessed for HMOs with <50 cases.	1 Cohort[19] (N = 13,337)	No concerns	No concerns	No concerns	No concerns	Low confidence
Speech or language delay	One cohort study[19] of U.S. infants in three VSD sites (HMO A-C) reported no difference in the risk of an speech or language delay diagnosis after the first year of life with the receipt of a thimerosal-containing Hep B vaccine within 1 month of age, when stratified by HMO, year of birth, and sex, and adjusted for birth weight (HMO A: aHR: 1.14 (95%CI 0.88-1.46)); adjusted for clinic (HMO B: aHR: 1.03 (95%CI 0.91-1.17)); (HMO C: HR: 0.91 (95%CI 0.79-1.04)).	1 Cohort[19] (N = 140,887)	No concerns	No concerns	No concerns	No concerns	Low confidence
Eating disorders	One cohort study[19] of U.S. infants in VSD site HMO B reported no difference in the risk of an eating disorder diagnosis after the	1 Cohort[19] (N = 110,833)	No concerns	No concerns	No concerns	No concerns	Low confidence

[mm] No adjustment age at administration, birthweight, year of administration, cases and controls taken from different study years.

[nn] No adjustment for birthweight, age at administration, year of administration taken from different study years, outcome is not medically validated.

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
	first year of life with the receipt of a thimerosal-containing Hep B vaccine within 1 month of age, when stratified by year of birth, and sex, and adjusted for birth weight and clinic HMO B: aHR: 0.90 (95%CI 0.50-1.61). Measures of association not assessed for HMOs with <50 cases.						
Emotional disorders/ Emotional disturbances	One cohort study[19] of U.S. infants in two VSD sites (HMO A,B) reported no difference in the risk of an emotional disturbances diagnosis (313.8) after the first year of life with the receipt of a thimerosal-containing Hep B vaccine within 1 month of age, when stratified by HMO, year of birth, and sex, and adjusted for birth weight (HMO A: aHR: 1.00 (95%CI 0.42-2.36)); adjusted for clinic (HMO B: aHR: 0.76 (95%CI 0.54-1.07)). Measures of association not assessed for HMOs with <50 cases. One case-control study[22] of children in the VSD (KPNW, KPC, KPNCK) between 1991 – 2000, suggested that the unadjusted odds of an exposure to a thimerosal-containing HepB vaccine within the first month of life was greater among children with ICD-9 diagnosis code for emotional disorder (313.xx) than children without that code in their records [OR: 1.34; 95 %CI: 1.12-1.60; p<0.005, 204/517 vs 9003/27,491]. This association remained consistent in a sub-analysis restricted to males [OR: 1.36; 95% CI: 1.11, 1.66); p<0.005; 158/399 vs 4568/14,013) but not females [OR: 1.30; (95% CI: 0.90, 1.89); p=0.15, 46/118 vs 4435/13,478].	1 Cohort[19] (N = 124,170) 1 case-control study[22] (n=28,008)	No concerns Serious concerns[pp]	No concerns No concerns	Some concerns[qq]	No concerns No concerns	Low confidence Very low confidence
Other childhood psychosis	One cohort study[19] of U.S. infants in VSD site HMO B reported no difference in the risk of a otherhood childhood psychosis diagnosis after the first year of life with the receipt of a thimerosal-containing Hep B vaccine within 1 month of age, when stratified by year of birth, and sex, and adjusted for birth weight and clinic HMO B: aHR: 1.03 (95%CI 0.60-1.74). Measures of association not assessed for HMOs with <50 cases.	1 Cohort[19] (N = 110,833)	No concerns	No concerns	No concerns	No concerns	Low confidence
Sleep disorders	One cohort study[19] of U.S. infants in three VSD sites (HMO A-C) reported no difference in the risk of a sleep disorder diagnosis after the first year of life with the receipt of a thimerosal-containing Hep B vaccine within 1 month of age, when stratified by HMO, year of birth, and sex, and adjusted for birth weight (HMO A: aHR: 0.79 (95%CI 0.38-1.61)); adjusted for clinic (HMO B: aHR: 1.24 (95%CI 0.80-1.93)); (HMO C: HR: 0.97 (95%CI 0.79-1.19)).	1 Cohort[19] (N = 140,887)	No concerns	No concerns	No concerns	No concerns	Low confidence

[pp] No adjustment age at administration, birthweight, year of administration, cases and controls taken from different study years.

[qq] Inconsistent results across studies using different inclusion criteria, different analytic approaches, and differences in adjustment for confounding.

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
Specific delays in development	One retrospective cohort study[24] of children in the VSD born between 1991 – 1994, suggested that the risk of specific delays in development (ICD-9 code 315.xx) was greater among children who were exposed to a thimerosal-containing HepB vaccine within the first month of life compared to children who were not exposed to a thimerosal-containing HepB vaccine in the first month of life [RR: 1.22, (95% CI: 1.12, 1.33), p<0.001, 828/18,637 vs 1127/31,198]. This association remained consistent in a sub-analysis restricted to males [RR: 1.23, (95%CI: 1.11, 1.37), p<0.001, 567/9514 vs 771/16,110] and females [RR: 1.21; (95% CI: 1.03, 1.41); p<0.05, 261/9,122 vs 356/15,088].	1 Cohort study[24] (n=49,835)	Serious concerns[rr]	No concerns	No concerns	No concerns	Very low confidence
Stammering	One cohort study[19] of U.S. infants in two VSD sites (HMO A-C) reported no difference in the risk of a stammering diagnosis after the first year of life with the receipt of a thimerosal-containing Hep B vaccine within 1 month of age, when stratified by HMO, year of birth, and sex, and adjusted for birth weight (HMO A: aHR: 0.89 (95%CI 0.40-1.97)); and adjusted for clinic in HMO B (HMO B: aHR: 0.61 (95%CI 0.33-1.14)); (HMO C: HR: 0.77 (95%CI 0.47-1.26)).	1 Cohort[19] (N = 140,887)	No concerns	No concerns	No concerns	No concerns	Low confidence
Tic Disorder, Tics	One cohort[19] and one case control[23] examined infants in the U.S. VSD during the same time period and reported inconsistent results. When stratifying results by location, year of birth, sex, HMO and clinic, there was no difference in the risk of Tic disorder among infants who received a dose of thimerosal-containing Hep B vaccine in the first month of life, compared to those who did not[19]. However, a case control[23] using different enrollment criteria and not adjusting for confounding factors. • One cohort study[19] of U.S. infants in three VSD sites between 1991 – 1998 (HMO A-C) reported no difference in the risk of a tics diagnosis after the first year of life with the receipt of a thimerosal-containing Hep B vaccine within 1 month of age, when stratified by HMO, year of birth, and sex, and adjusted for birth weight (HMO A: aHR: 1.25 (95%CI 0.47-3.29)); adjusted for clinic (HMO B: aHR: 0.85 (95%CI 0.55-1.30)); (HMO C: HR: 0.93 (95%CI 0.45-1.92)).	1 Cohort[19] (N = 140,887) 1 Case-control[23] (N = 28,360)	No concerns Serious Concerns[ss]	No concerns No concerns	Some concerns[tt]	No concerns No concerns	Low confidence Very low confidence

[rr] No adjustment age at administration, birthweight, year of administration, cases and controls taken from different study years.

[ss] Unadjusted for confounding of age at administration, birthweight, healthcare seeking behavior, duration of follow up, and different inclusion criteria & study years for each group.

[tt] Inconsistent results across studies using different inclusion criteria, different analytic approaches, and differences in adjustment for confounding.

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
	• One case-control study[23] of children in the VSD (KPNW, KPC, NCK) between 1991 - 2000, suggested the odds of an exposure to thimerosal-containing HepB vaccine within the first month of life was greater among children with a medical diagnosis code for a tic disorder diagnosis than among those with no tic disorder diagnosis[OR: 1.59; (95%CI: 1.29-1.98); p<0.00001; 151/344 vs 9222/28016]. This association remained consistent in a sub-analysis restricted to males [OR: 1.65; (95%CI: 1.29-2.12); p<0.0001; 113/253 vs 4697/14327], but not females [OR: 1.45; (95%CI: 0.95-2.21); p=0.09; 38/91 vs 4525/13,689].						

Table 15. GRADE Table: Neurologic outcomes and administration of the Hepatitis B Vaccine in the first 30 days of life

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
All Neurologic outcomes	**The evidence from cohort[6] suggested there is no difference in the risk of seizures and neurologic disease other than seizures among infants receiving with Hep B vaccine in the first 21 days of life, compared to those who did not, and this did not change when restricted to those vaccinated in the first day of life.**	**1 Cohort[6] (N = 5,655)**	**No concerns**	**No concerns**	**No concerns**	**No concerns**	**Low confidence**
	One case control study[23] did not one case series suggested a lower odds of exposure to a thimerosal-containing hep B vaccine in the first 30 days of life among infants diagnosed with cerebral degeneration compared to those who were not diagnosed.	**1 Case-control[23] (N = 136,536)**	**Serious concerns[uu]**	**No concerns**	**No concerns**	**No concerns**	**Very low confidence**
	Two case series[12,16] identified reports of abnormal CSF, convulsions, and nervous system disorders among the reports in the U.S. VAERS between 1991-1995 and 2005 – 2015.	**2 Case Series[12,16] (N = 300)**	**Some concerns[vv]**	**No concerns**	**No concerns**	**No concerns**	**Very low confidence**

[uu] Unadjusted for confounding of age at administration, birthweight, healthcare seeking behavior, duration of follow up, and different inclusion criteria & study years for each group.

[vv] Descriptive study, no comparison

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
Abnormal CSF	In one case series of reports[12] following single antigen thimerosal-containing Hepatitis B vaccine in U.S. infants aged <1 month in VAERS between 1991-1995, there were 4 (6.7%) serious reports of abnormal CSF.	1 Case Series[12] (N = 60)	Some concerns[ww]	No concerns	No concerns	No concerns	Very low confidence
Cerebral degeneration	One case-control study[23] of children in the VSD (KPNW, KPC, NCK), suggested the unadjusted odds of exposure to thimerosal-containing Hepatitis B vaccine within the first month of life was lower among children diagnosed with cerebral degeneration than among those without a diagnosis of cerebral degeneration [OR: 0.43; (95%CI: 0.36-0.52); p<0.00001; 175/647 vs 62637/135,889].	1 Case-control[23] (N = 136,536)	Serious concerns[xx]	No concerns	No concerns	No concerns	Very low confidence
Convulsions	One case series[12] of 60 VAERS reports for neonates <0.1 years of age who received a thimerosal-containing Hepatitis B vaccine between 1991 – 1995 reported 6 (10%) reports of convulsions, 4 of which were considered serious.	1 DES[12] (N = 60)	Some concerns[q]	No concerns	No concerns	No concerns	Very low confidence
Seizure	One cohort[6] of normal birthweight, full term U.S. infants in the VSD (NCK) suggested there is no difference in the risk of seizures in the first three weeks of life when comparing infants with a record of receiving thimerosal-containing Hepatitis B vaccine in the first 21 days of life to infants with no record of Hepatitis B vaccination [RR: 0.18 (95%CI: 0.02-1.6); p=0.17; 1/3,302 vs 4/2,353]. This remained consistent in a sub-analysis restricting the infants with a record of Hepatitis B vaccination on the day of birth or day after birth compared with infants with no record of Hepatitis B vaccination [RR: 0.22; (95%CI: 0.02-1.9); p=0.19; 1/2,718 vs 4/2,353].	1 Cohort[6] (N = 5,655)	No concerns	No concerns	No concerns	No concerns	Low confidence
Nervous system disorders	In one case series[16] of reports following single antigen thimerosal containing Hepatitis B vaccine in U.S. infants aged <1 month in the VAERS between 2005 - 2015, 6.3% (15/240) were non-death serious reports coded using the Medical Dictionary for Regulatory Activities as "Nervous Systems Disorders".	1 DES[16] (N = 240)	Some concerns[yy]	No concerns	No concerns	No concerns	Very low confidence
Neurologic disease, other than seizure	One cohort[6] of normal birthweight, full term U.S. infants in the VSD (NCK) suggested there is no difference in the	1 Cohort[6] (N = 5,655)	No concerns	No concerns	No concerns	No concerns	Low confidence

[ww] Descriptive study, no comparison

[xx] Unadjusted for confounding of age at administration, birthweight, healthcare seeking behavior, duration of follow up, and different inclusion criteria & study years for each group.

[yy] Descriptive study, no comparison

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
	risk of neurologic disease in the first three weeks of life when comparing infants with a record of receiving thimerosal-containing Hepatitis B vaccine in the first 21 days of life to infants with no record of Hepatitis B vaccination [RR: 1.4 (95%CI: 0.3-7.8); p=0.99; 4/3,302 vs 2/2,353]. This remained consistent in a sub-analysis restricting the infants with a record of Hepatitis B vaccination on the day of birth or day after birth compared with infants with no record of Hepatitis B vaccination [RR: 1.7; (95%CI: 0.3-9.4); p=0.69; 4/2,718 vs 2/2,353].						

Table 16. GRADE Table: Cardiopulmonary outcomes and administration of the Hepatitis B Vaccine in the first 30 days of life

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
All Cardiopulmonary outcomes	**The evidence from one cohort[7] suggests that receipt of Hepatitis B vaccine in the first 24 hours of life is not associated with an increase in the risk of bronchopulmonary dysplasia.** **The evidence from one case series[12] suggests that between 1991-1995, 13 of 60 events in VAERS were cardiopulmonary (including apnea, bradycardia, and cyanosis).**	**2 studies** **1 Cohort[7] (N = 818)** **1 DES[12] (N = 60)**	**No concerns** **Some concerns[zz]**	**No concerns** **No concerns**	**No concerns** **No concerns**	**No concerns** **No concerns**	**Low confidence** **Very low confidence**
Bronchopulmonary dysplasia	One cohort[7] of extremely preterm infants (<29 wks gestation) in Australia's Surveillance of Adverse Events Following Immunization in the Community suggested there is a reduction in the adjusted risk of bronchopulmonary dysplasia when comparing infants with a record of receiving hepatitis b vaccine within 24 hours of birth to infants with no record [aRR: 0.83; (95%CI: 0.68-1.0); 155/306 vs 317/512].	1 Cohort[7] (N = 818)	No concerns	No concerns	No concerns	No concerns	Low confidence
Apnea	In a case series[12] of 60 VAERS reports for neonates <0.1 years of age who received a thimerosal-containing Hepatitis B vaccine between 1991 – 1995 there were 5 (8.3%) reports of apnea, 3 of which were considered serious.	1 DES[12] (N = 60)	Some concerns[t]	No concerns	No concerns	No concerns	Very low confidence
Bradycardia	In a case series[12] of 60 VAERS reports for neonates <0.1 years of age who received a thimerosal-containing Hepatitis B vaccine between 1991 - 1995, there was 1 (1.7%) serious report of bradycardia.	1 DES[12] (N = 60)	Some concerns[t]	No concerns	No concerns	No concerns	Very low confidence

[zz] No comparison group

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
Cyanosis	In a case series[12] of 60 VAERS reports for neonates <0.1 years of age who received a thimerosal-containing Hepatitis B vaccine between 1991 - 1995, there were 7 (11.7%) reports of cyanosis, 5 of which were considered serious.	1 DES[12] (N = 60)	Some concerns[t]	No concerns	No concerns	No concerns	Very low confidence

Table 17. GRADE Table: Systemic reactions and administration of the Hepatitis B Vaccine in the first 30 days of life

