

ACIP BRIEFING MATERIALS FOR PUBLIC POSTING

The Non-specific Effects of Hepatitis B Vaccines: A Rapid Systematic Review

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A. Background

Non-specific effects of vaccination include broader impacts that may be conferred by vaccines beyond protection against their target pathogen, including the potential for effects on all-cause morbidity and mortality, non-targeted infections, allergic and atopic disease, autoimmune and immune-mediated disease, and malignancy.¹ While the non-specific effects of certain vaccines, including Bacille Calmette-Guérin (BCG) vaccine, measles-containing vaccines, and diphtheria-tetanus-pertussis vaccines, among others,¹ have been previously studied, an evidence-based review of non-specific effects associated with hepatitis B-containing vaccines is needed. Given the need to ensure the safety of all vaccinations administered in childhood, we propose a systematic review of the literature to understand any non-specific effects of childhood vaccinations. In this report, we focused on the literature that evaluated non-specific effects of hepatitis B vaccination.

B. Methods

B.1. Key Question Development

The Key Question was developed by infectious disease and systematic review methodology subject matter experts using the PICO framework² (Population, Intervention, Comparator, and Outcome). The Key Question and PI/ECO(ST) Criteria used to guide the literature review are:

1. What are the non-specific effects of childhood vaccines?

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

PI/ECO(ST) ELEMENT	Description for this Review
Population	Infants and children through 6 years of age
Intervention or Exposure	Hepatitis A (HAV) – Havrix, VAQTA, Hepatitis B (HBV) – Recombivax HB, Engerix-B, Rotavirus – ROTARIX, RotaTeq, Diphtheria, tetanus, acellular pertussis (DTaP) – Infanrix, Daptacel, Haemophilus influenzae type B (Hib) – PedvaxHIB, ActHIB, Hiberix, Poliomyelitis/polio (IPV) – IPOL, Pneumococcal (PCV15, PCV20) –VAXNEUVANCE, Prevnar 20, Measles, mumps rubella (MMR) – PRIORIX, M-M-R II, Varicella - Varivax RSV – Nirsevimab, Clesrovimab, Combination vaccines – Pediarix, Kinrix, Quadracel, Vaxelis, Pentacel, ProQuad
Comparator (if applicable)	Any or none
Outcome(s)	Non-specific effects, all-cause morbidity, all-cause mortality (death), non-targeted infection (sepsis, respiratory tract), allergic and atopic disease (asthma, eczema, atopic dermatitis, food allergy), autoimmune and immune-mediated disease (type 1 diabetes mellitus, inflammatory bowel disease – ulcerative colitis and Crohn’s disease, juvenile idiopathic arthritis, systemic lupus erythematosus, Hashimoto’s thyroiditis, alopecia), malignancy (cancer, leukemia)
Setting	Any
Time Frame	Any publication years Any duration of follow up

B.2. Literature Search

A CDC informationist (JT) developed search strategies from the Key Questions and PICO criteria, and performed the search in MEDLINE, EMBASE, CINAHL, and Cochrane Library from the start of each database to August 20, 2025. Search strategies and results are provided in *Table 8*.

