

# Non-specific effects following hepatitis B vaccination

**John Su**

**Acting Director**

**Immunization Safety Office**

**Centers for Disease Control and Prevention**

**September 18, 2025**

## Request to CDC from ACIP chair

Present the results for the HepB vaccine from the study by Garly ML, Jensen H, Martins CL, Balé C, Baldé MA, Lisse IM, Aaby P. Hepatitis B vaccination associated with higher female than male mortality in Guinea-Bissau: an observational study. The Pediatric infectious disease journal. 2004 Dec 1;23(12):1086-92.

# Outline

- Review non-specific effects following vaccination
- Summarize Garly, et al. 2004 paper
- Through a rapid systematic review of non-specific effects following hepatitis B vaccination, provide available evidence related to mortality following hepatitis B vaccination

# Non-specific effects following vaccination

- In addition to protecting against their target disease, vaccines may induce changes in the immune system that have broader effects
- Non-specific effects (NSE) are distinct from adverse events, cross-protective, and downstream indirect effects
- Clinical manifestations of NSE
  - All-cause mortality
  - Unrelated infections
  - Risk of allergic and autoimmune disease
- Live-attenuated and non-live vaccines may have differential NSE

# Summary of Garly, et al. 2004 article

# Background

- Several studies have examined the non-specific effects of vaccines on all-cause mortality
- Few studies had examined a potential impact of hepatitis B vaccination and mortality
- Objective of Garly, et al. 2004 paper:
  - Is hepatitis B vaccine associated with sex-specific differences in mortality?

# Methods

- **Study setting:**
  - Guinea-Bissau Bandim Health Project surveillance system
  - Enrolled in measles vaccine trial<sup>1</sup>
- **Study population:**
  - Birth cohorts, March 1994 – February 2000
  - Children born March 1996 – February 1997, eligible for hepatitis B vaccine
- **Study design: prospective cohort**
- **Exposure:**
  - 3 doses of hepatitis B vaccine given at 7.5, 9, and 10.5 months of age
  - Human plasma-derived hepatitis B vaccine, Hepaccine (not a U.S. licensed vaccine)<sup>2</sup>

1. Garly ML, Martins CL, Balé C, da Costa F, Dias F, Whittle H, Aaby P. Early two-dose measles vaccination schedule in Guinea-Bissau: good protection and coverage in infancy. *Int J Epidemiol.* 1999 Apr;28(2):347-52. doi: 10.1093/ije/28.2.347. PMID: 10342702.

2. Hepaccine is not approved for use in the United States; [HEPACCINE-B INJECTION- 27/30.1/0128](#); [HEPACCINE-B MULTIDOSE INJECTION- 27/30.1/0129](#); [HEPACCINE-B PAEDIATRIC INJECTION- 27/30.1/0127](#); [HEPACCINE-B PAEDIATRIC 2 DOSE INJECTION - 27/30.1/0422](#); [HEPACCINE-B PAEDIATRIC MULTIDOSE INJECTION- 27/30.1/0423](#)

# Methods

- **Three mortality comparisons:**

1. Children aged 7.5 - 12 vs 1.5 - 7.5 months, all birth cohorts
2. Hepatitis B-vaccinated vs hepatitis B-unvaccinated (subset in 2-dose measles vaccine (MV) trial)
3. Female-to-male, hepatitis B-vaccinated vs hepatitis B-unvaccinated (among those who received MV; HBV+MV vs MV alone)

Comparison	Groups Compared (MR)	Age Group (mo)	Children Included in Study	Remarks
1	MR for 7½–12 mo versus 1½–7½ mo	1½–12	8906 infants	Six annual birth cohorts were compared: the 7½- to 12-mo age group was compared with the 1½- to 7½-mo age group because HBV was introduced at 7½ mo of age
2	MR for HBV-vaccinated versus no HBV	7½–12	876 HBV-vaccinated and 4565 HBV-unvaccinated	HBV-vaccinated children compared with HBV-unvaccinated cohorts enrolled in the 2-dose measles vaccination trial
3	F:M MR for MV + HBV-vaccinated versus MV alone	9–24	823 MV and HBV-vaccinated and 4238 MV alone	The F:M ratios were compared for children enrolled in the 2-dose measles vaccination trial

F:M indicates female-male ratio; MV, measles vaccine.