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
All Systemic Reactions	**The evidence[8-14,18] suggested that systemic reactions do occur after vaccination, and there may be no difference in the occurrence of some outcome when comparing infants vaccinated with a Hepatitis B dose in the first 30 days of life compared with those who receive a different vaccine, or a Hepatitis B vaccine later or never. Outcomes for which the evidence suggests there is no difference include fever[8-14,18], rash[13], constipation[13], diarrhea[8-10,12-14,18], unusual crying[14,18], and vomiting[13,14,18].** **Systemic reactions for which the evidence reported inconsistent results include anorexia/ decreased appetite/ feeding issues[9 14,18] and restlessness/ sleeping less[14,18]. The differences in these outcomes may be due to parent perceptions (all were based on parent reports), differences in vaccines, or differences in outcome definitions used across these studies.** **Evidence was sufficient to determine that agitation[12] occurs in 13 of 60 neonatal U.S. VAERS reports between 1991-1995, but not sufficient to determine if this is different from the rate of occurrence in the general neonatal population.**	**5 RCT[8,9,13,14,18] (N = 1,627)** **1 cohort[10] (N = 10,829)** **2 DES[11,12] (N = 177)**	**Some concerns[aaa]** **Serious concerns[bbb]** **Some concerns[ccc]**	**No concerns** **No concerns** **No concerns**	**No concerns** **No concerns** **No concerns**	**No concerns** **No concerns** **No concerns**	**Moderate confidence** **Very low confidence** **Very low confidence**
Agitation	In a case series[12] of 60 VAERS reports for neonates <0.1 years of age who received a thimerosal-containing Hepatitis B vaccine between 1991 – 1995, there were 13 (21.7%) reports of agitation, 7 of which were considered serious.	1 DES[12] (N = 60)	Some concerns[ccc]	No concerns	No concerns	No concerns	Very low confidence

[aaa] Unclear allocation concealment and no blinding

[bbb] No adjustment for confounding, unclear presence of outcomes at start of study

[ccc] Descriptive study, no comparator

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
Anorexia/Decreased appetite/ Feeding Issues	Three RCTs of healthy infants reported inconsistent results for the outcome of decreased appetite. That may be attributable to differences in the comparator vaccine or the timing of comparator vaccine or the differences in outcome definitions used in each study. • One RCT[14] of full-term U.S. infants reported a higher proportion of decreased appetite within 3 days of vaccination among infants who received DTPa-HepB, OPV, and Hib vaccines at 2 months of age compared with those who received Engerix-B within 4 days of birth [25.6% of 129 vs 14% of 136;]. • In a RCT of Israeli infants[9], 0/52 infants who received Engerix-B within 24 hours of birth and 3/153 (2.0%) who received BioHepB within 24 hours of birth experienced anorexia within 5 days of vaccination. The HepB vaccine BioHepB is not approved for use in the United States. • In a randomized non-blinded clinical trial of Australian infants[18], 28/221 (13%) infants who received an investigational acellular pertussis vaccine and Engerix-B within 120 hours of birth and 17/103 (17%) infants who received Engerix-B within 120 hours of birth experienced feeding issues within 2 days of vaccination. One grade 3 feeding reaction (defined as preventing normal activities or requiring significant medical intervention) was reported among the 103 infants (0.9%) who received only Engerix within 120 hours of birth. One single group cohort of 117 Columbian neonates[11] who received an Engerix-B Hepatitis B birth dose, 3 (2.6%) experienced a loss of appetite during the 4 days following vaccination,1.7% (2/117) were considered severe. In one single group cohort of 117 Columbian neonates who received an Engerix-B Hepatitis B birth dose (Lopez 2002), 3 (2.6%) experienced a loss of appetite during the 4 days following vaccination,1.7% (2/117) were considered severe.	3 RCTs[9 14,18] (N = 794) 1 DES[11] (N = 117)	Some concerns[ddd] Some concerns[eee]	No concerns No concerns	Some concerns[fff]	No concerns No concerns	Moderate confidence Very low confidence

[ddd] Unanalyzed loss to follow up

[eee] Descriptive study, no comparator, unclear timing of dosing ("at birth")

[fff] Inconsistent results across studies using different inclusion criteria, different analytic approaches, and differences in adjustment for confounding.

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
Constipation	One RCT of healthy infants in India[13] reported no cases of constipation in infants vaccinated with Engerix-B in the first 2 weeks of life or in infants vaccinated with HepB Gene Vac-B within first 2 weeks of life (0/130 vs. 0/132). The HepB Gene Vac-B is not approved for use in the United States.	1 RCT[13] (N = 262)	No concerns	No concerns	No concerns	No concerns	High confidence
Diarrhea	Four RCTs suggested no difference in the proportion of diarrhea cases among infants who received the HBV vaccine in the first 2 weeks of life or less, and those who receive the dose later, or a different vaccine. • One RCT of Israeli infants[9], reported no difference in diarrhea or vomiting within 5 days of vaccination among infants who received Engerix-B within 24 hours of birth and who received BioHepB within 24 hours of birth0/52 vs. 1/153 (0.64%). The HepB vaccine BioHepB is not approved for use in the United States. • One RCT[14] of full-term U.S. infants reported no difference in the proportion of parents reporting diarrhea within 4 days of birth when comparing infants who received Engerix B within 3 days of birth and infants who received DTaP-HepB, OPV, and Hib vaccines at 2 months of age, (8.1% vs. 10.1%). There was no difference in the proportion experiencing a grade 3 reaction (defined as preventing normal activities) (0.7% vs. 0). • One RCT of healthy infants in India[13] reported no cases of loose motions in infants vaccinated with Engerix-B in the first 2 weeks of life or in infants vaccinated with HepB Gene Vac-B within first 2 weeks of life (0/130 vs. 0/132, p=NR). The HepB Gene Vac-B is not approved for use in the United States. • In a RCT of Australian infants[18], 38/221 (17.0%) infants who received an investigational acellular pertussis vaccine and Engerix-B within 120 hours of birth and 12/103 (12%) infants who received Engerix-B within 120 hours of birth experienced	4 RCT[9,13,14,18] (N = 927) 1 DES[12] (N = 60)	Some concerns[ggg] Some concerns[hhh]	No concerns No concerns	No concerns No concerns	No concerns No concerns	Low confidence Very low confidence

[ggg] Unclear allocation concealment, no blinding, unclear assessment of loss to follow up

[hhh] Descriptive study, no comparator

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
	diarrhea within 2 days of vaccination. No grade 3 reactions (defined as preventing normal activities or requiring significant medical intervention) were reported. In one case series[12] of 60 VAERS reports for neonates <0.1 years of age who received a thimerosal-containing Hepatitis B vaccine between 1991 – 1995, there was 1 report of diarrhea, which was not categorized as serious.						
Drowsiness or sleeping more	Two RCTs report inconsistent results for increased drowsiness when comparing Engerix B as a birth dose with DTPA-HepB[14] or both acellular pertussis and Engerix-B vaccines[18] at 2 months of age. Inconsistencies may be explained by the different comparison vaccine or by the different outcome definitions of "increased sleep" and "drowsiness" • One RCT[14] of full-term U.S. infants reported a lower proportion of parents reporting increased infant sleep within 3 days of birth when comparing infants who received Engerix B within 4 days of birth and infants who received DTPa-HepB, OPV, and Hib vaccines at 2 months of age, (32.4% vs. 40.3%). There was higher proportion of infants receiving Engerix B within 4 days of birth whose parents reported them experiencing a grade 3 reaction (defined as preventing normal activities) (2.9% vs. 0.8%). • One RCT of Australian infants[18] reported a higher proportion of parents reported drowsiness within 2 days of vaccination among parents of infants who received Engerix-B within 120 hours of birth compared with infants who received an investigational acellular pertussis vaccine and Engerix-B within 120 hours of birth and [29/103 (28%) vs. 39/221 (18%)]. There was no difference in drowsiness of grade 3 severity (defined as preventing normal activities or requiring significant medical intervention) between those	2 RCTs[14,18] (N = 591) 1 DES[11] (N = 117)	Some concerns[iii] Some concerns[jjj]	No concerns No concerns	Some concerns[kkk]	No concerns No concerns	Very low confidence Very low confidence

[iii] Unclear allocation concealment and no blinding

[jjj] Descriptive study, no comparator

[kkk] Inconsistent results across studies using different inclusion criteria, different analytic approaches, and differences in adjustment for confounding.

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
	receiving the both acellular pertussis and Engerix-B vaccines and by 1 (0.9%) of the infants receiving only Engerix-B vaccines at birth (1/221 (0.5%) vs. 1/103 (0.9%). Among a single group cohort of 117 Columbian neonates[11] who received an Engerix-B Hepatitis B birth dose (Lopez 2002), 6 (5.1%) experienced drowsiness during the 4 days following vaccination; 1 (0.9%) was reported to be severe.						
Fever	Five RCT suggested no difference in parent reports of fever between infants vaccinated with HBV vaccines in the first two weeks of life and infants vaccinated with the same vaccine HBV vaccine at later ages, different HBV vaccines at the same age, or different HBV and HBV combination vaccines at later ages. • One RCT of Egyptian infants[8], reported no difference in parent reports of fever (reported as 1-2 days of low-grade fever ≤102^{o}F) among those vaccinated with Recombinant HB vaccine immediately after birth (5.6% n=178), at 2 months (7.2%, n=167), or 18 months of age (2.1%, n=191). No relationship was found between side effects and weight or prematurity. • In a randomized non-blinded clinical trial of Australian infants[18], reported no difference in parent reports of fever ≥38^{o}C within 2 days of vaccination among infants who received an investigational acellular pertussis vaccine and Engerix-B within 120 hours of birth and infants who received Engerix-B within 120 hours of birth (0/221 vs 1/138 (0.7%)). No fevers ≥39^{o}C were reported among participants in either arm. • One RCT of Israeli infants[9] reported no difference in a temperature ≥38^{o}C within 5 days of vaccination infants who received Engerix-B within 24 hours of birth compared with those who received BioHepB within 24 hours of birth [0/52 vs. 2/153 (1.3%)]. The HepB vaccine BioHepB is not approved for use in the United States.	5 RCT[8,9,13,14,18] (N = 1,627)	Some concerns [III]	No concerns	No concerns	No concerns	Low confidence

[III] Unclear allocation concealment and no blinding

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
	• One RCT of full-term U.S. infants[14] reported no difference in fever (defined as rectal temperature ≥38^{o}C within 4 days of vaccination among infants who received Engerix B within 3 days of birth and infants who received DTPa-HepB, OPV, and Hib vaccines at 2 months of age, (5.9%, n = 136 vs. 14.7%, n=129). There was also no difference in parent reports grade 3 reaction (defined as temperature >39.5^{o}C) (0% vs. 0.8%). • An RCT of healthy infants in India[13] reported no difference in parent-reported fever (defined as axillary temperature ≥38^{o}C) in infants vaccinated with Engerix-B in the first 2 weeks of life and infants vaccinated with HepB Gene Vac-B within first 2 weeks of life [6/130 (4.6%) vs. 4/132 (3.0%)]. In a cohort study of full-term Israeli infants[10], 68/5,819 (1.2%) full-term infants receiving hepatitis B vaccination and 27/5,010 (0.54%) full-term infants not receiving hepatitis B vaccine had a birth hospitalization discharge diagnosis of "neonatal fever" above 37.5 C (p<0.001). Fevers above 38C were noted in 50 (0.9%) of vaccinated infants and 27 (0.54%) of unvaccinated infants (p<0.05). Identifiable causes of fever (e.g. sepsis, dehydration, maternal fever, respiratory distress) were noted among 15 vaccinated infants (0.3%) and 13 unvaccinated infants (0.3%). Unexplained fevers were noted among 35 (0.6%) vaccinated infants and 14 (0.3%) unvaccinated infants (p=0.013). Two single group studies, one cohort and one case series of adverse reports in neonates who received HBV vaccine as a birth does or within 1 month reported identified 18 U.S. VAERS reports of fever between 1991 – 1995, and 13 serious U.S. VAERS reports of fever, and reported 1 severe fever among 117 Columbian neonates, • Among a cohort of 117 Columbian neonates[11] who received an Engerix-B Hepatitis B birth dose, 1 (0.9%) experienced a severe fever during the 4 days following	1 cohort[10] (N = 10,829) 2 DES [11,12] (N = 177)	Serious concerns[mmm]	No concerns	No concerns	No concerns	Very low confidence

[mmm] No adjustment for confounding, unclear presence of outcomes at start of study

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
	vaccination (severe: >39°C axillary or >39.5°C rectal).In a case series[12] of 60 VAERS reports for neonates <0.1 years of age who received a thimerosal-containing Hepatitis B vaccine between 1991 – 1995, there were 18 (30%) reports of fever, 13 of which were considered serious. Median number of days from vaccination to onset of fever was 1 day and mean maximum temperature was 38.9°C (range: 38.0-40.6°C). Of 10 infants with follow-up from fever, all 10 had recovered.		Some concerns[nnn]	No concerns	No concerns	No concerns	Very low confidence
Irritability or fussiness	Three RCTs report inconsistent results for irritability or fussiness among infants vaccinated with Engerix B within 24h[9], 3 days[14], and 120 hours of birth[18]. These differences could be due to timing of birth dose, differences in outcome definitions, or comparison vaccine. • One RCT[14] of full-term U.S. infants reported a lower proportion of parents reporting irritability or fussiness within 3 days of vaccination when comparing infants who received Engerix B within 4 days of birth and infants who received DTPa-HepB, OPV, and Hib vaccines at 2 months of age, (22.1% vs. 54.3%). • One randomized non-blinded clinical trial of Australian infants[18] reported no difference in irritability within 2 days of vaccination among infants who received an investigational acellular pertussis vaccine and Engerix-B within 120 hours of birth compared with infants who received Engerix-B within 120 hours of birth [54/221 (24.0%) vs.21/103 (20%)]. There was also no difference in Grade 3 irritability reactions reported by parents (defined as preventing normal activities or requiring significant medical intervention) [2/221 (0.9%) vs. 1/103 (0.9%)]. • One RCT of Israeli infants[9] reported a higher proportion of irritability among infants who	3 RCT[9,14,18] (N = 794) 1 DES[11] (N = 117)	Serious concerns[ooo] Some concerns[ppp]	No concerns No concerns	Some concerns[qqq]	No concerns No concerns	Very low confidence Very low confidence

[nnn] Descriptive study, no comparator

[ooo] Unclear allocation concealment and no blinding, no assessment of loss to follow up or missing data

[ppp] Descriptive study, no comparator

[qqq] Inconsistent results across studies using different inclusion criteria, different analytic approaches, and differences in adjustment for confounding.

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
	received Engerix-B within 24 hours of birth and [6/52 (11.5%) vs. 5/153 (3.3%)] who received BioHepB within 24 hours of birth experienced irritability within 5 days of vaccination. The HepB vaccine BioHepB is not approved for use in the United States. One cohort of 117 Columbian neonates[11] who received an Engerix-B Hepatitis B birth dose, reported 3 (2.6%) infants experienced irritability during the 4 days following vaccination; 2 cases (1.7%) were reported to be severe.						
Rash	One RCT of healthy infants in India[13] reported no cases of rashes in infants vaccinated with Engerix-B in the first 2 weeks of life or in infants vaccinated with HepB Gene Vac-B within first 2 weeks of life (0/130 vs. 0/132, p=NR). The HepB vaccine BioHepB is not approved for use in the United States. In a case series[12] of 60 VAERS reports for neonates <0.1 years of age who received a thimerosal-containing Hepatitis B vaccine between 1991 – 1995 were 2 serious reports (3.3%) reports of rash that included fever.	1 RCT[13] (N = 262) 1 DES[12] (N = 60)	No Concerns Some concerns[rrr]	No concerns No concerns	No concerns No concerns	No concerns No concerns	High confidence Very low confidence
Restlessness or sleeping less	Two randomized trials of full-term infants reported inconsistent results for restlessness and sleeping less which could be due to the differences in outcome definition, timing of HepB birth dose, or comparator vaccine. • One randomized trial[14] of full-term U.S. infants reported a lower proportion of parents reporting restlessness or sleeping less within 3 days of vaccination when comparing infants who received Engerix B within 4 days of birth and infants who received DTPa-HepB, OPV, and Hib vaccines at 2 months of age, (16.9% vs. 26.4%;). • One randomized non-blinded clinical trial of Australian infants[18] reported was a higher proportion of parent	2 RCT[14,18] (N = 585)	Serious concerns[sss]	No concerns	Some concerns[ttt]	No concerns	Very Low confidence

[rrr] Descriptive study, no comparator

[sss] Unclear allocation concealment and no blinding, no assessment of loss to follow up.