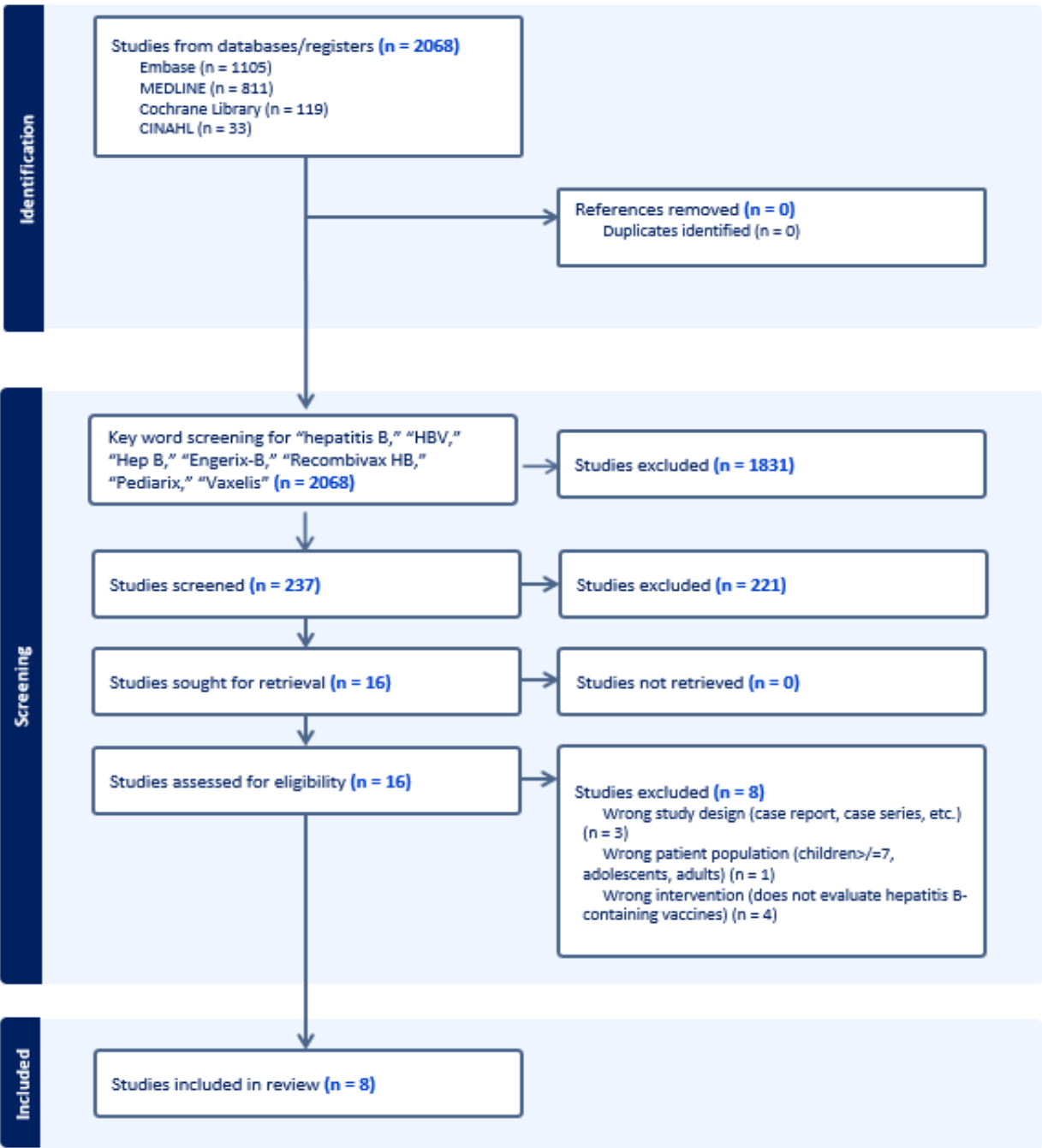
B.3. Study Selection

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. As this was the first of several planned systematic reviews on non-specific effects of childhood vaccination, a keyword search was conducted to filter records with title and abstracts relevant for hepatitis B vaccines (Hepatitis B, HBV, HepB, Engerix-B, Recombivax HB, Pediarix, Vaxelis). Two reviewers (EQ, EM, BE) independently screened all titles and abstracts and removed irrelevant references. Relevant full texts were screened independently by two reviewers (EQ, LZ) 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 (study population did not include children vaccinated at ≤ 6 years of age);
5. No intervention of interest (no hepatitis B vaccine exposure);
6. No outcome of interest;
7. No primary data or secondary data not systematically collected (no reproducible methods); or
8. Insufficient methodologic reporting (i.e., meeting abstract or poster);

Figure 1. Results of the Study Selection Process



B.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 (*Table 5*). 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 region, time, age, weight, and prematurity, 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. The signaling questions used to assess study conduct and risk of bias and results are presented in *Table 6*. The evidence was narratively synthesized for each outcome domain, and for specific outcomes where definitions aligned.

B.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 for each outcome.³

C. Summary of Evidence

C.1. Evidence Tables

C.1.a. GRADE-ed Summary of Findings

Key Question: Among children, what are the non-specific effects of hepatitis B vaccines administered in the first 6 years of life?

Table 2. GRADE Table: Mortality and administration of monovalent hepatitis B vaccines in the first 6 years of life

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
All Mortality Outcomes, Monovalent Hepatitis B Vaccines	Evidence from 3 cohorts suggests hepatitis B vaccine administration may not be associated with an increase in risk of mortality in high-income countries (HIC) and may be associated with an increase in risk in low-and middle-income countries (LMIC). Two studies from HIC suggest either a protective or no effect of hepatitis B vaccination on mortality and one study from an LMIC suggests an increase in mortality after hepatitis B vaccination. Evidence from 1 cohort and 1 nested case series is inconsistent about sex-specific mortality after receipt of hepatitis B vaccines; one study suggests both no difference and an increase in the female-to-male mortality ratio and one study suggests no difference in mortality by sex. One cohort suggests either a protective or no effect on hepatitis B vaccines and cancer-related and cardiovascular-related mortality.	4 Studies (N=46,628)	Some concerns ^a	No concerns	No concerns ^b	Some concerns ^c	Very low confidence
Mortality	Summary: The evidence from 2 cohort studies (He 2022 and Morgan 2025) in HIC suggests no association or a decrease in mortality after hepatitis B vaccination. The evidence from 1 cohort in Guinea-Bissau (Garly 2004) suggests an increase in mortality after hepatitis B vaccination; these findings had some concerns for bias.	3 Cohorts (He 2022, Morgan 2025, Garly 2004) (N=46,515)	Some concerns ^d	No concerns	No concerns ^e	Some concerns ^f	Very low confidence

^a Confounding by weight/weight-for-age z score or health service utilization in 2 studies, temporal variation in 2 studies, regional differences in 2 studies, concern for exposure misclassification in 1 study and inadequate follow up in 1 study.

