Gallagher CM, Goodman MS. Hepatitis B Vaccination of Male Neonates and Autism Diagnosis, NHIS 1997–2002. *J Toxicol Environ Health A*. 2010;73:1665-1677.

Hepatitis B is a life-long disease when acquired at birth. About 90% of infants infected perinatally become chronically infected, with a meaningful fraction later dying of cirrhosis or hepatocellular carcinoma. That's why ACIP recommends a universal birth-dose of Hep B vaccine for all newborns (with HBIG for infants of HBsAg-positive parents). Getting that dose on board at birth is a foundational aspect of primary prevention.

Autism spectrum disorder (ASD) is a common and serious condition. Its causes are complex and thought to be multifactorial. Over the last two decades, multiple large, well-designed studies and systematic reviews and meta-analyses (SRMAs) have found no causal link between vaccines, including thimerosal-containing products, MMR, or aluminum and ASD. The best available evidence does not support the claim that vaccines cause autism.[1],[2],[3],[4]

Clinical Question: Among US boys aged 3 to 17 years born before 1999, is receiving the Hep B vaccine in the first month of life (neonatal period) associated with higher parent-reported autism diagnosis compared with boys vaccinated later or never?

- **Population:** Children from the NHIS immunization and sample child files, 1997 to 2002. The cohort of interest was boys aged 3-to-17 years, born before 1999, with a vaccination record available.
    - **Excluded:** Children without a vaccination record, those outside the 3-to-17-year age range, born in or after 1999, and observations with missing key data (missing birth date or vaccine month/year, or "*don't know/refused*" responses). Females were not included in the primary domain of interest.
- **Instrument:** The study used the National Health Interview Survey (NHIS). Exposure (neonatal Hep B) came from the vaccination record transcribed during NHIS interviews.
- **Control/Comparison:** None. Autism was parent-reported (not clinically confirmed), and neonatal Hep B exposure was based on the recorded month/year of first Hep B dose. There was no diagnostic "*gold standard*" or medical record validation.
- **Outcome:** The report of autism came from the Sample Child module question. It was whether a doctor or professional had ever told the parent the child had autism (card-prompted diagnosis list).
- **Exploratory:** There were no prespecified secondary outcomes. However, the authors performed exploratory specificity analyses (substituting unrelated conditions such as Down syndrome, cystic fibrosis, etc., and substituting other vaccines as the exposure), which were null.
- **Type of Study:** An observational, cross-sectional survey analysis of a complex, probability-sampled US dataset with weighted multivariable logistic regression.

Authors' Conclusions: "*Findings suggest that U.S. male neonates vaccinated with the hepatitis B vaccine prior to 1999 (from vaccination record) had a threefold higher risk for parental report of autism diagnosis compared to boys not vaccinated as neonates during that same time period. Nonwhite boys bore a greater risk.*"

Quality Checklist for Reporting of Survey Studies

1. Hypotheses/aims stated? **Yes.**
2. Operational definitions provided? **Yes** (neonatal vaccine timing, autism question & covariates).
3. Eligibility criteria explicit? **Yes** (boys 3 to 17, born before 1999, shot record)
4. Acceptable recruitment strategy? **Yes** (NHIS probability household survey)
5. Random/probability sampling? **Yes** (NHIS complex sampling)
6. Sample size appropriate? **Unsure** (very small case count in domain & no power calculation)
7. Random assignment to groups? **No** (observational)
8. Response/participation rate provided? **No** (not reported for this analysis)
9. Attrition rate acceptable? **Unsure** (not applicable to cross-sectional)
10. Attrition handled appropriately? **Unsure** (not applicable)
11. Appropriate statistical tests? **Yes** (weighted logistic regression & Taylor linearization)
12. Formative/pilot phase included? **No** (secondary analysis)
13. Measures provided in full? **Unsure** (key question shown, but full NHIS modules not reproduced)
14. Measures validated or validation undertaken? **Unsure** (parent report not validated here)
15. Sample described demographically? **Yes** (age, sex, race/ethnicity, household & maternal education)
16. Data collection process replicable? **Yes** (NHIS files & variable coding described)
17. Generalizations appropriately restricted? **Yes** (US probability sample)
18. IRB/ethics approval reported? **Unsure** (not stated, it was public NHIS data)
19. Informed consent reported? **Unsure** (NHIS obtains consent but it was not reported here)
20. Funding/COI disclosed? **Yes** ("*unfunded*" and the NCHS was not responsible for analyses)

Result: Across the NHIS immunization file (1997 to 2002), there were 193 children with and 79,690 without a parent-reported autism diagnosis. The male-to-female ratio among autism cases was 5.43:1. In the primary analytic domain (boys 3 to 17 years, born before 1999, with a vaccination record), autism prevalence was 4.32 per 1,000 boys. Within this domain, 33 boys had autism, and 7,640 did not. 48% of autism cases were non-Hispanic white, 58% lived in a two-parent household, and 75% had mothers with at least a high-school education.