[ttt] Inconsistent proportions for Engerix-B associated symptoms, and inconsistent directionality of comparisons

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
	reports of restlessness within 2 days of vaccination among of infants who received Engerix-B within 120 hours of birth compared to infants who received an investigational acellular pertussis vaccine and Engerix-B within 120 hours of birth [32/103 (31%) vs. 49/221 (22.0%)]. There was no difference in parent reports of grade 3 restless reactions (defined as preventing normal activities or requiring significant medical intervention) [3/103 (3%) vs. 2/221 (1%)].						
Unusual crying	One RCT[14] of full-term U.S. infants reported a no difference in parent reports of unusual crying within 4 days of vaccination when comparing infants who received Engerix-B within 3 days of birth and those who received DTPa-HepB, OPV, and Hib vaccines at 2 months of age (1.5% of 136 infants vs. 3.1% of 129 infants). Results were similar for parent reports of grade 3 unusual crying (defined as preventing normal daily activity) (0 vs. 0.8%).	1 RCT[14] (N = 136)	Some concerns[uuu]	No concerns	No concerns	No concerns	Moderate confidence
Vomiting	Three RCTs suggested no difference in the incidence vomiting when comparing infants who received HBV at birth with those who received HBV 1 month after birth, infants who received a different HBV at birth, or infants who received HBV co-administered with an acellular pertussis vaccine. • One RCT[14] of full-term U.S. infants reported no difference in the incidence of vomiting within 4 days of vaccination as reported by parents between infants who received Engerix-B within 3 days of birth and those who received DTPa-HepB, OPV, and Hib vaccines at 2 months of age (4.4% of 136 infants vs. 7.8% of 129 infants). None reported a grade 3 reaction of vomiting. • One RCT of healthy infants in India[13] reported no cases of vomiting among infants who received Engerix-B or GeneVac-B within 30 days of birth. (0/130 v. 0/132) GeneVac-B is not approved for use in the U.S.	3 RCT[13,14,18] (N = 853)	Some concerns[vvv]	No concerns	No concerns	No concerns	Moderate confidence

[uuu] -1 absence of randomization & blinding, and no assessment of loss to follow up.

[vvv] -1 absence of randomization & blinding, and no assessment of loss to follow up.

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
	• In a randomized non-blinded clinical trial of Australian infants[18], 45/221 (20.0%) infants who received an investigational acellular pertussis vaccine and Engerix-B within 120 hours of birth and 23/103 (24%) infants who received Engerix-B within 120 hours of birth experienced vomiting within 2 days of vaccination. No grade 3 vomiting reactions (defined as preventing normal activities or requiring significant medical intervention) were reported.						

Table 18. GRADE Table: Other outcomes and administration of the Hepatitis B Vaccine in the first 30 days of life

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
All Other outcomes	**One case control[25] reported an increase in the odds of thimerosal-containing Hepatitis B vaccine exposure in the first month of life among children with an ICD9 code for premature puberty in their HMO medical records, compared to children without the code, and when stratified by sex, this increase was seen among females but not males.** **One case series[16] of VAERS reports following single antigen thimerosal containing Hepatitis B vaccine between 2000 – 2015 reported ten reports coded using the Medical Dictionary of Regulatory Activities of "general disorders and administration site conditions" in 15 years (10/240); and an earlier case series[12] of VAERS reports of U.S. neonates with HepB exposure between 1991 – 1995 reported one report for Hyperbilirubenemia /HbSAg+ (1/60).**	**1 case control[25] (N=58,675)** **2 DES[12,16] (n=300)**	**Serious concerns** **Some concerns[www]**	**No concerns** **No concerns**	**No concerns** **No concerns**	**No concerns** **No concerns**	**Very low confidence** **Very low confidence**
Premature puberty	One case-control study[25] of children enrolled in the VSD (KPNW, KPC, KPNC) suggested the odds of exposure to to thimerosal-containing HepB vaccine within the first month of life was greater among children with a medical record of am ICD9 code for premature puberty compared to children who did not [OR: 1.80, (95% CI: 1.51, 2.16), p<0.00001; 255/486 vs 20582/54199]. When stratified by sex, the association was observed among females [OR: 1.87, (95% CI: 1.55, 2.25,	1 case control[25] (N = 58,685)	Serious concerns[xxx]	No concerns	No concerns	No concerns	Very low confidence

[www] Descriptive study, no comparison

[xxx] -2 Very serious concerns for confounding factors such as prematurity or birthweight, age at administration, or year of administration.

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
	p<0.00001), 245/458 vs 9997/26209] but not among males [OR: 0.91, (95% CI: 0.42, 1.98), p>0.99; 10/28 vs 10584/27989].						
General disorders and administration site conditions	One case series[16] of reports following single antigen thimerosal containing Hepatitis B vaccine in U.S. infants aged <1 month in VAERS between 2005 – 2015, reported 4.2% (10/240)- were coded using the Medical Dictionary for Regulatory Activities (MedDRA) as general disorders and administration site conditions".	1 DES[16] (N = 240)	Some concerns[yyy]	No concerns	No concerns	No concerns	Very low confidence
Hyperbilirubenemia /HbSAg+	In a case series[12] of 60 VAERS reports for neonates <0.1 years of age who received a thimerosal-containing Hepatitis B vaccine between 1991-1995, there was 1 (1.7%) serious report of hyperbilirubenemia/HbSAg+.	1 DES[12] (N = 60)	Some concerns[h]	Some concerns[zzz]	No concerns	No concerns	Very low confidence

[yyy] Descriptive study, no comparison

[zzz] Small sample size

C. Extracted Evidence from Included Studies

C.1. Study Characteristics for All Included Studies

Table 19. Characteristics of Studies Meeting Inclusion Criteria

Author Year	Study design	Data Collection Period	Sample size, N	Surveillance System (if Applicable)	Country
Bassily 1995[8]	Randomized Controlled Trial	Not reported	536 infants	Not reported	Egypt
Eriksen 2004[15]	Retrospective cohort	January 1, 1993 - December 31, 1998	361,696 newborns in Kaiser SCK & NCK HMO birth cohort 268 neonatal deaths analyzed for expected and unexpected death	Vaccine Safety Datalink (Kaiser Permanente, Southern California and Kaiser Permanente Northern California)	United States
Gallagher 2010[21]	Cross-sectional	1997-2002	7,381 boys aged 3-17	Not reported	United States
Geier 2013[20]	Case-control	1991-1999	Not reported 25,939 infants in analysis	Vaccine Safety Datalink	United States
Geier 2015[23]	Case control	1991-2000	28,360 (344 cases with tics: 253 male, 91 female; 28,016 controls, 14,327 males, 13,689 females) 136,536 (647 cases with cerebral degeneration: 359 male, 288 female; 135,888 controls, 69,426 males, 66,462 females)	Vaccine Safety Datalink	United States
Geier 2016[24]	Retrospective cohort	1991-2000	49,835 children	Vaccine Safety Datalink	United States
Geier 2017[22]	Nested case control	1991-2000	28,008 children	Vaccine Safety Datalink (Kaiser Permanente North-West and Kaiser Permanente Northern California)	United States
Geier 2018[25]	Case control	1991-2000	54,685 children	Vaccine Safety Datalink	United States
Greenberg 2002[14]	Randomized Trial	Not reported	280 infants	Kaiser Permanente, Southern California	United States
Haber 2018[16]	Case series	January 1, 2005 – December 31, 2015	20,231 VAERS reports	Vaccine Adverse Event Reporting System	United States

Author Year	Study design	Data Collection Period	Sample size, N	Surveillance System (if Applicable)	Country
Lewis 2001[6]	Cohort	November 1, 1991 – April 30, 1994	5,655 normal birthweight, full term infants	Vaccine Safety Datalink (Northern California Kaiser Permanente)	United States
Linder 1999[10]	Cohort	Birth/record January 1, 1991 – December 31, 1992	10,829 neonates	Not reported	Israel
Lopez 2002[11]	Cohort	NR	117 neonates	Centro Materno Infantil Los Farallones	Colombia
Morgan 2025[7]	Cohort	January 1, 2017 – December 31, 2020	818 extremely preterm infants	Surveillance of Adverse Events Following Immunization in the Community	Australia
Niu 1996[12]	Case series	January 1, 1991 – May 31, 1995	12,520 VAERS reports	Vaccine Adverse Event Reporting System	United States
Niu 1999[17]	Case series	January 1, 1991 – October 5,1998	1,771	Vaccine Adverse Event Reporting System	United States
Sapru 2007[13]	Randomized Controlled Trial (control arm)	Not reported	262	Not reported	India
Verstraeten 2003[19]	Retrospective cohort study	1995-end of 2000	140,887 at 3 HMOs (13,337 at A, 110,833 at B, 16,717 at C)	Vaccine Safety Datalink	United States
Wood 2018[18]	Randomized Controlled Trial	June 11, 2010 - March 14, 2013	440	Not reported	Australia
Yerushalmi 1997[9]	Randomized Controlled Trial	Not reported	205 (46% were male)	Not reported	Israel

C.2. Outcomes for All Included Studies

Table 20. Adverse Events Following Immunization (AEFI) Results of Studies Meeting Inclusion Criteria

Study	Study Type	Outcome	Outcome Identification	Intervention (Thimerosal Y/N/NR)	Intervention % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
Niu 1996[12]	Case series	Cerebral venous thrombosis/intraventricular hemorrhage	NR	HepB vaccine (unspecified) in neonates aged <0.1 years (Y)	1.7% (1/60)	NR	NR	NR	NR	NR	Some concerns[aaaa]
Niu 1996[12]	Case series	Disseminated intravascular coagulation	NR	HepB vaccine (unspecified) in neonates aged <0.1 years (Y)	1.7% (1/60)	NR	NR	NR	NR	NR	Some concerns[a]
Niu 1996[12]	Case series	Necrotizing enterocolitis	NR	HepB vaccine (unspecified) in neonates aged <0.1 years (Y)	1.7% (1/60)	NR	NR	NR	NR	NR	Some concerns[bbbb]
Lopez 2002[11]	Cohort	Serious adverse events	Unsolicited symptoms collected during 30-day follow-up window	HepB Engerix-B at birth (Y)	0.9% (1/117)	NR	NR	NR	NR	NR	Some concerns[2]

Table 21. Allergic Reaction and Atopy Results of Studies Meeting Inclusion Criteria

Study	Study Type	Outcome	Outcome Identification	Intervention (Thimerosal Y/N/NR)	Intervention % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
Lewis 2001[6]	Cohort	Allergic reaction	ICD 10 Codes	Hep B Vax (unspecified) within first 21 d (Y)	<0.1% (1/3302)	Unvaccinated within first 21 d	<0.1% (1/2353)	NR	RR: 0.71 (0.04-11.4); p = 0.99	None	Some concerns

[aaaa] Descriptive study, no comparison

[bbbb] Descriptive study, no comparison

Study	Study Type	Outcome	Outcome Identification	Intervention (Thimerosal Y/N/NR)	Intervention % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
Lewis 2001[6]	Cohort	Allergic reaction	ICD 10 Codes	Hep B Vax (unspecified) within day of birth or day after birth (Y)	<0.1% (1/2718)	Unvaccinated within first 21 d	<0.1% (1/2937)	NR	RR: 0.87 (0.05-13.8); p = 0.99	None	Some concerns
Sapru 2007[13]	RCT	Eczema	Parent assessment or medical exam	HepB Engerix-B within first 2 wks	0 (0/130)	HepB Gene Vac-B within first 2 wks	0 (0/132)	NA	NR	NR	No concerns

Table 22. All Death Outcomes Results of Studies Meeting Inclusion Criteria

Study	Study Type	Outcome	Outcome Identification	Intervention (Thimerosal Y/N/NR)	Intervention % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
Greenberg 2002[14]	RCT	All -cause mortality	NR; at 7 months follow-up	Engerix-B vaccine at birth, 1 month, and 6 months of age and DTaP, OPV, and Hib vaccines at 2, 4, and 6 months of age (NR)	0% (0/140)	DTaP-HepB, OPV, and Hib vaccines at 2, 4, and 6 months of age	0% (0/140)	NR	NR	NR	Some concerns[e]
Morgan 2025[7]	Cohort	All -cause mortality	Victorian Deaths index; all cause mortality occurring in the 3 months after birth	Hep B vaccine (unspecified) within 24h of birth for extremely premature infants (<29 weeks gestation) (NR)	2.30% (7/306)	No recorded Hep B vaccine within 24h of birth for extremely premature infants (<29 weeks gestation)	2.70% (14/512)	NR	aRR: 1.13; (95%CI: 0.42-2.81)	Maternal age, low Apgar at 1 minute, low Apgar at 5 minutes, maternal smoking, gestation period and congenital heart	No concerns

Study	Study Type	Outcome	Outcome Identification	Intervention (Thimerosal Y/N/NR)	Intervention % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
										disease status	
Haber 2018[16]	Case series	All -cause mortality	VAERS reports of death verified by death certificate or autopsy report	Hep B vaccine (unspecified) infants aged <1 month (Y)	11.3% (27/240)	NR	NR	NR	NR	NR	Some concerns[cccc]
Niu 1996[12]	Case series	All -cause mortality	VAERS reports of death	Hep B vaccine (unspecified) infants aged <0.1 yrs of age (Y)	10% (6/60)	NR	NR	NR	NR	NR	Some concerns[dddd]
Niu 1999[17]	Case series	All -cause mortality	VAERS reports of death	Hep B vaccine (unspecified) infants aged <28 days (Y)	1% (18/1771)	NR	NR	NR	NR	NR	Some concerns[eeee]
Eriksen 2004[15]	Cohort	Expected neonatal death	ICD-9 codes and determined by medical autopsy; four categories considered expected	Hep B vaccine (unspecified) before 29 days of age (Y); 85% vaccinated of day of birth, none beyond 8 days of life	69% (50/72)	No HepB vaccine with death at <29 days of age	65% (128/196)	0.6	NR	NR	No concerns
Eriksen 2004[15]	Cohort	Unexpected neonatal death	ICD-9 codes and determined by medical autopsy	Hep B vaccine (unspecified) before 29 days of age (Y); 85% vaccinated of day of birth, none beyond 8 days of life	31% (22/72)	No HepB vaccine with death at <29 days of age	35% (68/196)	0.6	NR	NR	No concerns

[cccc] Descriptive study, no comparison

[dddd] Descriptive study, no comparison

[eeee] Descriptive study, no comparison

Study	Study Type	Outcome	Outcome Identification	Intervention (Thimerosal Y/N/NR)	Intervention % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
Eriksen 2004[15]	Cohort	Unexpected neonatal death from SIDS	ICD-9 codes and determined by medical autopsy	Hep B vaccine (unspecified) before 29 days of age (Y); 85% vaccinated of day of birth, none beyond 8 days of life	8/240,717 (3.3 deaths per 100,000 births)	No HepB vaccine at <29 days of age	4/120,979 (3.3 deaths per 100,000 births)	0.99	NR	NR	Serious concerns[27]