^b Inconsistency may be explained by direct and indirect population differences.

^c Aaby 2006 and Garly 2004 are conducted in LMIC populations.

^d Confounding by weight/weight-for-age z score or health service utilization in 2 studies, temporal variation in 2 studies, regional differences in 2 studies, and inadequate follow up in 1 study.

^e Inconsistency may be explained by direct and indirect population differences.

^f Garly 2004 is conducted in a LMIC population.

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Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
	<ul style="list-style-type: none"> One cohort (He, 2022) of 36,791 participants in the National Health and Nutrition Examination Survey in the United States suggested a reduced risk of all-cause mortality associated with hepatitis B vaccination [aHR 0.78 (95%CI: 0.68-0.90); 390/10,785 PY vs 4,185/26,006 PY] following vaccination prior to 1.5 years of age with a median follow-up of 8 years. One cohort (Morgan 2025) of extremely preterm infants (<29 weeks 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 of receiving hepatitis B vaccine within 24 hours of life [aRR: 1.13; (95%CI: 0.42-2.81); 7/306 vs 14/512]. One cohort study (Garly 2004) of 8,906 children from Bandim Health Project's Health and Demographic Surveillance System in Guinea-Bissau suggested increased mortality rate at 7 ½ - 12 months of age compared to mortality rate at 1 ½ - 7 ½ months of age [aMRR: 1.62, 95% CI: 1.09, 2.41) for the birth cohort in which most children received hepatitis B vaccination (Hepaccine) at 7 ½ months of age. In a subgroup analysis within a measles vaccine (MV) trial, mortality rate for children 7 ½-12 months of age was elevated among those receiving hepatitis B vaccine (+MV) compared to hepatitis B-unvaccinated (+MV) children (5,441 children), [MRR 1.81 (95%CI: 1.19-2.75)]. Hepaccine is not approved for use in the United States. 						

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
Female and male mortality	<p>One cohort (Garly 2004) from Bandim Health Project's Health and Demographic Surveillance System in Guinea-Bissau suggested elevated female-to-male (F/M) mortality in a subgroup of 5,061 children ages, evaluated through 12 and 24 months within a 2-dose measles trial, among those vaccinated for hepatitis B (Hepaccine) 12 months: [F/M MRR 1.66 (95%CI: 0.80-3.45); 18/143.8 PY vs 12/159.1 PY] 24 months: [F/M MRR 2.20 (95%CI: 1.07-4.54); 22/358 PY vs 11/394.3 PY].</p> <p>In a nested case series (Aaby 2006) in The Gambia's Medical Research Council Laboratories' Demographic Surveillance System, hepatitis B vaccine was the last vaccination received among 7% (4/60) of female infants and 0% (0/53) male infants who died and had vaccination status available from 2-17 months of age.</p>	<p>1 Cohort (Garly 2004) (N= 8,906)</p> <p>1 Case series (Aaby 2006) (N=113)</p>	Some concerns ^g	No concerns	No concerns	Some concerns ^h	Very low confidence
Cancer-related mortality	One cohort (He 2022) of 36,791 participants in the United States' National Health and Nutrition Examination Survey suggested a trend toward reduction in cancer-related mortality among people 6 years and older who had received a hepatitis B vaccine compared to those who were unvaccinated for hepatitis B [aHR 0.76 (95%CI: 0.58-1.00); 97/10,785 PY vs 881/26,006 PY]. Most of the vaccinated population had received hepatitis B vaccine in the first 1.5 years of life with a median follow-up of 8 years.	1 Cohort (He 2022) (N=36,791)	No concerns	No concerns	No concerns	No concerns	Low confidence
Cardiovascular-related mortality	One cohort (He 2022) of 36,791 participants in the United States' National Health and Nutrition Examination Survey suggested no association between cancer-related mortality in people 6 years and older and hepatitis B vaccination [aHR 0.83 (95%CI: 0.60-1.15); 53/10,785 PY vs 732/26,006 PY]. Most of the vaccinated population had received hepatitis B vaccine in the first 1.5 years of life with a median follow-up of 8 years.	1 Cohort (He 2022) (N=36,791)	No concerns	No concerns	No concerns	No concerns	Low confidence

^g Confounding by weight/weight-for-age z score or health service utilization and concern for exposure misclassification in 1 study.