# Results

- *Comparison 1 (N = 8,906)*
  - Mortality rate ratio (MRR) was 0.97 (95% CI, 0.77-1.23) for the HBV-unvaccinated cohorts comparing 7.5-12-month to 1.5-7.5 month age groups
  - Among the birth cohorts when most children received HBV (7.5 months of age), children had increased mortality [MRR 1.62 (95% CI 1.09, 2.41)] comparing 7.5-12-month to 1.5-7.5 month age groups
- *Comparison 2 (N= 5,441)*
  - Among children enrolled in the MV trial, compared with HBV-unvaccinated children, the MRR for children 7.5-12 months of age from the HBV-vaccinated cohort was 1.81 (95% CI 1.19, 2.75)
- *Comparison 3 (N=5,061)*
  - The female-to-male MRR was 1.66 (95% CI 0.80-3.45) in the cohort who received both HBV and MV through 12 months of age
  - The female-to-male MRR was 2.20 (95% CI 1.07, 4.54) in cohort who received both HBV and MV and 0.96 (95% CI 0.70, 1.32) in the MV only cohort through 24 months of age

# Conclusions

- Garly, et al. concludes, using 3 different tests of the same intervention:
  - Changes in the mortality pattern after the introduction of hepatitis B vaccine in a high mortality setting
  - Higher mortality between 7.5 and 12 months of age among children who received hepatitis B vaccine compared to those who did not, within a 2-dose measles vaccine trial
  - The effect was found to be stronger for females than for males
  - Hepatitis B vaccine may have sex-differential non-specific effects

# Limitations and Implications

- Analyses were not planned when the trial was designed
- The study was not randomized, so an unbiased comparison of hepatitis B-vaccinated and unvaccinated children from the same period could not be made
- Effects may differ when hepatitis B vaccine is given at birth and with BCG
- An increase in the female-to-male mortality ratio could also represent a reduction in male mortality

# **Rapid systematic review of non-specific effects of hepatitis B vaccine**

# Rapid systematic review of non-specific effects after hepatitis B vaccination

- To inform the Garly et al. 2004 paper, we conducted a rapid systematic review on the non-specific effects (e.g., mortality) after hepatitis B vaccination in children
- The key question used to guide the review: **What are the non-specific effects of hepatitis B-containing vaccines administered in childhood?**

# Rapid systematic review of data on non-specific effects

- Key question: **What are the non-specific effects of hepatitis B-containing vaccines administered in childhood?**
- Conducted a new rapid systematic review of published literature through August 20, 2025
- Electronic databases searched: MEDLINE, EMBASE, CINAHL, and Cochrane Library

PI/ECO(ST) ELEMENT	Description for this Review
<b>Population</b>	Infants and children through 6 years of age
<b>Intervention or Exposure*</b>	Hepatitis B (HBV) – Recombivax HB, Engerix-B  Combination vaccines – Pediarix, Kinrix, Quadracel, Vaxelis, Pentacel, ProQuad
<b>Comparator (if applicable)</b>	Any or none
<b>Outcome(s)</b>	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)
<b>Setting</b>	Any
<b>Time Frame</b>	Any publication years  Any duration of follow up