Table 23. Infection Results of Studies Meeting Inclusion Criteria

Study	Study Type	Outcome	Outcome Identification	Intervention (Thimerosal Y/N/NR)	Intervention % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
Lewis 2001[6]	Cohort	Blood or CSF culture performed	Clinical laboratory data	Hep B vaccine (unspecified) within first 21 days of life (Y)	4% (133/3,302)	No Hep B vaccine within first 21 days of life	8.6% (203/2,353)	<0.001	RR: 0.73 (95%CI: 0.65-0.82)	NR	No concerns
Lewis 2001[6]	Cohort	Blood or CSF culture performed	Clinical laboratory data	Hep B vaccine (unspecified) on day of birth or day after birth (Y)	4.6% (126/2,718)	No Hep B vaccine within first 21 days of life	8.6% (203/2,353)	<0.001	RR: 0.71; (95%CI: 0.63-0.80)	NR	No concerns
Lewis 2001[6]	Cohort	Blood or CSF culture positive	Clinical laboratory data	Hep B vaccine (unspecified) within first 21 days of life (Y)	0.2% (8/3,302)	No Hep B vaccine within first 21 days of life	0.7% (16/2,353)	0.030	RR: 0.60 (95%CI: 0.38-0.95)	NR	No concerns
Lewis 2001[6]	Cohort	Blood or CSF culture positive	Clinical laboratory data	Hep B vaccine (unspecified) on day of birth or day after birth (Y)	0.3% (7/2,718)	No Hep B vaccine within first 21 days of life	0.7% (16/2,353)	0.027	RR: 0.57; (95%CI: 0.35-0.94)	NR	No concerns
Lewis 2001[6]	Cohort	Fever (in first 3 weeks of life)	ICD-9 codes, computerized database search	Hep B vaccine (unspecified) within first 21 days of life (Y)	(26/3,302)	No Hep B vaccine within first	(25/2,353)	0.51	aRR: 0.92 (95%CI: 0.7-1.2)	Adjusted by age in days	No concerns

Study	Study Type	Outcome	Outcome Identification	Intervention (Thimerosal Y/N/NR)	Intervention % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
						21 days of life					
Lewis 2001[6]	Cohort	Fever (in first 3 weeks of life)	ICD-9 codes, computerized database search	Hep B vaccine (unspecified) on day of birth or day after birth (Y)	(21/2,718)	No Hep B vaccine within first 21 days of life	(25/2,353)	0.28	aRR: 0.85; (95%CI: 0.6-1.1)	Adjusted by age in days	No concerns
Haber 2018[16]	Case series	Infections and infestations	VAERS, non-death, serious reports	Hep B vaccine (unspecified) infants aged <1 month (Y)	4.6% (11/240)	NR	NR	NR	NR	NR	Some concerns[7]

Table 24. Local Injection-site Outcomes Results of Studies Meeting Inclusion Criteria

Study	Study Type	Outcome	Outcome Identification	Intervention (Thimerosal Y/N/NR)	Intervention % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
Bassily 1995[8]	RCT	Local side effects	Parental report of local soreness or temporary redness/induration at the injection site	Recombivax immediately after birth (Y)	2.8% (5/178)	Recombivax at 18 months of age (Y)	1.6% (3/191)	NR	NR	NR	Serious concerns[8]
Bassily 1995[8]	RCT	Local side effects	Parental report of local soreness or temporary redness/induration at the injection site	Recombivax at 2 months of age (Y)	7.2% (12/167)	Recombivax at 18 months of age (Y)	1.6% (3/191)	NR	NR	NR	Serious concerns[8]
Yerushalmi 1997[9]	RCT	Pain with movement	Parental report on diary card for 5 days post-vaccination	Engerix-B vaccine within 24 hrs of birth (Y)	7.7% (4/52)	BioHepB vaccine within 24 hrs of birth (Y)	2.6% (4/153)	NR	NR	NR	Serious concerns[9]
Yerushalmi 1997[9]	RCT	Pain with pressure	Parental report on diary card for 5 days post-vaccination	Engerix-B vaccine within 24 hrs of birth (Y)	7.7% (4/52)	BioHepB vaccine within 24 hrs of birth (Y)	1.3% (2/153)	NR	NR	NR	Serious concerns[9]
Wood 2018[18]	RCT	Pain or soreness (any)	Parental report of pain at injection site within 2 days after dose	Engerix-B vaccine given alone within 120 hrs of	9% (14/150)	Engerix-B co-administered with investigational	20% (41/208)	NR	NR	NR	Some concerns[11]

Study	Study Type	Outcome	Outcome Identification	Intervention (Thimerosal Y/N/NR)	Intervention % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
				birth (Y); 87.6% vaccinated days 0-2		acellular Pertussis vaccine within 120 hrs of birth (Y); 91% vaccinated days 0-2					
Wood 2018[18]	RCT	Pain or soreness (severe)	Parental report of pain at injection site within 2 days after dose, severe classified as crying when limb is moved/spontaneously painful or prevents daily activities	Engerix-B vaccine given alone within 120 hrs of birth (Y); 87.6% vaccinated days 0-2	0% (0/150)	Engerix-B co-administered with investigational acellular Pertussis vaccine within 120 hrs of birth (Y); 91% vaccinated days 0-2	0.5% (1/208)	NR	NR	NR	Some concerns[11]
Greenberg 2002[14]	RCT	Pain or soreness (Any)	Solicited parental report for day of vaccination and 3 days following vaccination	Engerix-B vaccine within 4 days of birth (NR)	8.1% (NR/136)	DTaP-HepB, OPV, and Hib vaccines at 2 months of age (NR)	35.7% (NR/129)	NR	NR	NR	Some concerns[11]
Greenberg 2002[14]	RCT	Pain or soreness (Grade 3/Severe)	Solicited parental report for day of vaccination and 3 days following vaccination; Grade 3-soreness that caused crying when limb was moved; reported at any vaccination site	Engerix-B vaccine within 4 days of birth (NR)	0% (0/136)	DTaP-HepB, OPV, and Hib vaccines at 2 months of age (NR)	1.6% (NR/129)	NR	NR	NR	Some concerns[11]
Lopez 2002[11]	Cohort	Pain or soreness (Any)	Solicited self-report by diary card during 4-day follow-up window	HepB Engerix-B at birth (Y)	6% (7/117)	NR	NR	NR	NR	NR	Some concerns[12]
Lopez 2002[11]	Cohort	Pain or soreness (Severe)	Solicited self-report by diary card during 4-day follow-up window	HepB Engerix-B at birth (Y)	4.3% (5/117)	NR	NR	NR	NR	NR	Some concerns[12]

Study	Study Type	Outcome	Outcome Identification	Intervention (Thimerosal Y/N/NR)	Intervention % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
Wood 2018[18]	RCT	Redness or erythema (Any)	Parental report, within 2 days of dose; grade 1: <10mm, grade 2-10-<30mm; grade 3: >=30mm	Engerix-B vaccine given alone within 120 hrs of birth (Y); 87.6% vaccinated days 0-2	20% (30/150)	Engerix-B co-administered with investigational acellular Pertussis vaccine within 120 hrs of birth (Y); 91% vaccinated days 0-2	27% (57/208)	NR	NR	NR	Some concerns[13]
Wood 2018[18]	RCT	Redness or erythema (Severe/Grade 3)	Parental report, within 2 days of dose; grade 3: >=30mm	Engerix-B vaccine given alone within 120 hrs of birth (Y); 87.6% vaccinated days 0-2	0	Engerix-B co-administered with investigational acellular Pertussis vaccine within 120 hrs of birth (Y); 91% vaccinated days 0-2	0	NR	NR	NR	Some concerns[13]
Yerushalmi 1997[9]	RCT	Redness or erythema	Parental report on diary card for 5 days post-vaccination	Engerix-B vaccine within 24 hrs of birth (Y)	0/52	BioHepB vaccine within 24 hrs of birth (Y)	0/153	NR	NR	NR	Some concerns[14]
Greenberg 2002[14]	RCT	Redness or erythema (Any)	Solicited parental report for day of vaccination and 3 days following vaccination	Engerix-B vaccine within 4 days of birth (NR)	8.8% (NR/136)	DTaP-HepB, OPV, and Hib vaccines at 2 months of age (NR)	11.6% (NR/129)	NR	NR	NR	Some concerns[14]
Greenberg 2002[14]	RCT	Redness or erythema (Severe/Grade 3)	Solicited parental report for day of vaccination and 3 days following vaccination; Grade 3-diameter >20mm; reported at any vaccination site	Engerix-B vaccine within 4 days of birth (NR)	0% (0/136)	DTaP-HepB, OPV, and Hib vaccines at 2 months of age (NR)	0% (0/129)	NR	NR	NR	Some concerns[14]
Lopez 2002[11]	Cohort	Redness or erythema (Any)	Solicited self-report by diary card during	HepB Engerix-B at birth (Y)	11.1% (13/117)	NR	NR	NR	NR	NR	Serious concerns[15]

Study	Study Type	Outcome	Outcome Identification	Intervention (Thimerosal Y/N/NR)	Intervention % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
			4-day follow-up window								
Lopez 2002[11]	Cohort	Redness or erythema (Severe)	Solicited self-report by diary card during 4-day follow-up window; severe >20mm	HepB Engerix-B at birth (Y)	0% (0/117)	NR	NR	NR	NR	NR	Serious concerns[15]
Sapru 2007[13]	RCT	Swelling	Parental report until total follow-up period of 18 weeks	Engerix-B vaccine within first 2 weeks of life (NR)	0% (0/130)	GeneVacB (HepB) vaccine within first 2 weeks of life (NR)	0% (0/132)	NR	NR	NR	Some concerns[n]
Greenberg 2002[14]	RCT	Swelling (Any)	Solicited parental report for day of vaccination and 3 days following vaccination	Engerix-B vaccine within 4 days of birth (NR)	0% (0/136)	DTaP-HepB, OPV, and Hib vaccines at 2 months of age (NR)	16.3% (NR/129)	NR	NR	NR	Some concerns[n]
Greenberg 2002[14]	RCT	Swelling (Severe/Grade 3)	Solicited parental report for day of vaccination and 3 days following vaccination; Grade 3-diameter >20mm; reported at any vaccination site	Engerix-B vaccine within 4 days of birth (NR)	0% (0/136)	DTaP-HepB, OPV, and Hib vaccines at 2 months of age (NR)	3.1% (NR/129)	NR	NR	NR	Some concerns[n]
Yerushalmi 1997[9]	RCT	Swelling	Parental report on diary card for 5 days post-vaccination	Engerix-B vaccine within 24 hrs of birth (Y)	7.7% (4/52)	BioHepB vaccine within 24 hrs of birth (Y)	2.0% (3/153)	NR	NR	NR	Some concerns[n]
Wood 2018[18]	RCT	Swelling (Any)	Parental report, within 2 days of dose; grade 1: <10mm, grade 2-10-<30mm; grade 3: >=30mm	Engerix-B vaccine given alone within 120 hrs of birth (Y); 87.6% vaccinated days 0-2	4% (6/150)	Engerix-B co-administered with investigational acellular Pertussis vaccine within 120 hrs of birth (Y); 91% vaccinated days 0-2	12.5% (26/208)	NR	NR	NR	Some concerns[16]

Study	Study Type	Outcome	Outcome Identification	Intervention (Thimerosal Y/N/NR)	Intervention % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
Wood 2018[18]	RCT	Swelling (Severe/Grade 3)	Parental report, within 2 days of dose; grade 3: >=30mm	Engerix-B vaccine given alone within 120 hrs of birth (Y); 87.6% vaccinated days 0-2	0	Engerix-B co-administered with investigational acellular Pertussis vaccine within 120 hrs of birth (Y); 91% vaccinated days 0-2	0	NR	NR	NR	Some concerns[16]
Lopez 2002[11]	Cohort	Swelling (Any)	Solicited self-report by diary card during 4-day follow-up window	HepB Engerix-B at birth (Y)	4.3% (5/117)	NR	NR	NR	NR	NR	Serious concerns[17]
Lopez 2002[11]	Cohort	Swelling (Severe)	Solicited self-report by diary card during 4-day follow-up window; severe >20mm	HepB Engerix-B at birth (Y)	0% (0/117)	NR	NR	NR	NR	NR	Serious concerns[17]

Table 25. Neurodevelopmental Results of Studies Meeting Inclusion Criteria

Study	Study Type	Outcome or Case	Outcome Identification	Intervention or Exposure (Thimerosal Y/N/NR)	Intervention or Exposure % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
Verstraeten 2003[19]	Cohort	Attention deficit disorder (ADD)	ICD-9 codes	HepB vaccine (unspecified) within 1 month of age at HMO A (Y)	(Not stratified by dose timing)	NR	NR	NR	aHR: 0.92 (95%CI 0.52-1.59)	Stratified by HMO, year of birth, and sex, and adjusted for birth weight	No concerns
Verstraeten 2003[19]	Cohort	Attention deficit disorder (ADD)	ICD-9 codes	HepB vaccine (unspecified) within 1	(Not stratified by dose timing)	NR	NR	NR	aHR: 0.90 (95%CI 0.74-1.10)	Stratified by HMO, year of birth, and	No concerns

Study	Study Type	Outcome or Case	Outcome Identification	Intervention or Exposure (Thimerosal Y/N/NR)	Intervention or Exposure % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
				month of age at HMO B (Y)						sex, and adjusted for birth weight and clinic	
Verstraeten 2003[19]	Cohort	Attention deficit disorder (ADD)	Costar codes	HepB vaccine (unspecified) within 1 month of age at HMO C (Y)	(Not stratified by dose timing)	NR	NR	NR	HR: 0.88 (95CI% 0.53-1.48)	none	No concerns
Verstraeten 2003[19]	Cohort	Autism/Autism Spectrum Disorder	ICD-9 codes	HepB vaccine (unspecified) within 1 month of age at HMO B (Y)	(Not stratified by dose timing)	NR	NR	NR	aHR: 1.16 (95%CI 0.78-1.71)	Stratified by HMO, year of birth, and sex, and adjusted for birth weight and clinic	No concerns
Geier 2013[20]	Case-control	Autism/Autism Spectrum Disorder	ICD-9 codes	HepB vaccine (unspecified) (Y) or combined Hib-HepB vaccine or no vaccine within first month of life for cases (diagnosed with autism spectrum disorder)	Exposure/Cases: (155/302)	HepB vaccine (unspecified) (Y) or combined Hib-HepB vaccine or no vaccine within first month of life for controls (no diagnosis of autism spectrum disorder)	Exposure/Controls: (8161/25632)	<0.00001	OR: 2.18; (95%CI: 1.74-2.73) (assessed as OR of exposure to thimerisol-containing vaccine in cases v. controls)	NR	Serious concerns[38]
Gallagher 2010[21]	Cross-sectional	Autism/Autism Spectrum Disorder	Parent reported autism diagnosis to National Health	HepB vaccine (unspecified) within 1 month of age in males born before 1999 (NR)	NR	No HepB vaccine (unspecified) in first month of life (vaccinated late or never	NR	0.031	aOR: 3.002; (95%CI: 1.109-8.126)	when adjusting for race and ethnicity, family structure,	Serious concerns[39]

Study	Study Type	Outcome or Case	Outcome Identification	Intervention or Exposure (Thimerosal Y/N/NR)	Intervention or Exposure % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
			Interview Survey			vaccinated) in males born before 1999 (NR)				and maternal education	
Verstraeten 2003[19]	Cohort	Coordination Disorder	ICD-9 codes	HepB vaccine (unspecified) within 1 month of age at HMO A (Y)	(Not stratified by dose timing)	NR	NR	NR	aHR: 1.67 (95%CI 0.78-3.57)	Stratified by HMO, year of birth, and sex, and adjusted for birth weight	No concerns
Verstraeten 2003[19]	Cohort	Speech or language delay	ICD-9 codes	HepB vaccine (unspecified) within 1 month of age at HMO A (Y)	(Not stratified by dose timing)	NR	NR	NR	aHR: 1.14 (95%CI 0.88-1.46)	Stratified by HMO, year of birth, and sex, and adjusted for birth weight	No concerns
Verstraeten 2003[19]	Cohort	Speech or language delay	ICD-9 codes	HepB vaccine (unspecified) within 1 month of age at HMO B (Y)	(Not stratified by dose timing)	NR	NR	NR	aHR: 1.03 (95%CI 0.91-1.17)	Stratified by HMO, year of birth, and sex, and adjusted for birth weight and clinic	No concerns
Verstraeten 2003[19]	Cohort	Speech or language delay	Costar codes	HepB vaccine (unspecified) within 1 month of age at HMO C (Y)	(Not stratified by dose timing)	NR	NR	NR	HR: 0.91 (95%CI 0.79-1.04)	none	No concerns
Verstraeten 2003[19]	Cohort	Eating disorders	ICD-9 codes	HepB vaccine (unspecified) within 1 month of age at HMO B (Y)	(Not stratified by dose timing)	NR	NR	NR	aHR: 0.90 (95%CI 0.50-1.61)	Stratified by HMO, year of birth, and sex, and adjusted	No concerns