^h Conducted in LMIC population.

Table 3. GRADE Table: Mortality and administration of all hepatitis B-containing vaccines in the first 6 years of life

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
All mortality outcomes, all hepatitis B-containing vaccines	Evidence from 4 cohorts is inconclusive about whether receipt of a hepatitis B-containing vaccine is associated with mortality. Studies (n=2) from HIC suggest a protective or no effect of hepatitis B vaccination on mortality and studies (n=2) from LMIC suggest an increase in mortality after hepatitis B vaccination. Evidence from 4 cohorts and 1 nested case series about sex-specific mortality after hepatitis B-containing vaccines varies. One cohort suggested either a protective or no effect of hepatitis-B containing vaccines on cancer-related and cardiovascular-related mortality. Findings may differ due to differences in types of vaccines administered. Some studies evaluated monovalent hepatitis-B vaccines, and some studies evaluated pentavalent vaccines, which contain antigens to protect against diphtheria, tetanus, pertussis, haemophilus influenzae type B and hepatitis B.	8 Studies (N=82,849)	Some concerns ⁱ	No concerns	No concerns ^j	Some concerns ^k	Very low confidence
Mortality	Summary: The evidence from 2 cohort studies (He 2022 and Morgan 2025) in HIC suggests no increase in the risk of mortality with hepatitis-B vaccination at a follow up of 3 months of life and a median follow up of 8 years of life. <ul style="list-style-type: none"> One cohort (He, 2022) of 36,791 participants in the United States' National Health and Nutrition Examination Survey suggested a reduced risk of all-cause mortality associated with hepatitis B vaccination [aHR 0.78 (95%CI: 	4 Cohorts (He 2022, Morgan 2025, Fisker 2018, Garly 2004) (N=53,609)	Some concerns ^l	No concerns	No concerns ^m	Some concerns ⁿ	Very low confidence

ⁱ Confounding by weight/weight-for-age z score or health service utilization in 4 studies, temporal variation in 3 studies, regional differences in 2 studies, concern for exposure misclassification in 1 study, outcome misclassification in 2 studies and inadequate follow up in 1 study.

^j Inconsistency may be explained by direct and indirect population differences

^k Aamand 2023, Hanifi 2021, Fisker 2018, Fisker 2016, Aaby 2006, Garly 2004 are conducted in a LMIC population

^l Confounding by weight/weight-for-age z score or health service utilization in 3 studies, age at administration in 1 study, temporal variation in 2 studies, regional differences in 2 studies, concern for outcome misclassification in 1 study and inadequate follow up in 1 study.

^m Inconsistency may be explained by direct and indirect population differences

ⁿ Fisker 2018 and Garly 2004 are conducted in a LMIC population

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Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
	<p>0.68-0.90); 390/10,785 PY vs 4,185/26,006 PY] following vaccination prior to 1.5 years of age with a median follow-up of 8 years.</p> <ul style="list-style-type: none"> One cohort (Morgan 2025) of extremely preterm infants (<29 weeks 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 of receiving hepatitis B vaccine within 24 hours of life [aRR: 1.13; (95%CI: 0.42-2.81); 7/306 vs 14/512]. <p>Indirect evidence from 2 cohort studies in Guinea-Bissau (Fisker 2018, Garly 2004) suggests there may be an increase in the risk of mortality after hepatitis-B containing vaccination (pentavalent and hepatitis B vaccine). There are concerns about the generalizability of LMIC infant mortality data to HIC infants.</p> <ul style="list-style-type: none"> In one cohort (Fisker 2018) in Guinea-Bissau, pentavalent vaccine is administered at a younger age than measles vaccine. 7,094 infants in Bandim Health Project's Health and Demographic Surveillance System suggested no association between receiving a measles vaccine first and then a pentavalent vaccine [aHR 1.19 (95%CI: 0.84-1.69); 43/2,847 PY vs 160/14,186 PY], receiving missing pentavalent doses [aHR 1.87 (95%CI: 0.96-3.65); 10/430 PY vs 160/14,186 PY] or not receiving missing pentavalent doses [aHR 0.93 (95%CI: 0.57-1.54); 17/1,537 PY vs 160/14,186 PY] compared to receipt of a pentavalent vaccine first and then a measles vaccine. One cohort study (Garly 2004) of 8,906 children from Bandim Health Project's Health and Demographic Surveillance System in Guinea-Bissau suggested increased mortality rate at 7 						