Key Result: In adjusted analyses, neonatal Hep B vaccination was associated with 3.00-fold higher odds of parent-reported autism.

- **Primary Outcome:** Parent-reported autism diagnosis had an OR 3.00 (95% CI 1.11 to 8.13) for neonatal Hep B vs later/never, adjusted for race/ethnicity, maternal education, and two-parent household.
- **Exploratory Outcomes:** Substituting unrelated conditions (Down syndrome, cystic fibrosis, cerebral palsy & heart problems) for autism, and substituting other vaccines (varicella, MMR) for neonatal Hep B showed no significant associations.

Five Things that Threaten the Validity:

1. **Cross-Sectional Design & Temporality:** This is a cross-sectional analysis of survey data. The exposure and outcome are ascertained at one point in time from historical records and parental reports. Although autism is typically diagnosed years after birth, cross-sectional designs cannot establish temporal precedence or causality. These types of studies are susceptible to unmeasured differences between early-vaccinated and later/never-vaccinated children.

2. **Outcome Misclassification:** Autism was measured by parental report of a prior professional diagnosis, with no chart review or standardized diagnostic instrument. The paper itself notes the potential for case ascertainment bias and inability to distinguish ASD subtypes. The overall autism rate in the NHIS subsample differs from surveillance estimates, suggesting possible under- or misclassification. Any non-differential misclassification would bias effects toward the null. Differential misclassification could inflate or deflate associations.

3. **Exposure Misclassification:** *"Neonatal vaccination"* was defined as birth month/year equal to Hep B dose month/year. Records with partial dates were set to missing, and analyses were limited to those with a shot record, which may correlate with sociodemographics. The authors themselves discuss potential misclassification bias in vaccine exposure in administrative datasets and the high proportion of missing data, both of which could bias estimates.

4. **Small Event Counts & Imprecision:** In the key adjusted model, there were 30 autism cases and 7,044 non-cases. Only nine autism cases had neonatal Hep B in unadjusted counts. The resulting wide 95% confidence interval (1.11 to 8.13) signals substantial statistical uncertainty and the possibility of an unstable point estimate sensitive to modelling choices.

5. **Residual Confounding:** Adjustment was limited to race/ethnicity, maternal education & two-parent households. Important factors such as prematurity, birthweight, maternal HBV status, neonatal jaundice, perinatal complications, healthcare-seeking patterns, and other environmental or genetic risks were unavailable. The restriction to boys born before 1999 with a shot record further narrows generalizability and raises concern for selection bias if inclusion correlates with both vaccination timing and autism diagnosis.

SGEM Bottom Line: A small, cross-sectional analysis of 1997 to 2002 NHIS data reports an association between neonatal Hep B vaccination and parent-reported autism in boys, but substantial risks of bias, misclassification, and imprecision mean this study is hypothesis-generating only and should not change practice. This is especially true given the broader literature showing no causal link between vaccines and autism and strong public-health benefits of the Hep B vaccination at birth.

Clinical Application: For clinicians counselling families today, the Hep B vaccine birth dose remains recommended and important for preventing chronic HBV infection from perinatal and early-childhood exposures. The totality of high-quality evidence continues to show no causal association between vaccines and autism, while the benefits of the birth dose are clear in terms of preventing life-long HBV.

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[1] Institute of Medicine (US) Immunization Safety Review Committee. Immunization Safety Review: Vaccines and Autism. Washington (DC): National Academies Press (US); 2004. PMID: 20669467.

[2] Taylor LE, Swerdfeger AL, Eslick GD. Vaccines are not associated with autism: an evidence-based meta-analysis of case-control and cohort studies. Vaccine. 2014 Jun 17;32(29):3623-9. doi: 10.1016/j.vaccine.2014.04.085. Epub 2014 May 9. PMID: 24814559.

[3] Di Pietrantonj C, Rivetti A, Marchione P, Debalini MG, Demicheli V. Vaccines for measles, mumps, rubella, and varicella in children. Cochrane Database of Systematic Reviews 2021, Issue 11. Art. No.: CD004407. DOI: 10.1002/14651858.CD004407.pub5. Accessed 18 September 2025.

[4] Andersson NW, Bech Svalgaard I, Hoffmann SS, Hviid A. Aluminum-Adsorbed Vaccines and Chronic Diseases in Childhood : A Nationwide Cohort Study. Ann Intern Med. 2025 Jul 15. doi: 10.7326/ANNALS-25-00997. Epub ahead of print. Erratum in: Ann Intern Med. 2025 Jul 17. doi: 10.7326/ANNALS-25-03233. PMID: 40658954.