Study	Study Type	Outcome or Case	Outcome Identification	Intervention or Exposure (Thimerosal Y/N/NR)	Intervention or Exposure % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
										for birth weight and clinic	
Geier 2017[22]	Case-control	Emotional disorders	ICD-9 codes	HepB vaccine (unspecified) (Y) or combined Hib-HepB vaccine or no vaccine within first month of life for cases (diagnosed with emotional disorders)	Exposure/Cases: (204/513)	HepB vaccine (unspecified) (Y) or combined Hib-HepB vaccine or no vaccine within first month of life for controls (no diagnosis of emotional disorders)	Exposure/Controls: (9003/27491)	<0.005	OR: 1.34 (95 %CI: 1.12-1.60) (assessed as OR of exposure to thimerisol-containing vaccine in cases v. controls)	none	Serious concerns[41]
Geier 2017[22]	Case-control	Emotional disorders	ICD-9 codes	HepB vaccine (unspecified) (Y) or combined Hib-HepB vaccine or no vaccine within first month of life for male cases (diagnosed with emotional disorders)	Exposure/Cases: (158/399)	HepB vaccine (unspecified) (Y) or combined Hib-HepB vaccine or no vaccine within first month of life for male controls (no diagnosis of emotional disorders)	Exposure/Controls: (4568/14013)	<0.005	OR: 1.36; (95% CI: 1.11-1.66) (assessed as OR of exposure to thimerisol-containing vaccine in cases v. controls)	Stratified by sex	Serious concerns[41]
Geier 2017[22]	Case-control	Emotional disorders	ICD-9 codes	HepB vaccine (unspecified) (Y) or combined Hib-HepB vaccine or no vaccine within first	Exposure/Cases: (46/118)	HepB vaccine (unspecified) (Y) or combined Hib-HepB vaccine or no vaccine within first	Exposure/Controls: (4435/13478)	0.15	OR: 1.30; (95% CI: 0.90-1.89) (assessed as OR of exposure to thimerisol-containing	Stratified by sex	Serious concerns[41]

Study	Study Type	Outcome or Case	Outcome Identification	Intervention or Exposure (Thimerosal Y/N/NR)	Intervention or Exposure % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
				month of life for female cases (diagnosed with emotional disorders)		month of life for female controls (no diagnosis of emotional disorders)			vaccine in cases v. controls)		
Verstraeten 2003[19]	Cohort	Emotional disturbances	ICD-9 codes	HepB vaccine (unspecified) within 1 month of age at HMO A (Y)	(Not stratified by dose timing)	NR	NR	NR	aHR: 1.00 (95%CI 0.42-2.36)	Stratified by HMO, year of birth, and sex, and adjusted for birth weight	No concerns
Verstraeten 2003[19]	Cohort	Emotional disturbances	ICD-9 codes	HepB vaccine (unspecified) within 1 month of age at HMO B (Y)	(Not stratified by dose timing)	NR	NR	NR	aHR: 0.76 (95%CI 0.54-1.07)	Stratified by HMO, year of birth, and sex, and adjusted for birth weight and clinic	No concerns
Verstraeten 2003[19]	Cohort	Other childhood psychosis	ICD-9 codes	HepB vaccine (unspecified) within 1 month of age at HMO B (Y)	(Not stratified by dose timing)	NR	NR	NR	aHR: 1.03 (95%CI 0.60-1.74)	Stratified by HMO, year of birth, and sex, and adjusted for birth weight and clinic	No concerns
Verstraeten 2003[19]	Cohort	Sleep disorders	ICD-9 codes	HepB vaccine (unspecified) within 1 month of age at HMO A (Y)	(Not stratified by dose timing)	NR	NR	NR	aHR: 0.79 (95%CI 0.38-1.61)	Stratified by HMO, year of birth, and sex, and adjusted	No concerns

Study	Study Type	Outcome or Case	Outcome Identification	Intervention or Exposure (Thimerosal Y/N/NR)	Intervention or Exposure % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
										for birth weight	
Verstraeten 2003[19]	Cohort	Sleep disorders	ICD-9 codes	HepB vaccine (unspecified) within 1 month of age at HMO B (Y)	(Not stratified by dose timing)	NR	NR	NR	aHR: 1.24 (95%CI 0.80-1.93)	Stratified by HMO, year of birth, and sex, and adjusted for birth weight and clinic	No concerns
Verstraeten 2003[19]	Cohort	Sleep disorders	Costar codes	HepB vaccine (unspecified) within 1 month of age at HMO C (Y)	(Not stratified by dose timing)	NR	NR	NR	HR: 0.97 (95%CI 0.79-1.19)	none	No concerns
Geier 2016[24]	Cohort	Specific delays in development	ICD-9 codes	HepB vaccine (unspecified) within first month of life (Y)	(828/18,637)	No HepB vaccine within first month of life	(1127/31,198)	<0.001	RR: 1.22, (95% CI: 1.12-1.33)	none	Serious concerns[42]
Geier 2016[24]	Cohort	Specific delays in development	ICD-9 codes	HepB vaccine (unspecified) within first month of life for males (Y)	(567/9514)	No HepB vaccine within first month of life for males	(771/16,110)	<0.001	OR: 1.23, (95%CI: 1.11-1.37)	none	Serious concerns[42]
Geier 2016[24]	Cohort	Specific delays in development	ICD-9 codes	HepB vaccine (unspecified) within first month of life for females (Y)	(261/9122)	No HepB vaccine within first month of life for females	(356/15,088)	<0.05	OR: 1.21; (95% CI: 1.03-1.41)	none	Serious concerns[42]
Verstraeten 2003[19]	Cohort	Stammering	ICD-9 codes	HepB vaccine (unspecified) within 1 month of age at HMO A (Y)	(Not stratified by dose timing)	NR	NR	NR	aHR: 0.89 (95%CI 0.40-1.97)	Stratified by HMO, year of birth, and sex, and adjusted for birth weight	No concerns

Study	Study Type	Outcome or Case	Outcome Identification	Intervention or Exposure (Thimerosal Y/N/NR)	Intervention or Exposure % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
Verstraeten 2003[19]	Cohort	Stammering	ICD-9 codes	HepB vaccine (unspecified) within 1 month of age at HMO B (Y)	(Not stratified by dose timing)	NR	NR	NR	aHR: 0.61 (95%CI 0.33-1.14)	Stratified by HMO, year of birth, and sex, and adjusted for birth weight and clinic	No concerns
Verstraeten 2003[19]	Cohort	Stammering	Costar codes	HepB vaccine (unspecified) within 1 month of age at HMO C (Y)	(Not stratified by dose timing)	NR	NR	NR	HR: 0.77 (95%CI 0.47-1.26)	none	No concerns
Verstraeten 2003[19]	Cohort	Tic Disorder, Tics	ICD-9 codes	HepB vaccine (unspecified) within 1 month of age at HMO A (Y)	(Not stratified by dose timing)	NR	NR	NR	aHR: 1.25 (95%CI 0.47-3.29)	Stratified by HMO, year of birth, and sex, and adjusted for birth weight	No concerns
Verstraeten 2003[19]	Cohort	Tic Disorder, Tics	ICD-9 codes	HepB vaccine (unspecified) within 1 month of age at HMO B (Y)	(Not stratified by dose timing)	NR	NR	NR	aHR: 0.85 (95%CI 0.55-1.30)	Stratified by HMO, year of birth, and sex, and adjusted for birth weight and clinic	No concerns
Verstraeten 2003[19]	Cohort	Tic Disorder, Tics	Costar codes	HepB vaccine (unspecified) within 1 month of age at HMO C (Y)	(Not stratified by dose timing)	NR	NR	NR	HR: 0.93 (95%CI 0.45-1.92)	none	No concerns
Geier 2015[23]	Case-control	Tic Disorder, Tics	ICD-9 codes	HepB vaccine (unspecified) (Y) or combined	Exposure/Cases: (151/344)	HepB vaccine (unspecified) (Y) or combined	Exposure/Controls: (9222/28016)	<0.00001	OR: 1.59; (95%CI: 1.29-1.98) (assessed as	none	Serious Concerns[43]

Study	Study Type	Outcome or Case	Outcome Identification	Intervention or Exposure (Thimerosal Y/N/NR)	Intervention or Exposure % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
				Hib-HepB vaccine or no vaccine within first month of life for cases (diagnosed with tic disorder)		Hib-HepB vaccine or no vaccine within first month of life for controls (no diagnosis of tic disorder)			OR of exposure to thimerisol-containing vaccine in cases v. controls)		
Geier 2015[23]	Case-control	Tic Disorder, Tics	ICD-9 codes	HepB vaccine (unspecified) (Y) or combined Hib-HepB vaccine or no vaccine within first month of life for male cases (diagnosed with tic disorder)	Exposure/Cases: (113/253)	HepB vaccine (unspecified) (Y) or combined Hib-HepB vaccine or no vaccine within first month of life for male controls (no diagnosis of tic disorder)	Exposure/Controls: (4697/14327)	<0.0001	OR: 1.65; (95%CI: 1.29-2.12) (assessed as OR of exposure to thimerisol-containing vaccine in cases v. controls)	Stratified by sex	Serious Concerns[43]
Geier 2015[23]	Case-control	Tic Disorder, Tics	ICD-9 codes	HepB vaccine (unspecified) (Y) or combined Hib-HepB vaccine or no vaccine within first month of life for female cases (diagnosed with tic disorder)	Exposure/Cases: (38/91)	HepB vaccine (unspecified) (Y) or combined Hib-HepB vaccine or no vaccine within first month of life for female controls (no diagnosis of tic disorder)	Exposure/Controls: (4525/13689)	0.09	OR: 1.45; (95%CI: 0.95-2.21) (assessed as OR of exposure to thimerisol-containing vaccine in cases v. controls)	Stratified by sex	Serious Concerns[43]

Table *26*. Neurologic Results of Studies Meeting Inclusion Criteria

Study	Study Type	Outcome or Case	Outcome Identification	Intervention or Exposure (Thimerosal Y/N/NR)	Intervention or Exposure % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
Niu 1996[12]	Case series	Abnormal CSF (Any)	NR	Hep B vaccine (unspecified) infants aged <0.1 yrs of age (Y)	6.7% (4/60)	NR	NR	NR	NR	NR	Some concerns[20]
Niu 1996[12]	Case series	Abnormal CSF (Serious)	NR	Hep B vaccine (unspecified) infants aged <0.1 yrs of age (Y)	6.7% (4/60)	NR	NR	NR	NR	NR	Some concerns[20]
Geier 2015[23]	Case-control	Cerebral degeneration	ICD-9 codes	HepB vaccine (unspecified) (Y) or combined Hib-HepB vaccine or no vaccine within first month of life for cases (diagnosed with cerebral degeneration)	Exposure/Cases: (175/647)	HepB vaccine (unspecified) (Y) or combined Hib-HepB vaccine or no vaccine within first month of life for controls (no diagnosis of tic disorder)	Exposure/Controls: (62637/135889)	<0.00001	OR: 0.43; (95%CI: 0.36-0.52) (assessed as OR of exposure to thimerisol-containing vaccine in cases v. controls)	none	Serious concerns[47]
Niu 1996[12]	Case series	Convulsions (Any)	NR	Hep B vaccine (unspecified) infants aged <0.1 yrs of age (Y)	10% (6/60)	NR	NR	NR	NR	NR	Some concerns[20]
Niu 1996[12]	Case series	Convulsions (Serious)	NR	Hep B vaccine (unspecified) infants aged <0.1 yrs of age (Y)	6.7% (4/60)	NR	NR	NR	NR	NR	Some concerns[20]
Lewis 2001[6]	Cohort	Seizure	ICD-9 codes, computerized database search	Hep B vaccine (unspecified) within first 21 days of life (Y)	(1/3302)	No Hep B vaccine within first	(4/2353)	0.17	RR: 0.18 (95%CI: 0.02-1.6)	NR	No concerns

Study	Study Type	Outcome or Case	Outcome Identification	Intervention or Exposure (Thimerosal Y/N/NR)	Intervention or Exposure % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
						21 days of life					
Lewis 2001[6]	Cohort	Seizure	ICD-9 codes, computerized database search	Hep B vaccine (unspecified) on day of birth or day after birth (Y)	(1/2718)	No Hep B vaccine within first 21 days of life	(4/2353)	0.19	RR: 0.22; (95%CI: 0.02-1.9)	NR	No concerns
Haber 2018[16]	Case series	Nervous system disorders	VAERS, non-death, serious reports	Hep B vaccine (unspecified) infants aged <1 month (Y)	6.3% (15/240)	NR	NR	NR	NR	NR	Some concerns[39]
Lewis 2001[6]	Cohort	Neurologic disease, other than seizure	computerized database search	Hep B vaccine (unspecified) within first 21 days of life (Y)	(4/3,302)	No Hep B vaccine within first 21 days of life	(2/2,353)	0.99	RR: 1.4 (95%CI: 0.3-7.8)	NR	No concerns
Lewis 2001[6]	Cohort	Neurologic disease, other than seizure	computerized database search	Hep B vaccine (unspecified) on day of birth or day after birth (Y)	(4/2,718)	No Hep B vaccine within first 21 days of life	(2/2,353)	0.69	RR: 1.7; (95%CI: 0.3-9.4)	NR	No concerns

Table 27. Cardiopulmonary Results of Studies Meeting Inclusion Criteria

Study	Study Type	Outcome	Outcome Identification	Intervention (Thimerosal Y/N/NR)	Intervention % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
Morgan 2025[7]	Cohort	Bronchopulmonary dysplasia	ICD-10 Australian modification codes	Hep B vaccine (unspecified) within 24h of birth for extremely premature infants (<29 weeks gestation) (NR)	(155/306)	No recorded Hep B vaccine within 24h of birth for extremely premature infants (<29 weeks gestation)	(317/512)	NR	aRR: 0.83; (95%CI: 0.68-1.0)	Maternal age, low Apgar at 1 minute, low Apgar at 5 minutes, maternal smoking, gestation period and congenital	No concerns

Study	Study Type	Outcome	Outcome Identification	Intervention (Thimerosal Y/N/NR)	Intervention % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
										heart disease status	
Niu 1996[12]	Case series	Apnea (Any)	NR	Hep B vaccine (unspecified) infants aged <0.1 yrs of age (Y)	8.3% (5/60)	NR	NR	NR	NR	NR	Some concerns[t]
Niu 1996[12]	Case series	Apnea (Serious)	NR	Hep B vaccine (unspecified) infants aged <0.1 yrs of age (Y)	(3/60)	NR	NR	NR	NR	NR	Some concerns[t]
Niu 1996[12]	Case series	Bradycardia (Any)	NR	Hep B vaccine (unspecified) infants aged <0.1 yrs of age (Y)	1.7% (1/60)	NR	NR	NR	NR	NR	Some concerns[t]
Niu 1996[12]	Case series	Bradycardia (Serious)	NR	Hep B vaccine (unspecified) infants aged <0.1 yrs of age (Y)	1.7% (1/60)	NR	NR	NR	NR	NR	Some concerns[t]
Niu 1996[12]	Case series	Cyanosis (Any)	NR	Hep B vaccine (unspecified) infants aged <0.1 yrs of age (Y)	11.7% (7/60)	NR	NR	NR	NR	NR	Some concerns[t]
Niu 1996[12]	Case series	Cyanosis (Serious)	NR	Hep B vaccine (unspecified) infants aged <0.1 yrs of age (Y)	(5/60)	NR	NR	NR	NR	NR	Some concerns[t]