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
	<p>½ - 12 months of age compared to mortality rate at 1 ½ - 7 ½ months of age [aMRR: 1.62, 95% CI: 1.09, 2.41) for the birth cohort in which most children received hepatitis B vaccination (Hepaccine) at 7 ½ months of age. In a subgroup analysis within a measles vaccine (MV) trial, mortality rate for children 7 ½-12 months of age was elevated among those receiving hepatitis B vaccine (+MV) compared to hepatitis B-unvaccinated (+MV) children (5,441 children), [MRR 1.81 (95%CI: 1.19-2.75)]. Hepaccine is not approved for use in the United States.</p>						
Female-to-male mortality	<p>Summary: Indirect evidence from 4 cohort studies in LMIC suggests there may be an increase in risk of mortality among female compared to male children receiving hepatitis B vaccines. An increased female-to male mortality rate was observed in 2 cohorts (Hanifi 2021, Fisker 2016) but not in 1 cohort (Aamand 2023). One cohort in LMIC reported no difference in female to male mortality at 12 months of age and an increase in female mortality at 24 months (Garly 2004).</p> <ul style="list-style-type: none"> One cohort (Aamand 2023) of 12,753 infants in Bandim Health Project's Health and Demographic Surveillance System in Guinea-Bissau suggested no association between female and male mortality and pentavalent vaccination [F/M aMRR 1.01 (95%CI: 0.82-1.25); 73/2,901 PY vs 78/2,930 PY] through 6 months of follow-up post-vaccination. One cohort (Hanifi 2021) of 7,644 children ages 6 weeks- 9 months in the International Center for Diarrheal Diseases Research Bangladesh's 	<p>4 Cohorts (Aamand 2023, Hanifi 2021, Fisker 2016, Garly 2004) (N=38,033)</p> <p>1 Case series (Aaby 2006) (N=113)</p>	Some concerns ^o	Some concerns ^p	No concerns	Some concerns ^q	Very low confidence

^o Confounding by weight/weight-for-age z score or health service utilization in 2 studies and concern for exposure misclassification in 1 study and outcome misclassification in 1 study.

^p Wide confidence intervals in the study reporting the highest female to male mortality differences.

^q Conducted in LMIC populations.

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Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
	<p>Health and Demographic Surveillance System suggested elevated female-to-male mortality after pentavalent vaccination [F/M MRR 9.91 (95%CI: 1.16-84.44)].</p> <ul style="list-style-type: none"> One cohort (Fisker 2016) of 8,730 infants in Bandim Health Project's Health and Demographic Surveillance System in Guinea-Bissau suggested elevated female-to-male mortality after pentavalent vaccination [F/M aMRR 1.86 (95%CI: 1.16-2.98), 52/1,939 PY vs 31/1,999 PY] through 6-months post-vaccination. One cohort (Garly 2004) from Bandim Health Project's Health and Demographic Surveillance System in Guinea-Bissau suggested no difference in F/M mortality at 12 months [F/M MRR 1.66 (95%CI: 0.80-3.45); 18/143.8 PY vs 12/159.1 PY] and elevated F/M mortality at 24 months [F/M MRR 2.20 (95%CI: 1.07-4.54); 22/358 PY vs 11/394.3 PY]. after hepatitis B vaccination (Hepaccine) in a subgroup of 5,061 children In a nested case series (Aaby 2006) in The Gambia's Medical Research Council Laboratories' Demographic Surveillance System, hepatitis B vaccine was the last vaccination received by 7% (4/60) of female infants and 0% (0/53) male infants who died and had vaccination status information available. 						
Cancer-related mortality	<p>One cohort (He 2022) of 36,791 participants in the United States' National Health and Nutrition Examination Survey suggested a trend toward a reduction in cancer-related mortality among people 6 years and older who had received a hepatitis B vaccine compared to those who were unvaccinated for hepatitis B [aHR 0.76 (95%CI: 0.58-1.00)]. Most of the vaccinated population had received hepatitis B vaccine in the first 1.5 years of life with a median follow-up of 8 years.</p>	<p>1 Cohort</p> <p>(He 2022) (N=36,791)</p>	No concerns	No concerns	No concern	No concerns	Low confidence

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
Cardiovascular-related mortality	One cohort (He 2022) of 36,791 participants in the United States' National Health and Nutrition Examination Survey suggested no association between cancer-related mortality in people 6 years and older and hepatitis B vaccination [aHR 0.83 (95%CI: 0.60-1.15)]. Most of the vaccinated population had received hepatitis B vaccine in the first 1.5 years of life with a median follow-up of 8 years.	1 Cohort (He 2022) (N=36,791)	No concerns	No concerns	No concerns	No concerns	Low confidence

Table 4. GRADE Table: Cardiopulmonary outcomes and administration of hepatitis B vaccines in the first 6 years of life