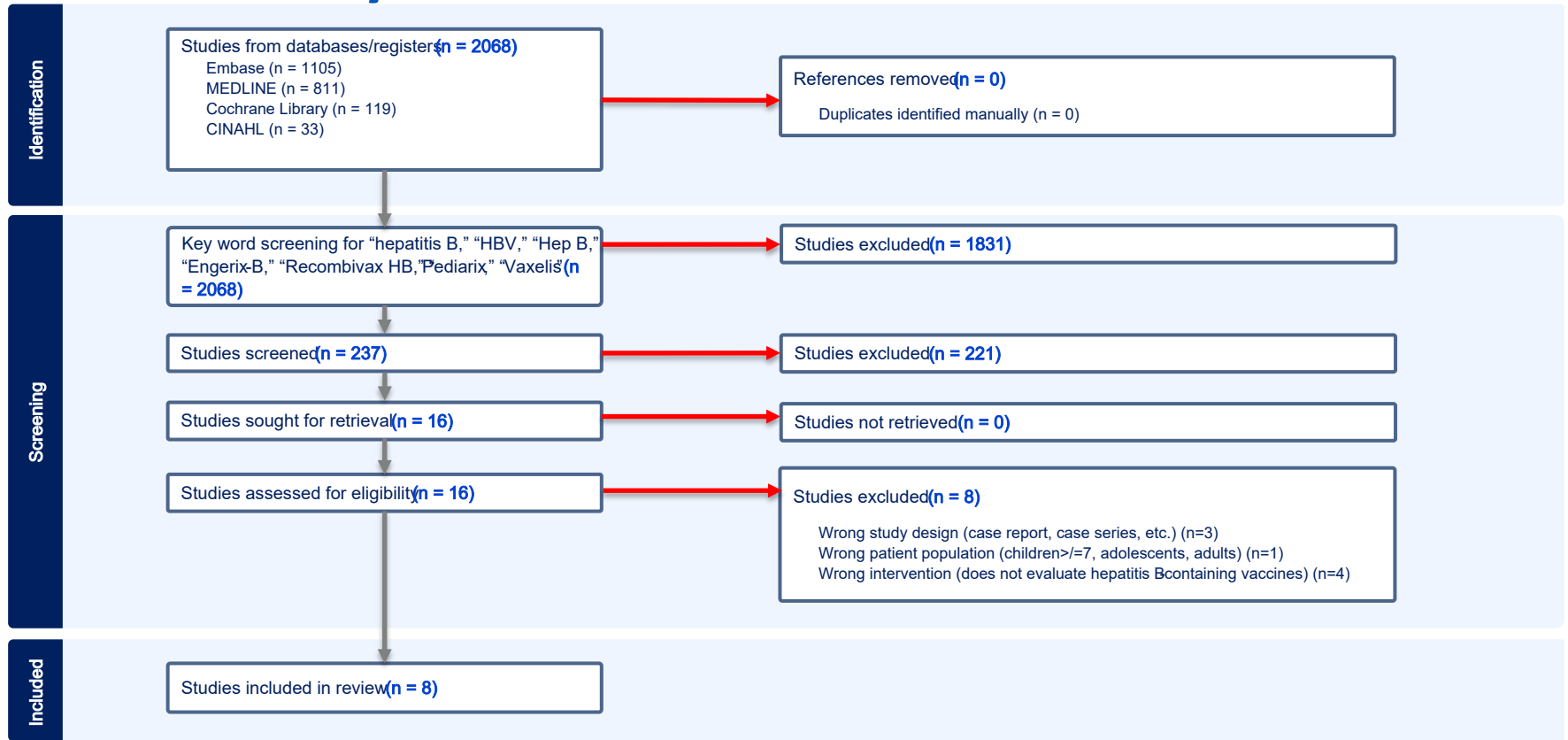
# Results

# Systematic review inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"><li>• Clinical trials</li><li>• Observational studies</li><li>• Surveillance reports</li><li>• Systematic reviews</li></ul>	<ul style="list-style-type: none"><li>• Case reports</li><li>• Case series</li><li>• Narrative reviews</li><li>• Animal studies</li></ul>
<ul style="list-style-type: none"><li>• Infants</li><li>• Children <math>\leq 6</math> years of age</li></ul>	<ul style="list-style-type: none"><li>• Older children <math>\geq 7</math> years of age</li><li>• Adults</li></ul>
<ul style="list-style-type: none"><li>• Hepatitis B vaccines (Hepatitis B, HBV, HepB, Engerix-B, Recombivax HB, Pediarix, Vaxelis)</li></ul>	<ul style="list-style-type: none"><li>• Other vaccines</li></ul>
<ul style="list-style-type: none"><li>• Outcomes include any of the following: non-specific effects, all-cause morbidity, all-cause mortality, non-targeted infection, allergic and atopic disease, autoimmune and immune-mediated disease, malignancy</li></ul>	<ul style="list-style-type: none"><li>• Any other outcome</li></ul>



# Results of systematic review



# Summary of publications meeting search criteria

- **Total of 8 studies included in review**
  - 4 studies evaluated pentavalent, hepatitis B-containing vaccines\* and non-specific effects
  - 4 studies evaluated monovalent hepatitis B vaccines and non-specific effects
- **Study characteristics (N=8)**
- **Presenting results of studies (N=4) evaluating monovalent hepatitis B vaccination**