Table 28. Systemic Reactions Results of Studies Meeting Inclusion Criteria

Study	Study Type	Outcome	Outcome Identification	Intervention (Thimerosal Y/N/NR)	Intervention % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
Niu 1996[12]	Case series	Agitation (Any)	NR	Hep B vaccine (unspecified) infants aged <0.1 yrs of age (Y)	21.7% (13/60)	NR	NR	NR	NR	NR	Some concerns[q]
Niu 1996[12]	Case series	Agitation (Serious)	NR	Hep B vaccine (unspecified) infants aged <0.1 yrs of age (Y)	11.7% (7/60)	NR	NR	NR	NR	NR	Some concerns[q]
Yerushalmi 1997[9]	RCT	Anorexia/Decreased appetite	Parental report on diary card for 5 days post-vaccination	Engerix-B vaccine within 24 hrs of birth (Y)	0% (0/52)	BioHepB vaccine within 24 hrs of birth (Y)	2.0% (3/153)	NR	NR	NR	Some concerns[28]
Greenberg 2002[14]	RCT	Anorexia/Decreased appetite (Any)	Solicited parental report for day of vaccination and 3 days following vaccination	Engerix-B vaccine within 4 days of birth (NR)	14.0% (NR/136)	DTaP-HepB, OPV, and Hib vaccines at 2 months of age (NR)	25.6% (NR/129)	NR	NR	NR	Some concerns[28]
Greenberg 2002[14]	RCT	Anorexia/Decreased appetite (Severe/Grade 3)	Solicited parental report for day of vaccination and 3 days following vaccination; Grade 3-prevented normal daily activities	Engerix-B vaccine within 4 days of birth (NR)	1.5% (NR/136)	DTaP-HepB, OPV, and Hib vaccines at 2 months of age (NR)	0.8% (NR/129)	NR	NR	NR	Some concerns[28]
Wood 2018[18]	RCT	Feeding issues/Anorexia (Any)	Parental report, within 2 days of dose	Engerix-B vaccine given alone within 120 hrs of birth (Y); 87.6%	17% (17/103)	Engerix-B co-administered with investigational acellular Pertussis	13% (28/221)	NR	NR	NR	Some concerns[32]

Study	Study Type	Outcome	Outcome Identification	Intervention (Thimerosal Y/N/NR)	Intervention % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
				vaccinated days 0-2		vaccine within 120 hrs of birth (Y); 91% vaccinated days 0-2					
Wood 2018[18]	RCT	Feeding issues/Anorexia (Grade 3/Severe)	Parental report, within 2 days of dose; Grade 3-prevents normal everyday activities or requires significant medical intervention	Engerix-B vaccine given alone within 120 hrs of birth (Y); 87.6% vaccinated days 0-2	0.9% (1/103)	Engerix-B co-administered with investigational acellular Pertussis vaccine within 120 hrs of birth (Y); 91% vaccinated days 0-2	0	NR	NR	NR	Some concerns[32]
Lopez 2002[11]	Cohort	Anorexia/Decreased appetite (Any)	Solicited self-report by diary card during 4-day follow-up window	HepB Engerix-B at birth (Y)	2.6% (3/117)	NR	NR	NR	NR	NR	Some concerns[54]
Lopez 2002[11]	Cohort	Anorexia/Decreased appetite (Severe)	Solicited self-report by diary card during 4-day follow-up window	HepB Engerix-B at birth (Y)	1.7% (2/117)	NR	NR	NR	NR	NR	Some concerns[54]
Sapru 2007[13]	RCT	Constipation	Parental report until total follow-up period of 18 weeks	Engerix-B vaccine within first 2 weeks of life (NR)	0% (0/130)	GeneVacB (HepB) vaccine within first 2 weeks of life (NR)	0% (0/132)	NR	NR	NR	No concerns
Wood 2018[18]	RCT	Diarrhea (Any)	Parental report, within 2 days of dose	Engerix-B vaccine given alone within 120 hrs of birth (Y); 87.6% vaccinated days 0-2	12% (12/103)	Engerix-B co-administered with investigational acellular Pertussis vaccine within 120 hrs of birth (Y); 91%	17.0% (38/221)	NR	NR	NR	Some concerns[25]

Study	Study Type	Outcome	Outcome Identification	Intervention (Thimerosal Y/N/NR)	Intervention % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
						vaccinated days 0-2					
Wood 2018[18]	RCT	Diarrhea (Severe/Grade 3)	Parental report, within 2 days of dose; Grade 3- prevents normal everyday activities or requires significant medical intervention	Engerix-B vaccine given alone within 120 hrs of birth (Y); 87.6% vaccinated days 0-2	0	Engerix-B co-administered with investigational acellular Pertussis vaccine within 120 hrs of birth (Y); 91% vaccinated days 0-2	0	NR	NR	NR	Some concerns[25]
Sapru 2007[13]	RCT	Diarrhea (loose motions)	Parental report until total follow-up period of 18 weeks	Engerix-B vaccine within first 2 weeks of life (NR)	0% (0/130)	GeneVacB (HepB) vaccine within first 2 weeks of life (NR)	0% (0/132)	NR	NR	NR	Some concerns[30]
Greenberg 2002[14]	RCT	Diarrhea (Any)	Solicited parental report for day of vaccination and 3 days following vaccination	Engerix-B vaccine within 4 days of birth (NR)	8.1% (NR/136)	DTaP-HepB, OPV, and Hib vaccines at 2 months of age (NR)	10.1% (NR/129)	NR	NR	NR	Some concerns[30]
Greenberg 2002[14]	RCT	Diarrhea (Severe/Grade 3)	Solicited parental report for day of vaccination and 3 days following vaccination; Grade 3- prevented normal daily activities	Engerix-B vaccine within 4 days of birth (NR)	0.7% (NR/136)	DTaP-HepB, OPV, and Hib vaccines at 2 months of age (NR)	0% (0/129)	NR	NR	NR	Some concerns[30]
Yerushalmi 1997[9]	RCT	Diarrhea	Parental report on diary card for 5 days	Engerix-B vaccine within 24 hrs of birth (Y)	0% (0/52)	BioHepB vaccine within 24 hrs of birth (Y)	0.64% (1/152)	NR	NR	NR	Some concerns[30]

Study	Study Type	Outcome	Outcome Identification	Intervention (Thimerosal Y/N/NR)	Intervention % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
			post-vaccination								
Niu 1996[12]	Case series	Diarrhea (Any)	NR	Hep B vaccine (unspecified) infants aged <0.1 yrs of age (Y)	1.7% (1/60)	NR	NR	NR	NR	NR	Some concerns[24]
Niu 1996[12]	Case series	Diarrhea (Serious)	NR	Hep B vaccine (unspecified) infants aged <0.1 yrs of age (Y)	1.7% (1/60)	NR	NR	NR	NR	NR	Some concerns[24]
Greenberg 2002[14]	RCT	Drowsiness or sleeping more (Any)	Solicited parental report for day of vaccination and 3 days following vaccination	Engerix-B vaccine within 4 days of birth (NR)	32.4% (NR/136)	DTaP-HepB, OPV, and Hib vaccines at 2 months of age (NR)	40.3% (NR/129)	NR	NR	NR	Some concerns[31]
Greenberg 2002[14]	RCT	Drowsiness or sleeping more (Severe/Grade 3)	Solicited parental report for day of vaccination and 3 days following vaccination; Grade 3-prevented normal daily activities	Engerix-B vaccine within 4 days of birth (NR)	2.9% (NR/136)	DTaP-HepB, OPV, and Hib vaccines at 2 months of age (NR)	0.8% (NR/129)	NR	NR	NR	Some concerns[31]
Wood 2018[18]	RCT	Drowsiness or sleeping more (Any)	Parental report, within 2 days of dose	Engerix-B vaccine given alone within 120 hrs of birth (Y); 87.6% vaccinated days 0-2	28% (28/103)	Engerix-B co-administered with investigational acellular Pertussis vaccine within 120 hrs of birth (Y); 91% vaccinated days 0-2	18% (39/221)	NR	NR	NR	Some concerns[29]

Study	Study Type	Outcome	Outcome Identification	Intervention (Thimerosal Y/N/NR)	Intervention % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
Wood 2018[18]	RCT	Drowsiness or sleeping more (Severe/Grade 3)	Parental report, within 2 days of dose; Grade 3- prevents normal everyday activities or requires significant medical intervention	Engerix-B vaccine given alone within 120 hrs of birth (Y); 87.6% vaccinated days 0-2	0.9% (1/103)	Engerix-B co-administered with investigational acellular Pertussis vaccine within 120 hrs of birth (Y); 91% vaccinated days 0-2	0.5% (1/221)	NR	NR	NR	Some concerns[29]
Lopez[11] 2002	Cohort	Drowsiness or sleeping more (Any)	Solicited self-report by diary card during 4-day follow-up window	HepB Engerix-B at birth (Y)	5.1% (6/117)	NR	NR	NR	NR	NR	Some concerns[26]
Lopez 2002[11]	Cohort	Drowsiness or sleeping more (Severe)	Solicited self-report by diary card during 4-day follow-up window	HepB Engerix-B at birth (Y)	0.9% (1/117)	NR	NR	NR	NR	NR	Some concerns[26]
Linder 1999[10]	Cohort	Fever (neonatal fever >37.5^{o}C)	Birth hospitalization discharge diagnosis	HepB vaccine (unspecified) on first day of life (NR)	1.2% (68/5819)	No HepB vaccine on first day of life	0.54% (27/5010)	0.001	NR	NR	Serious concerns[34]
Linder 1999[10]	Cohort	Fever (neonatal fever >38^{o}C)	Birth hospitalization discharge diagnosis	HepB vaccine (unspecified) on first day of life (NR)	0.9% (50/5819)	No HepB vaccine on first day of life	0.54% (27/5010)	0.05	NR	NR	Serious concerns[34]
Linder 1999[10]	Cohort	Fever (explained neonatal fever)	Birth hospitalization discharge diagnosis	HepB vaccine (unspecified) on first day of life (NR)	0.3% (15/5819)	No HepB vaccine on first day of life	0.3% (13/5010)	NR	NR	NR	Serious concerns[34]
Linder 1999[10]	Cohort	Fever (unexplained neonatal fever)	Birth hospitalization discharge diagnosis	HepB vaccine (unspecified) on first day of life (NR)	0.6% (35/5819)	No HepB vaccine on first day of life	0.3% (14/5010)	0.013	NR	NR	Serious concerns[34]
Lopez 2002[11]	Cohort	Fever (Any)	Solicited self-report by diary card during 4-	HepB Engerix-B at birth (Y)	0.9% (1/117)	NR	NR	NR	NR	NR	Some concerns[28]

Study	Study Type	Outcome	Outcome Identification	Intervention (Thimerosal Y/N/NR)	Intervention % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
			day follow-up window								
Lopez 2002[11]	Cohort	Fever (Severe)	Solicited self-report by diary card during 4-day follow-up window; severe >39 axillary or >39.5 rectal	HepB Engerix-B at birth (Y)	0.9% (1/117)	NR	NR	NR	NR	NR	Some concerns [28]
Niu 1996[12]	Case series	Fever (Any)	NR	Hep B vaccine (unspecified) infants aged <0.1 yrs of age (Y)	30% (18/60)	NR	NR	NR	NR	NR	Some concerns[24]
Niu 1996[12]	Case series	Fever (Serious)	NR	Hep B vaccine (unspecified) infants aged <0.1 yrs of age (Y)	21.7% (13/60)	NR	NR	NR	NR	NR	Some concerns[24]
Bassily 1995[8]	RCT	Fever	Parental report of 1-2 days of fever ≤102^{o}F	Recombivax immediately after birth (Y)	5.6% (NR/178)	Recombivax at 18 months of age (Y)	2.1% (NR/191)	NR	NR	NR	Some concerns [33]
Bassily 1995[8]	RCT	Fever	Parental report of 1-2 days of fever ≤102^{o}F	Recombivax at 2 months of age (Y)	7.2% (NR/167)	Recombivax at 18 months of age (Y)	2.1% (NR/191)	NR	NR	NR	Some concerns [33]
Yerushalmi 1997[9]	RCT	Fever (≥38^{o}C)	Parental report on diary card for 5 days post-vaccination	Engerix-B vaccine within 24 hrs of birth (Y)	0% (0/52)	BioHepB vaccine within 24 hrs of birth (Y)	1.3% (2/153)	NR	NR	NR	Some concerns [59]
Greenberg 2002[14]	RCT	Fever (Any)	Solicited parental report for day of vaccination and 3 days following vaccination; Rectal	Engerix-B vaccine within 4 days of birth (NR)	5.9% (NR/136)	DTaP-HepB, OPV, and Hib vaccines at 2 months of age (NR)	14.7% (NR/129)	NR	NR	NR	Some concerns [59]

Study	Study Type	Outcome	Outcome Identification	Intervention (Thimerosal Y/N/NR)	Intervention % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
			temperature ≥38°C								
Greenberg 2002[14]	RCT	Fever (Severe/Grade 3)	Solicited parental report for day of vaccination and 3 days following vaccination; Grade 3-fever >39.5°C	Engerix-B vaccine within 4 days of birth (NR)	0% (0/136)	DTaP-HepB, OPV, and Hib vaccines at 2 months of age (NR)	0.8% (NR/129)	NR	NR	NR	Some concerns [59]
Sapru 2007[13]	RCT	Fever (axillary temperature ≥38°C)	Parental report until total follow-up period of 18 weeks	Engerix-B vaccine within first 2 weeks of life (NR)	4.6% (6/130)	GeneVacB (HepB) vaccine within first 2 weeks of life (NR)	3.0% (4/132)	NR	NR	NR	Some concerns [59]
Wood 2018[18]	RCT	Fever (≥38°C)	Parental report, within 2 days of dose	Engerix-B vaccine given alone within 120 hrs of birth (Y); 87.6% vaccinated days 0-2	0.7% (1/138)	Engerix-B co-administered with investigational acellular Pertussis vaccine within 120 hrs of birth (Y); 91% vaccinated days 0-2	0	NR	NR	NR	Some concerns [59]
Wood 2018[18]	RCT	Fever (≥39°C)	Parental report, within 2 days of dose	Engerix-B vaccine given alone within 120 hrs of birth (Y); 87.6% vaccinated days 0-2	0	Engerix-B co-administered with investigational acellular Pertussis vaccine within 120 hrs of birth (Y); 91% vaccinated days 0-2	0	NR	NR	NR	Some concerns [59]
Wood 2018[18]	RCT	Irritability or fussiness (Any)	Parental report, within 2 days of dose	Engerix-B vaccine given alone within	20% (21/103)	Engerix-B co-administered with	24.0% (54/221)	NR	NR	NR	Serious concerns[34]