Outcome	Summary	Studies	Risk of Bias	Imprecision	Inconsistency	Indirectness	Confidence
Cardiopulmonary	The evidence from 1 cohort 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.	1 Study (N=818)	Some concerns	No concerns	No concerns	No concerns	Low confidence
Bronchopulmonary dysplasia	One cohort (Morgan 2025) of extremely preterm infants (<29 weeks 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 preterm infants with a record of receiving hepatitis b vaccine within 24 hours of birth to preterm infants with no record of hepatitis B vaccine within 24 hours of birth [aRR: 0.83; (95%CI: 0.68-1.0); 155/306 vs 317/512].	1 Cohort (Morgan 2025 N = 818)	No concerns	No concerns	No concerns	No concerns	Low confidence

D. Extracted Evidence from Included Studies

Table 5. Characteristics of Studies Meeting Inclusion Criteria

Author Year	Study design	Data Collection Period	Vaccine	Sample size, N	Surveillance System (if Applicable)	Country
Aaby 2006 ⁴	Nested case series	1998 -2002	Hepatitis B [unspecified manufacturer]	113 children who had died and had vaccination status	Medical Research Council Laboratories' Demographic Surveillance System in Farafenni	The Gambia

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Author Year	Study design	Data Collection Period	Vaccine	Sample size, N	Surveillance System (if Applicable)	Country
Aamand 2023 ⁵	Cohort	September 1, 2008 – December 31, 2017	Pentavalent*	12,753 children	Bandim Health Project's Health and Demographic Surveillance System	Guinea-Bissau
Fisker 2016 ⁶	Cohort	September 1, 2008 – April 18, 2011	Pentavalent *	8,730 children	Bandim Health Project's Health and Demographic Surveillance System	Guinea-Bissau
Fisker 2018 ⁷	Cohort	September 1, 2008 – June 22, 2015	Pentavalent*	7,094 children	Bandim Health Project's Health and Demographic Surveillance System	Guinea-Bissau
Garly 2004 ⁸	Cohort	March 1994 – February 2000	Hepatitis B (Hepaccine)	8,906 children	Bandim Health Project's Health and Demographic Surveillance System	Guinea-Bissau
Hanifi 2021 ⁹	Cohort	June 29, 2011 – April 20, 2016	Pentavalent*	7,644 children	International Center for Diarrheal Diseases Research Bangladesh's Health and Demographic Surveillance System in Chakaria	Bangladesh
He 2022 ¹⁰	Cohort	1999 – 2018	Hepatitis B [Unspecified manufacturer, thimerosal-free]	36,791 participants	National Health and Nutrition Examination Survey	United States
Morgan 2025 ¹¹	Cohort	January 1, 2017 – December 31, 2020	Hepatitis B [Engerix-B or HB-Vax-II, thimerosal-free]	818 extremely preterm infants	Surveillance of Adverse Events Following Immunization in the Community	Australia

*Pentavalent vaccine: *Diphtheria-Tetanus-whole cell Pertussis-Hemophilus influenzae type B-Hepatitis B*

Table 6. Results of Studies Meeting Inclusion Criteria

Study	Study Type	Exposure	Outcome	Follow-up	Outcome Identification	Intervention % or rate (n/N or person-time)	Control % or rate (n/N or person-time)	p-value	Measure of Association (95% CI)	Adjusted	Risk of Bias
Aaby 2006	Nested case series	Hepatitis B as last vaccine	Female deaths	Vaccination through 18 months of age	Verbal autopsy	7% (4/60)	NA	NA	NA	No	High risk of bias
Aaby 2006	Nested case series	Hepatitis B as last vaccine	Male deaths	Vaccination through 18 months of age	Verbal autopsy	0% (0/53)	NA	NA	NA	No	High risk of bias