Characteristic		# of Studies
Study design	Cohort	7
	Nested case series	1
Vaccine administered	Pentavalent vaccine	4
	Monovalent hepatitis B vaccine	4
Country of study	High income country	2
	Low- and middle-income country	6
Non-specific effects	Mortality	4
	Female-to-male mortality	5
	Other non-specific effects	1

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

# Studies evaluating mortality

Two cohort studies in high-income countries (HIC) showed no association between all-cause mortality and hepatitis B vaccination, and one cohort study in a low-and middle-income country (LMIC) suggested an increase in risk of all-cause mortality after hepatitis B vaccination.

Study	Study Type	Country	Outcome and Window	Comparison arms	Non-Specific Effects		Measure of Association
					Intervention Results % (n/N or PT)	Comparison Results % (n/N or PT)	
He 2022	Cohort	United States	All-cause mortality; median follow-up of 8 years	Hepatitis B vaccine* vs no hepatitis B vaccine	(390/10,785)	2.6 (4,185/26,006)	aHR 0.78 (95%CI: 0.68-0.90)
Morgan 2025	Cohort (extremely preterm infants)	Australia	All-cause mortality; within 3 months of life	Hepatitis B vaccine vs no hepatitis B vaccine	2.3 (7/306)	2.7 (14/512)	aRR: 1.13 (95%CI: 0.42-2.81)
Garly 2004	Cohort	Guinea-Bissau	All-cause mortality; 7.5 months – 12 months of age	Hepatitis B vaccine [Hepaccine] + measles vaccine vs measles vaccine	NR/876	NR/4,565	MRR 1.81 (95%CI: 1.19-2.75)

PT = person-time; aHR = adjust hazard ratio; aRR = adjusted rate ratio; NR = not reported; MRR = mortality rate ratio

- \*Unspecified manufacturer, thimerosal-free

# Studies evaluating female-to-male mortality

Evidence is inconsistent about sex-specific mortality after receipt of hepatitis B vaccines in LMIC; 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.

Study	Study Type	Country	Outcome and Window	Comparison arms	Non-Specific Effects		Measure of Association
					Intervention Results % (n/N or PT)	Comparison Results % (n/N or PT)	
Garly 2004	Cohort	Guinea-Bissau	Female-to-male mortality; 7.5 months – 12 months of age	Hepatitis B vaccine [Hepaccine] + measles vaccine vs measles vaccine	12.5 (18/143.8 female person-years)	7.5 (12159.1 male person-years)	MRR 1.66 (95%CI: 0.80-3.45)
Garly 2004	Cohort	Guinea-Bissau	Female-to-male mortality; 9-24 months	Hepatitis B vaccine [Hepaccine] + measles vaccine vs measles vaccine	6.1 (22/358 female person-years)	2.8 (11/394.3 male person-years)	MRR 2.20 (95%CI: 1.07-4.54)
Aaby 2004	Nested case series	The Gambia	Female-to-male mortality; 18 months of age	Hepatitis B as last vaccine vs no hepatitis B as last vaccine	7 (4/60)	0 (0/53)	NR

# Studies evaluating other mortality outcomes

One cohort study in a HIC suggests no effect of hepatitis B vaccines on cancer-related mortality and cardiovascular-related mortality.

Study	Study Type	Country	Outcome and Window	Comparison arms	Non-Specific Effects		Measure of Association
					Intervention Results % (n/N or PT)	Comparison Results % (n/N or PT)	
He 2022	Cohort	United States	Cancer-related mortality; median follow-up of 8 years	Hepatitis B vaccine* vs no hepatitis B vaccine	0.7 (97/10,785)	2.6 (881/26,006)	aHR 0.76 (95%CI: 0.58-1.00)
He 2022	Cohort	United States	Cardiovascular-related mortality; median follow-up of 8 years	Hepatitis B vaccine* vs no hepatitis B vaccine	0.4 (53/10,785)	1.9 (732/26,006)	aHR 0.83 (95%CI: 0.60-1.15]