Study	Study Type	Outcome	Outcome Identification	Intervention (Thimerosal Y/N/NR)	Intervention % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
				120 hrs of birth (Y); 87.6% vaccinated days 0-2		investigational acellular Pertussis vaccine within 120 hrs of birth (Y); 91% vaccinated days 0-2					
Wood 2018[18]	RCT	Irritability or fussiness (Severe/Grade 3)	Parental report, within 2 days of dose; Grade 3- prevents normal everyday activities or requires significant medical intervention	Engerix-B vaccine given alone within 120 hrs of birth (Y); 87.6% vaccinated days 0-2	0.9% (1/103)	Engerix-B co-administered with investigational acellular Pertussis vaccine within 120 hrs of birth (Y); 91% vaccinated days 0-2	0.9% (2/221)	NR	NR	NR	Serious concerns[34]
Greenberg 2002[14]	RCT	Irritability or fussiness (Any)	Solicited parental report for day of vaccination and 3 days following vaccination	Engerix-B vaccine within 4 days of birth (NR)	22.1% (NR/136)	DTaP-HepB, OPV, and Hib vaccines at 2 months of age (NR)	54.3% (NR/129)	NR	NR	NR	Serious concerns[34]
Greenberg 2002[14]	RCT	Irritability or fussiness (Severe/Grade 3)	Solicited parental report for day of vaccination and 3 days following vaccination; Grade 3- prevented normal daily activities	Engerix-B vaccine within 4 days of birth (NR)	0.7% (NR/136)	DTaP-HepB, OPV, and Hib vaccines at 2 months of age (NR)	3.9% (NR/129)	NR	NR	NR	Serious concerns[34]
Yerushalmi 1997[9]	RCT	Irritability or fussiness	Parental report on diary card for 5 days	Engerix-B vaccine within	11.5% (6/52)	BioHepB vaccine within	3.3% (5/153)	NR	NR	NR	Serious concerns[34]

Study	Study Type	Outcome	Outcome Identification	Intervention (Thimerosal Y/N/NR)	Intervention % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
			post-vaccination	24 hrs of birth (Y)		24 hrs of birth (Y)					
Lopez 2002[11]	Cohort	Irritability or fussiness (Any)	Solicited self-report by diary card during 4-day follow-up window	HepB Engerix-B at birth (Y)	2.6% (3/117)	NR	NR	NR	NR	NR	Some concerns[65]
Lopez 2002[11]	Cohort	Irritability or fussiness (Severe)	Solicited self-report by diary card during 4-day follow-up window	HepB Engerix-B at birth (Y)	1.7% (2/117)	NR	NR	NR	NR	NR	Some concerns[65]
Sapru 2007[13]	RCT	Rash	Parental report until total follow-up period of 18 weeks	Engerix-B vaccine within first 2 weeks of life (NR)	0% (0/130)	GeneVacB (HepB) vaccine within first 2 weeks of life (NR)	0% (0/132)	NR	NR	NR	No Concerns
Niu 1996[12]	Case series	Rash (Any)	NR	Hep B vaccine (unspecified) infants aged <0.1 yrs of age (Y)	3.3% (2/60)	NR	NR	NR	NR	NR	Some concerns[31]
Niu 1996[12]	Case series	Rash (Serious)	NR	Hep B vaccine (unspecified) infants aged <0.1 yrs of age (Y)	3.3% (2/60)	NR	NR	NR	NR	NR	Some concerns[31]
Wood 2018[18]	RCT	Restlessness or sleeping less (Any)	Parental report, within 2 days of dose	Engerix-B vaccine given alone within 120 hrs of birth (Y); 87.6% vaccinated days 0-2	31% (32/103)	Engerix-B co-administered with investigational acellular Pertussis vaccine within 120 hrs of birth (Y); 91% vaccinated days 0-2	22.0% (49/221)	NR	NR	NR	Serious concerns[38]
Wood 2018[18]	RCT	Restlessness or sleeping less (Severe/Grade 3)	Parental report, within 2 days of dose;	Engerix-B vaccine given alone within	3% (3/103)	Engerix-B co-administered with	1% (2/221)	NR	NR	NR	Serious concerns[38]

Study	Study Type	Outcome	Outcome Identification	Intervention (Thimerosal Y/N/NR)	Intervention % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
			Grade 3- prevents normal everyday activities or requires significant medical intervention	120 hrs of birth (Y); 87.6% vaccinated days 0-2		investigational acellular Pertussis vaccine within 120 hrs of birth (Y); 91% vaccinated days 0-2					
Greenberg 2002[14]	RCT	Restlessness or sleeping less (Any)	Solicited parental report for day of vaccination and 3 days following vaccination	Engerix-B vaccine within 4 days of birth (NR)	16.9% (NR/136)	DTaP-HepB, OPV, and Hib vaccines at 2 months of age (NR)	26.4% (NR/129)	NR	NR	NR	Serious concerns[38]
Greenberg 2002[14]	RCT	Restlessness or sleeping less (Severe/Grade 3)	Solicited parental report for day of vaccination and 3 days following vaccination; Grade 3- prevented normal daily activities	Engerix-B vaccine within 4 days of birth (NR)	1.5% (NR/136)	DTaP-HepB, OPV, and Hib vaccines at 2 months of age (NR)	0.8% (NR/129)	NR	NR	NR	Serious concerns[38]
Greenberg 2002[14]	RCT	Unusual crying (Any)	Solicited parental report for day of vaccination and 3 days following vaccination	Engerix-B vaccine within 4 days of birth (NR)	1.5% (NR/136)	DTaP-HepB, OPV, and Hib vaccines at 2 months of age (NR)	3.1% (NR/129)	NR	NR	NR	Some concerns[40]
Greenberg 2002[14]	RCT	Unusual crying (Severe/Grade 3)	Solicited parental report for day of vaccination and 3 days following vaccination;	Engerix-B vaccine within 4 days of birth (NR)	0% (0/136)	DTaP-HepB, OPV, and Hib vaccines at 2 months of age (NR)	0.8% (NR/129)	NR	NR	NR	Some concerns[40]

Study	Study Type	Outcome	Outcome Identification	Intervention (Thimerosal Y/N/NR)	Intervention % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
			Grade 3-prevented normal daily activities								
Wood 2018[18]	RCT	Vomiting (Any)	Parental report, within 2 days of dose	Engerix-B vaccine given alone within 120 hrs of birth (Y); 87.6% vaccinated days 0-2	24% (23/103)	Engerix-B co-administered with investigational acellular Pertussis vaccine within 120 hrs of birth (Y); 91% vaccinated days 0-2	20.0% (45/221)	NR	NR	NR	Some concerns[41]
Wood 2018[18]	RCT	Vomiting (Severe/Grade 3)	Parental report, within 2 days of dose; Grade 3-prevents normal everyday activities or requires significant medical intervention	Engerix-B vaccine given alone within 120 hrs of birth (Y); 87.6% vaccinated days 0-2	0	Engerix-B co-administered with investigational acellular Pertussis vaccine within 120 hrs of birth (Y); 91% vaccinated days 0-2	0	NR	NR	NR	Some concerns[41]
Sapru 2007[13]	RCT	Vomiting	Parental report until total follow-up period of 18 weeks	Engerix-B vaccine within first 2 weeks of life (NR)	0% (0/130)	GeneVacB (HepB) vaccine within first 2 weeks of life (NR)	0% (0/132)	NR	NR	NR	Some concerns[41]
Greenberg 2002[14]	RCT	Vomiting (Any)	Solicited parental report for day of vaccination and 3 days following vaccination	Engerix-B vaccine within 4 days of birth (NR)	4.4% (NR/136)	DTaP-HepB, OPV, and Hib vaccines at 2 months of age (NR)	7.8% (NR/129)	NR	NR	NR	Some concerns[41]
Greenberg 2002[14]	RCT	Vomiting (Severe/Grade 3)	Solicited parental	Engerix-B vaccine within	0% (0/136)	DTaP-HepB, OPV, and Hib	0% (0/129)	NR	NR	NR	Some concerns[41]

Study	Study Type	Outcome	Outcome Identification	Intervention (Thimerosal Y/N/NR)	Intervention % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
			report for day of vaccination and 3 days following vaccination; Grade 3- prevented normal daily activities	4 days of birth (NR)		vaccines at 2 months of age (NR)					

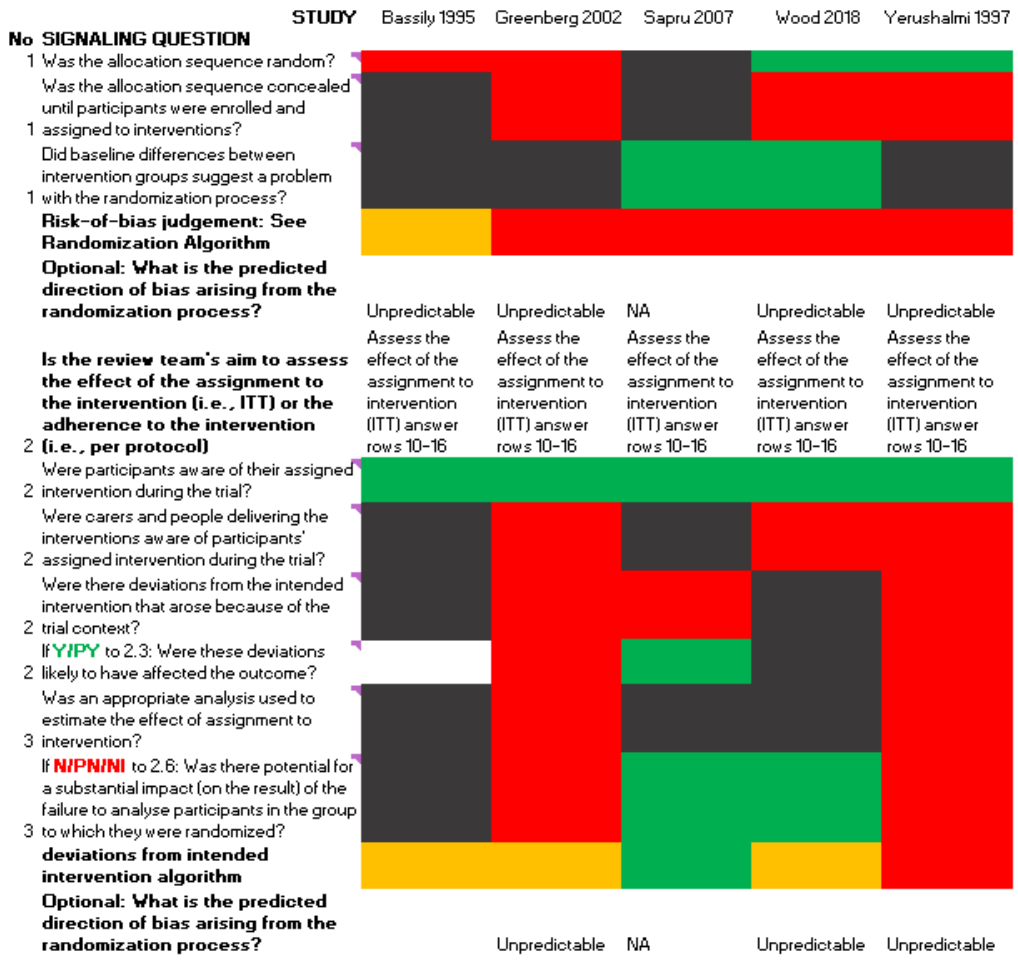
Table 29. Other Reactions Results of Studies Meeting Inclusion Criteria

Study	Study Type	Outcome or Case	Outcome Identification	Intervention or Exposure (Thimerosal Y/N/NR)	Intervention or Exposure % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
Geier 2018[25]	Case-control	Premature puberty	ICD-9 codes	HepB vaccine (unspecified) (Y) or combined Hib-HepB vaccine or no vaccine within first month of life for cases (diagnosed with premature puberty)	Exposure/Cases: (255/486)	HepB vaccine (unspecified) (Y) or combined Hib-HepB vaccine or no vaccine within first month of life for controls (no premature puberty)	Exposure/Controls: (20582/54199)	<0.00001	OR: 1.80, (95% CI: 1.51-2.16) (assessed as OR of exposure to thimerisol-containing vaccine in cases v. controls)	none	Serious concerns[67]
Geier 2018[25]	Case-control	Premature puberty	ICD-9 codes	HepB vaccine (unspecified) (Y) or combined Hib-HepB vaccine or no vaccine within first month of life	Exposure/Controls: (10/28)	HepB vaccine (unspecified) (Y) or combined Hib-HepB vaccine or no vaccine within first month of life	Exposure/Controls: (10584/27989)	>0.99	OR: 0.91, (95% CI: 0.42-1.98) (assessed as OR of exposure to thimerisol-containing vaccine in	Stratified by sex	Serious concerns[67]

Study	Study Type	Outcome or Case	Outcome Identification	Intervention or Exposure (Thimerosal Y/N/NR)	Intervention or Exposure % (n/N)	Control (Thimerosal Y/N/NR)	Control % (n/N)	p-value	Measure of Association	Adjusted	Risk of Bias
				for male cases (diagnosed with premature puberty)		for male controls (no premature puberty)			cases v. controls)		
Geier 2018[25]	Case-control	Premature puberty	ICD-9 codes	HepB vaccine (unspecified) (Y) or combined Hib-HepB vaccine or no vaccine within first month of life for female cases (diagnosed with premature puberty)	Exposure/Controls: (245/458)	HepB vaccine (unspecified) (Y) or combined Hib-HepB vaccine or no vaccine within first month of life for female controls (no premature puberty)	Exposure/Controls: (9997/26209)	<0.00001	OR: 1.87, (95% CI: 1.55-2.25) (assessed as OR of exposure to thimerisol-containing vaccine in cases v. controls)	Stratified by sex	Serious concerns[67]
Haber 2018[16]	Case series	General disorders and administration site conditions	VAERS, non-death, serious reports	Hep B vaccine (unspecified) infants aged <1 month (Y)	4.2% (10/240)	NR	NR	NR	NR	NR	Some concerns[39]
Niu 1996[12]	Case series	Hyperbilirubenemia /HbSAg+	NR	Hep B vaccine (unspecified) infants aged <0.1 yrs of age (Y)	1.7% (1/60)	NR	NR	NR	NR	NR	Some concerns[h]

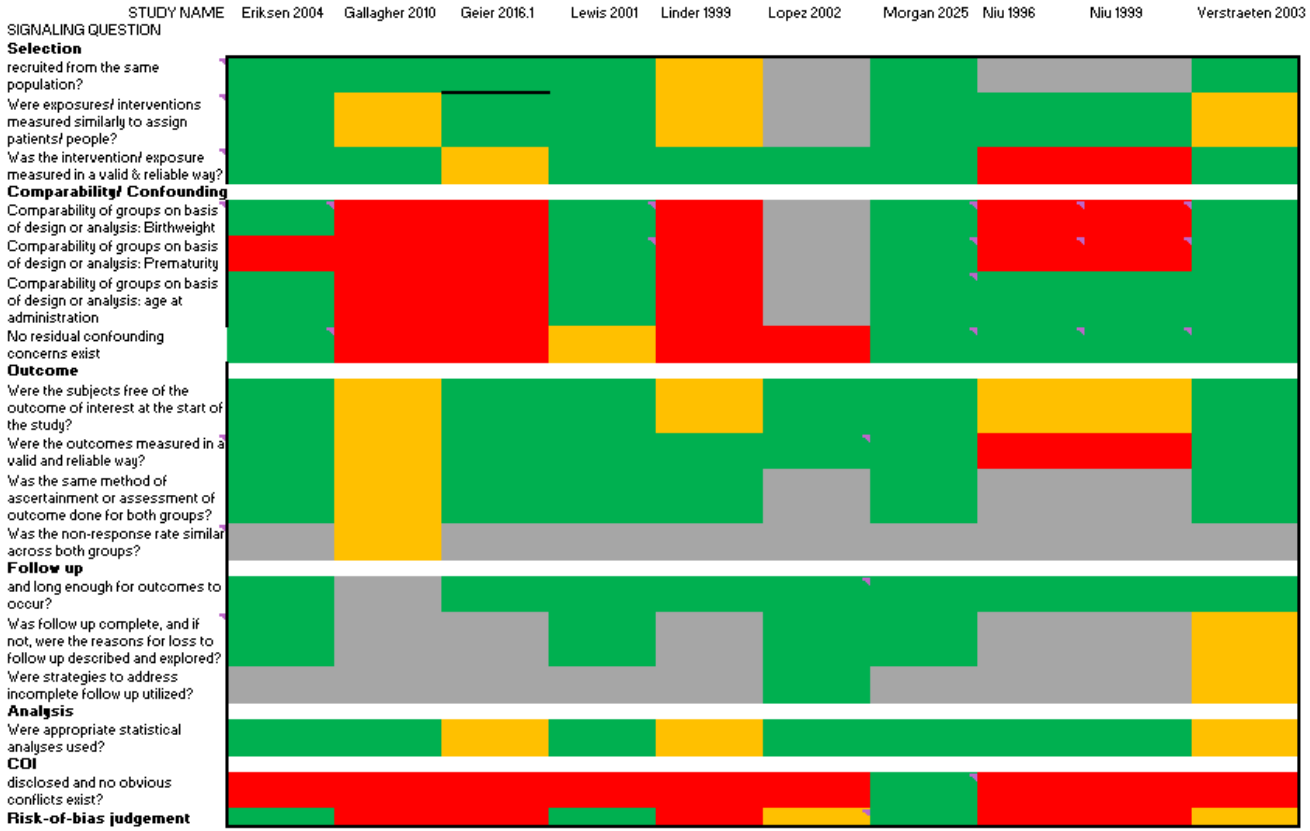
C.3. Risk of Bias Assessments for All Included Studies