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Study	Study Type	Exposure	Outcome	Follow-up	Outcome Identification	Intervention % or rate (n/N or person-time)	Control % or rate (n/N or person-time)	p-value	Measure of Association (95% CI)	Adjusted	Risk of Bias
Aamand 2023	Cohort	Pentavalent vaccination	Female/male mortality	Vaccination through 6 months post-vaccination	Reported cause of death	25.5 per 1,000 person-years (73/2,901 PY)	26.6 per 1,000 person-years (78/2,930 PY)	NR	1.01 (0.82-1.25)	Yes	Low risk of bias
Fisker 2016	Cohort	Pentavalent vaccination	Female/male mortality	Vaccination through either Subsequent vaccination contact or 6 months post-vaccination	Verbal autopsy, medical review	26.8 per 1,000 PY (52/1,939 PY)	15.5 per 1,000 PY (31/1,999 PY)	0.01	1.86 (1.16-2.98)	Yes	Moderate risk of bias
Fisker 2018	Cohort	Pentavalent after measles vaccine	Mortality	First home visit after 9 months to 5 years of age	Interview	15.1 per 1,000 PY (43/2,847 PY)	11.3 per 1,000 PY (160/14,186 PY)	NR	1.19 (0.84-1.69)	Yes	High risk of bias
Fisker 2018	Cohort	Received missing Pentavalent vaccine at most recent visit	Mortality	First home visit after 9 months to 5 years of age	Interview	23.3 per 1,000 PY (10/430 PY)	11.3 per 1,000 PY (160/14,186 PY)	NR	1.87 (0.96-3.65)	Yes	High risk of bias
Fisker 2018	Cohort	Did not receive missing pentavalent vaccine at most recent visit	Mortality	First home visit after 9 months to 5 years of age	Interview	11.1 per 1,000 PY (17/1,537 PY)	11.3 per 1,000 PY (160/14,186 PY)	NR	0.93 (0.57-1.54)	Yes	High risk of bias
Garly 2004	Cohort	7 ½ - 12 vs 1 ½ - 7 ½ months of age, cohort receiving hepatitis B vaccine (Hepaccine)	Mortality	1.5 months through 12 months of age	Death registration system	NR	NR	0.03	1.62 (1.09-2.41)	Yes	Moderate risk of bias

Study	Study Type	Exposure	Outcome	Follow-up	Outcome Identification	Intervention % or rate (n/N or person-time)	Control % or rate (n/N or person-time)	p-value	Measure of Association (95% CI)	Adjusted	Risk of Bias
Garly 2004	Cohort	Hepatitis B vaccination (Hepaccine)	Mortality	1.5 months through 12 months of age	Death registration system	nr/876	nr/4565	NR	1.81 (1.19-2.75)	No	Moderate risk of bias
Garly 2004	Cohort	Hepatitis B (Hepaccine) + measles vaccine vs measles vaccine	Female/male mortality	7 ½ months through 12 months of age	Death registration system	12.5% (18/143.8 PY)	7.5% (12/159.1 PY)	NR	1.66 (0.80-3.45)	No	Moderate risk of bias
Garly 2004	Cohort	Hepatitis B (Hepaccine) + measles vaccine vs measles vaccine	Female/male mortality	9 months through 24 months of age	Death registration system	6.1% (22/358 PY)	2.8% (11/394.3 PY)	0.04	2.20 (1.07-4.54)	No	Moderate risk of bias
Hanifi 2021	Cohort	Pentavalent vaccination	Female/male mortality	6 weeks through 9 months of age	Household visit	14.3 per 1,000 PY (9/618 PY)	1.4 (1/667 PY)	0.01	9.91 (1.16-84.44)	Yes	High risk of bias
He 2022	Cohort	Hepatitis B vaccination [Unspecified manufacturer, thimerosal free]	All-cause mortality	Median follow-up of 8 years	NHANES Linked Mortality File, 1999-2018	2.8% (390/10,785)	11.8% (4,185/26,006)	NR	0.78 (0.68-0.90)	Yes	Low risk of bias
He 2022	Cohort	Hepatitis B vaccination [Unspecified manufacturer, thimerosal free]	Cancer-related mortality	Median follow-up of 8 years	NHANES Linked Mortality File 1999-2018	0.7% (97/10,785)	2.6% (881/26,006)	NR	0.76 (0.58-1.00)	Yes	Low risk of bias
He 2022	Cohort	Hepatitis B vaccination [Unspecified manufacturer, thimerosal free]	Cardiovascular-related mortality	Median follow-up of 8 years	NHANES Linked Mortality File, 1999-2018	0.4% (53/10,785)	1.9% (732/26,006)	NR	0.83 (0.60-1.15)	Yes	Low risk of bias

Study	Study Type	Exposure	Outcome	Follow-up	Outcome Identification	Intervention % or rate (n/N or person-time)	Control % or rate (n/N or person-time)	p-value	Measure of Association (95% CI)	Adjusted	Risk of Bias
		thimerosal free]									
Morgan 2025	Cohort	Hepatitis B vaccine within 24 hours of birth (Engerix-B and H-B-Vax II, thimerosal-free)	All-cause mortality	Birth to 3 months	Victorian Deaths Index data set	2.3% (7/306)	2.7% (14/512)	0.87	1.13 (0.42-2.81)	Yes	Some concerns
Morgan 2025	Cohort	Hepatitis B vaccine within 24 hours of birth (Engerix-B and H-B-Vax II, thimerosal-free)	Bronchopulmonary dysplasia	Birth to 3 months	ICD-10	50.7% (155/306)	61.9% (317/512)	NR	0.83 (0.68-1.00)	Yes	Some concerns