PT = person-time; aHR = adjusted hazard ratio

\*Unspecified manufacturer, thimerosal-free

# Conclusions

- Few studies exist to inform the non-specific effects of hepatitis B vaccination
- Two cohort studies in HIC showed no association between all-cause mortality and hepatitis B vaccination
- One cohort study in an LMIC showed an increase in risk of all-cause mortality after hepatitis B vaccination
- Evidence is inconsistent about sex-specific mortality after receipt of hepatitis B vaccines

# CDC's interpretation on limitations and implications

- Non-specific effects (NSE) may vary in settings with different background mortality rates and infectious diseases burden
- NSE may not be generalizable across immunization programs
  - Heppacine is not licensed for use in the United States
  - In the United States, hepatitis B vaccine is given earlier and often in combination with other routine vaccines
- Biologic molecular and immunological mechanisms for non-specific effects are not fully understood
  - The interval between vaccination and the onset of NSE, as well as the persistence of effects are uncertain
  - The duration of a vaccine's NSE is complicated by a subsequent vaccination with a different vaccine

# References

1. Pittet L, Netea MG, Curtis N. Chapter 3 - Non-specific Effects of Vaccines. In: Stanley A. Plotkin WAO, Paul A. Offit, and Kathryn M. Edwards, ed. *Plotkin's Vaccines*. 8 ed. Elsevier; 2023:37-44.e7:chap 3.
2. Aaby P, Jensen H, Walraven G. Age-specific changes in the female-male mortality ratio related to the pattern of vaccinations: An observational study from rural Gambia. *Vaccine*. 29 May 2006;24(22):4701-4708. doi:10.1016/j.vaccine.2006.03.038
3. Aamand T, Fisker AB, Correia C, Fernandes M, Clipet-Jensen C, Thyssen SM. Do Pentavalent (DTwP-Hib-HBV) vaccines have sex-differential nonspecific effects? An observational study. *Observational Study Research Support, Non-U.S. Gov't. Hum Vaccin Immunother*. 12 15 2023;19(3):2288297. doi:10.1080/21645515.2023.2288297
4. Fisker AB, Biering-Sorensen S, Lund N, et al. Contrasting female-male mortality ratios after routine vaccinations with pentavalent vaccine versus measles and yellow fever vaccine. A cohort study from urban Guinea-Bissau. *Research Support, Non-U.S. Gov't. Vaccine*. 08 31 2016;34(38):4551-4557. doi:10.1016/j.vaccine.2016.07.034
5. Fisker AB, Thyssen SM. Non-live pentavalent vaccines after live measles vaccine may increase mortality. *Research Support, Non-U.S. Gov't. Vaccine*. 10 01 2018;36(41):6039-6042. doi:10.1016/j.vaccine.2018.08.083
6. Garly ML, Jensen H, Martins CL, et al. Hepatitis B vaccination associated with higher female than male mortality in Guinea-Bissau: An observational study. *Pediatr Infect Dis J*. December 2004;23(12):1086-1092. doi:10.1097/01.inf.0000145700.77286.94
7. Hanifi SMA, Biering-Sorensen S, Jensen AKG, Aaby P, Bhuiya A. Penta is associated with an increased female-male mortality ratio: cohort study from Bangladesh. *Research Support, Non-U.S. Gov't. Hum Vaccin Immunother*. 01 02 2021;17(1):197-204. doi:10.1080/21645515.2020.1763084
8. He WQ, Guo GN, Li C. The impact of hepatitis B vaccination in the United States, 1999-2018. *Hepatology*. 06 2022;75(6):1566-1578. doi:10.1002/hep.32265
9. Morgan HJ, Nold MF, Kattan GS, et al. Hepatitis B vaccination of preterm infants and risk of bronchopulmonary dysplasia: a cohort study, Australia. Vaccination contre l'hépatite B de prématurés et risque de dysplasie bronchopulmonaire: étude de cohorte en Australie, Vacunación contra la hepatitis B en neonatos prematuros y riesgo de displasia broncopulmonar: estudio de cohortes en Australia. *Bull World Health Organ*. 2025;103(3):187-193. doi:10.2471/BLT.24.291683



# Questions?

For more information, contact CDC  
1-800-CDC-INFO (232-4636)  
TTY: 1-888-232-6348 [www.cdc.gov](http://www.cdc.gov)

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