Figure 2. Risk of Bias Assessments for Randomized Controlled Trials



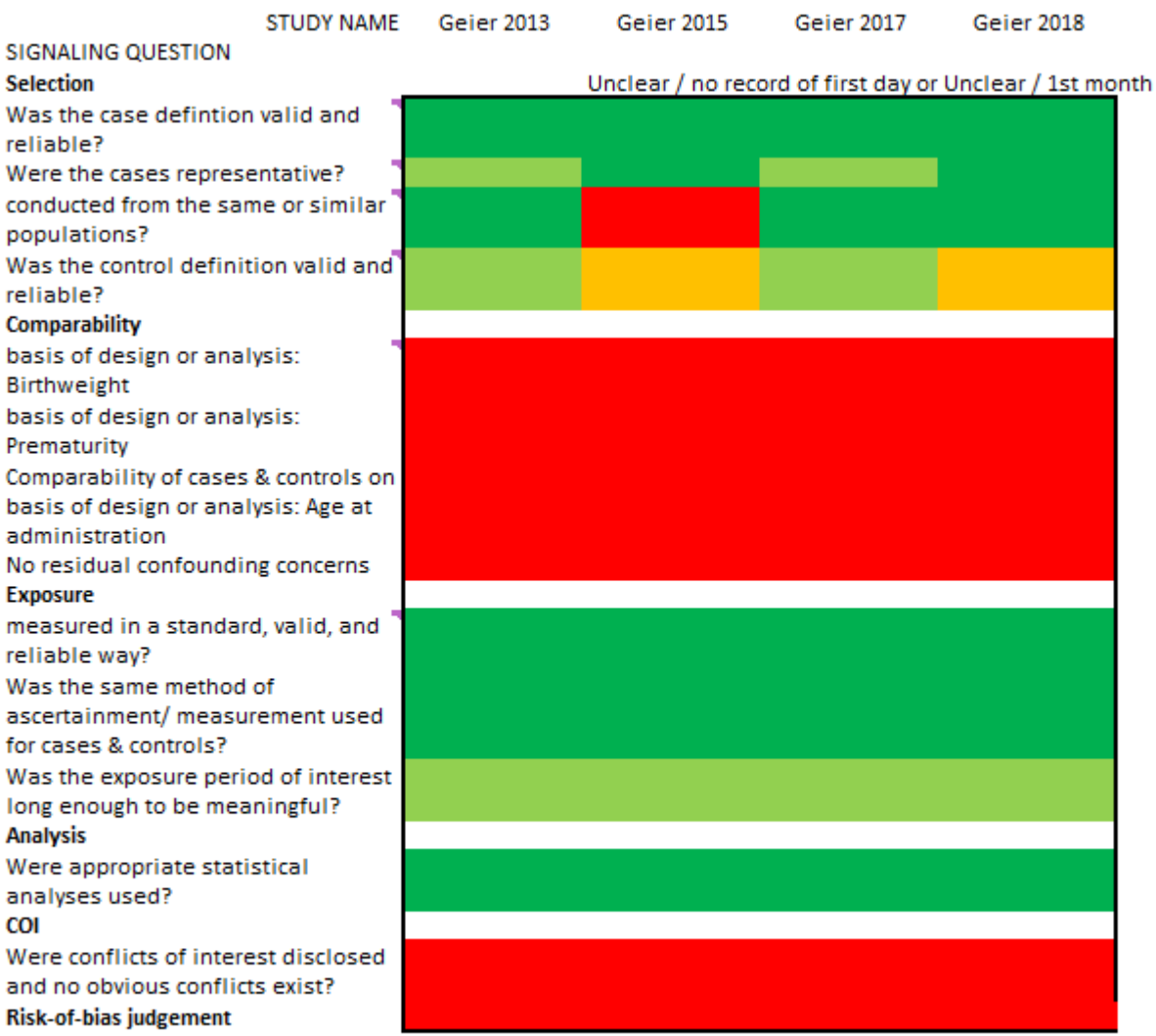
Legend: Green = Yes or Possibly Yes, Yellow = Unclear, Red = No or Possibly No, Grey or Black = Not applicable

Figure 3. Risk of Bias Assessments for Cohort Studies



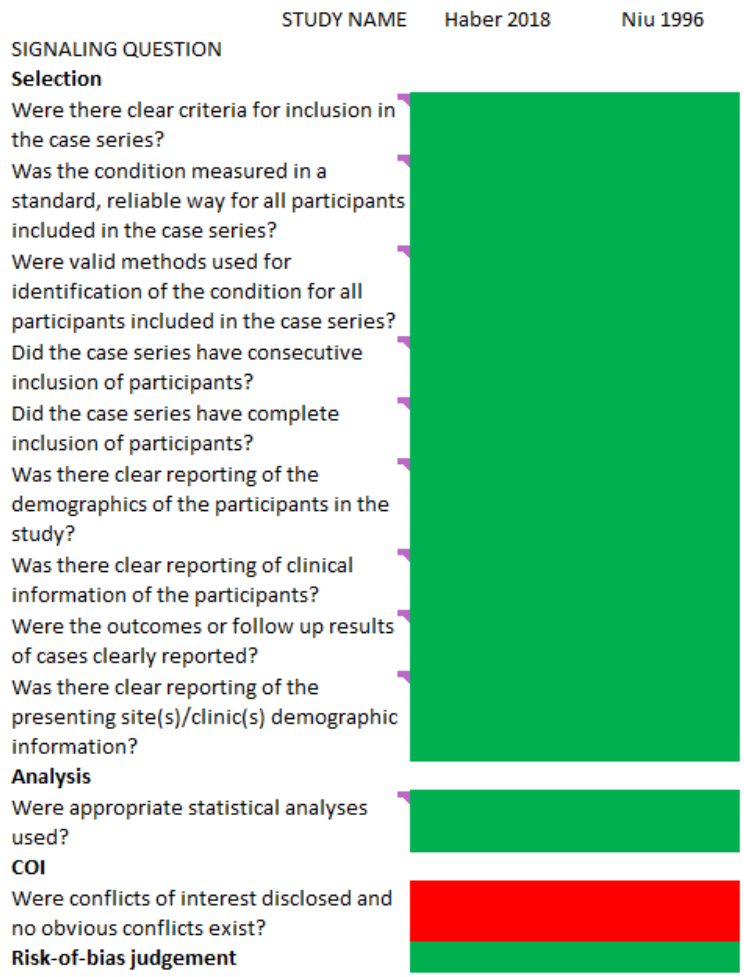
Legend: Green = Yes or Possibly Yes, Yellow = Unclear, Red = No or Possibly No, Grey or Black = Not applicable

Figure 4. Risk of Bias Assessments for Case Control Studies



Legend: Green = Yes or Possibly Yes, Yellow = Unclear, Red = No or Possibly No, Grey or Black = Not applicable

Figure 5. Risk of Bias Assessments for Case Series Studies



Legend: Green = Yes or Possibly Yes, Yellow = Unclear, Red = No or Possibly No, Grey or Black = Not applicable

D. Search Strategies

Table 30. Search Strategies and Results

DATABASE	STRATEGY	RUN DATE	RECORD COUNT
Medline (OVID) 1946-	1. exp Hepatitis B Vaccines/ 2. (((Hepatitis B OR HepB OR Hep B OR HBV) ADJ5 vaccin*) OR HepB-BD OR Engerix-B OR Recombivax HB).ti,ab,kf. 3. 1 OR 2 4. Exp Infant/ 5. (Infant* OR newborn* OR new born* OR neonat* OR birth OR birth-dose*).ti,ab,kf. 6. 4 OR 5 7. Exp Safety/ OR exp Treatment Outcome/ 8. (safety OR (vaccin* ADJ2 safe*) OR treatment outcome* OR adverse* OR harm OR harmful OR harms OR side effect* OR reaction*).ti,ab,kf. OR ae.fs 9. 7 OR 8 10. Exp Clinical Study/ OR exp Product Surveillance, Postmarketing/ 11. (trial* OR observational stud* OR observation stud* OR clinical stud* OR surveillance OR reporting system* OR VAERS OR postmarket* OR post-market*).ti,ab,kf,hw. 12. 10 OR 11 13. 3 AND 6 AND 9 AND 12	07/31/2025	599
Embase (OVID) 1947-	1. exp Hepatitis B Vaccine/ 2. (((Hepatitis B OR HepB OR Hep B OR HBV) ADJ5 vaccin*) OR HepB-BD OR Engerix-B OR Recombivax HB).ti,ab,kf. 3. 1 OR 2 4. Exp Infant/ 5. (Infant* OR newborn* OR new born* OR neonat* OR birth OR birth-dose*).ti,ab,kf. 6. 4 OR 5 7. Exp Safety/ OR exp Treatment Outcome/ OR adverse drug reaction/ 8. (safety OR (vaccin* ADJ2 safe*) OR treatment outcome* OR adverse* OR harm OR harmful OR harms OR side effect* OR reaction*).ti,ab,kf. OR ae.fs 9. 7 OR 8 10. Exp Clinical Study/ OR exp Postmarketing Surveillance/ 11. (trial* OR observational stud* OR observation stud* OR clinical stud* OR surveillance OR reporting system* OR VAERS OR postmarket* OR post-market*).ti,ab,kf,hw. 12. 10 OR 11 13. 3 AND 6 AND 9 AND 12 14. limit 13 to "pubmed/medline" 15. 13 NOT 14 16. limit 15 to conference abstract status 17. 15 NOT 16	07/31/2025	1527 - DUPLICATES =165 UNIQUE RECORDS
Cochrane Library	#1 [mh "Hepatitis B Vaccines"]	07/31/2025	400 -

DATABASE	STRATEGY	RUN DATE	RECORD COUNT
	#2 (("Hepatitis B":ti,ab,kw OR HepB:ti,ab,kw OR "Hep B":ti,ab,kw OR HBV:ti,ab,kw) NEAR/5 vaccin*:ti,ab,kw) OR HepB-BD:ti,ab,kw OR Engerix-B:ti,ab,kw OR "Recombivax HB":ti,ab,kw) #3 #1 OR #2 #4 [mh Infant] #5 (Infant*:ti,ab,kw OR newborn*:ti,ab,kw OR ("new" NEXT born*):ti,ab,kw OR neonat*:ti,ab,kw OR birth:ti,ab,kw OR birth-dose*:ti,ab,kw) #6 #4 OR #5 #7 [mh Safety] OR [mh "Treatment Outcome"] #8 (safety:ti,ab,kw OR (vaccin*:ti,ab,kw NEAR/2 safe*:ti,ab,kw) OR ("treatment" NEXT outcome*):ti,ab,kw OR adverse*:ti,ab,kw OR harm:ti,ab,kw OR harmful:ti,ab,kw OR harms:ti,ab,kw OR ("side" NEXT effect*):ti,ab,kw) #9 #7 OR #8 #10 [mh ^"Clinical Study"] OR [mh ^"Product Surveillance, Postmarketing"] #11 (trial*:ti,ab,kw OR ("observational" NEXT stud*):ti,ab,kw OR ("observation" NEXT stud*):ti,ab,kw OR ("clinical" NEXT stud*):ti,ab,kw OR surveillance:ti,ab,kw OR ("reporting" NEXT system*):ti,ab,kw OR VAERS:ti,ab,kw OR postmarket*:ti,ab,kw OR post-market*:ti,ab,kw) #12 #10 OR #11 #13 #3 AND #6 AND #9 AND #12		DUPLICATES =145 UNIQUE RECORDS
CINAHL (EBSCOHost)	S1 (MH "Hepatitis B Vaccines+") S2 ((((TI "Hepatitis B" OR AB "Hepatitis B" OR SU "Hepatitis B") OR (TI HepB OR AB HepB OR SU HepB) OR (TI "Hep B" OR AB "Hep B" OR SU "Hep B") OR (TI HBV OR AB HBV OR SU HBV)) N5 (TI vaccin* OR AB vaccin* OR SU vaccin*)) OR (TI HepB-BD OR AB HepB-BD OR SU HepB-BD) OR (TI Engerix-B OR AB Engerix-B OR SU Engerix-B) OR (TI "Recombivax HB" OR AB "Recombivax HB" OR SU "Recombivax HB")) S3 S1 OR S2 S4 (MH Infant+) S5 ((TI Infant* OR AB Infant* OR SU Infant*) OR (TI newborn* OR AB newborn* OR SU newborn*) OR (TI "new born*" OR AB "new born*" OR SU "new born*") OR (TI neonat* OR AB neonat* OR SU neonat*) OR (TI birth OR AB birth OR SU birth) OR (TI birth-dose* OR AB birth-dose* OR SU birth-dose*)) S6 S4 OR S5 S7 (MH Safety+) OR (MH "Treatment Outcomes+") OR (MH "Adverse Drug Event+") S8 ((TI safety OR AB safety OR SU safety) OR ((TI vaccin* OR AB vaccin* OR SU vaccin*) N2 (TI safe* OR AB safe* OR SU safe*)) OR (TI "treatment outcome*" OR AB "treatment outcome*" OR SU "treatment outcome*") OR (TI adverse* OR AB adverse* OR SU adverse*) OR (TI harm OR AB harm OR SU harm) OR (TI harmful OR AB harmful OR SU harmful) OR (TI harms OR AB harms OR SU harms) OR (TI "side effect*" OR AB "side effect*" OR SU "side effect*")) S9 S7 OR S8 S10 (MH "Clinical Study+") OR (MH "Product Surveillance, Postmarketing+") S11 ((TI trial* OR AB trial* OR SU trial*) OR (TI "observational stud*" OR AB "observational stud*" OR SU "observational stud*") OR (TI "observation stud*" OR AB "observation stud*" OR SU "observation stud*") OR (TI "clinical stud*" OR AB "clinical stud*" OR SU "clinical stud*") OR (TI surveillance OR AB surveillance OR SU surveillance) OR (TI "reporting system*" OR AB "reporting system*" OR SU "reporting system*") OR (TI VAERS OR AB VAERS OR SU VAERS) OR (TI postmarket* OR AB postmarket* OR SU postmarket*) OR (TI post-market* OR AB post-market* OR SU post-market*)) S12 S10 OR S11	07/31/2025	22 - DUPLICATES =7 UNIQUE RECORDS

DATABASE	STRATEGY	RUN DATE	RECORD COUNT
	S13 S3 AND S6 AND S9 AND S12 Limiters - Exclude MEDLINE records		

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