Table 7. Risk of Bias Assessment of Cohort Studies Meeting Inclusion Criteria

STUDY NAME	Aamand 2023	Fisker 2016	Fisker 2018	Hanifi 2021	He 2022	Garly 2004	Morgan 2025
SIGNALING QUESTION	Cohort	Cohort	Cohort	Cohort	Cohort	Cohort	Cohort
Selection							
Were the groups similar and recruited from the same population?	Green						
Were exposures/ interventions measured similarly to assign patients/ people?	Green						
Was the intervention/ exposure measured in a valid & reliable way?	Green						
Comparability/ Confounding							
Comparability of groups on basis of design or analysis	Green						
Comparability of groups on basis of design or analysis	Green						
Comparability of groups on basis of design or analysis	Green						
Comparability of groups on basis of design or analysis	Green						
Comparability of groups on basis of design or analysis	Green						
No residual confounding concerns exist	Green						
Outcome							
Were the subjects free of the outcome of interest at the start of the study?	Green						
Were the outcomes measured in a valid and reliable way?	Green						
Was the same method of ascertainment or assessment of outcome done for both groups?	Green						
Was the non-response rate similar across both groups?	Green						
Follow up							
Was the follow up time reported and long enough for outcomes to occur?	Green						
Was follow up complete, and if not, were the reasons for loss to follow up described and explored?	Green						
Were strategies to address incomplete follow up utilized?	Green						
Analysis							
Were appropriate statistical analyses used?	Green						
COI							
Were conflicts of interest disclosed and no obvious conflicts exist?	Green						
Risk-of-bias judgement							

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

Table 8. Risk of Bias Assessment of Case Series Studies Meeting Inclusion Criteria

STUDY NAME	Aaby 2006
SIGNALING QUESTION	Nested case series
Selection	
Were there clear criteria for inclusion in the case series?	Green
Was the condition measured in a standard, reliable way for all participants included in the case series?	Yellow
Were valid methods used for identification of the condition for all participants included in the case series?	Red
Did the case series have consecutive inclusion of participants?	Green
Did the case series have complete inclusion of participants?	Black
Was there clear reporting of the demographics of the participants in the study?	Red
Was there clear reporting of clinical information of the participants?	Red
Were the outcomes or follow up results of cases clearly reported?	Black
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Black
Analysis	
Were appropriate statistical analyses used?	Green
COI	
Were conflicts of interest disclosed and no obvious conflicts exist?	Yellow
Risk-of-bias judgement	Red
Legend: Green = Yes or Possibly Yes, Yellow = Unclear, Red = No or Possibly No, Grey or Black = Not applicable	

E. Search Strategies and Results

Table 9. Primary Search of MEDLINE (OVID), Embase (OVID), CINAHL (Ebsco), Scopus, Cochrane Library

Search Strategy:

DATABASE	STRATEGY	RUN DATE	RECORD COUNT
Medline (OVID) 1946-	<ol style="list-style-type: none"> exp Hepatitis B Vaccines/ ((Hepatitis B OR HepB OR Hep B OR HBV) ADJ5 vaccin*) OR HepB-BD OR Engerix-B OR Recombivax HB).ti,ab,kf. 1 OR 2 Exp Infant/ (Infant* OR newborn* OR new born* OR neonat* OR birth OR birth-dose*).ti,ab,kf. 4 OR 5 Exp Safety/ OR exp Treatment Outcome/ (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 7 OR 8 Exp Clinical Study/ OR exp Product Surveillance, Postmarketing/ (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. 10 OR 11 3 AND 6 AND 9 AND 12 	07/31/2025	599
Embase (OVID) 1947-	<ol style="list-style-type: none"> exp Hepatitis B Vaccine/ ((Hepatitis B OR HepB OR Hep B OR HBV) ADJ5 vaccin*) OR HepB-BD OR Engerix-B OR Recombivax HB).ti,ab,kf. 1 OR 2 Exp Infant/ (Infant* OR newborn* OR new born* OR neonat* OR birth OR birth-dose*).ti,ab,kf. 4 OR 5 Exp Safety/ OR exp Treatment Outcome/ OR adverse drug reaction/ (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 7 OR 8 Exp Clinical Study/ OR exp Postmarketing Surveillance/ (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. 10 OR 11 3 AND 6 AND 9 AND 12 limit 13 to "pubmed/medline" 13 NOT 14 limit 15 to conference abstract status 15 NOT 16 	07/31/2025	1527 - DUPLICATES =165 UNIQUE RECORDS

DATABASE	STRATEGY	RUN DATE	RECORD COUNT
Cochrane Library	#1 [mh "Hepatitis B Vaccines"] #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	07/31/2025	400 - 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	07/31/2025	22 - DUPLICATES =7 UNIQUE RECORDS

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

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