ESTIMATED RATE OF HEMOLYTIC DISEASE OF THE NEWBORN FROM 1996 TO 2010 IN THE UNITED STATES

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BACKGROUND

Hemolytic disease of the newborn (HDN) or fetus and newborn (HDFN) results from alloantibody-mediated neonatal or fetal hemolysis caused by incompatibility of fetal and maternal red cell antigens.[1] In newborns, short- and long-term clinical consequences have been observed, including icterus, kernicterus, anemia, thrombocytopenia, and in rare cases serious neurodevelopmental outcomes.[1,2] Severe alloimmunization with Rh or K antibodies can also place the fetus at risk for anemia, hydrops fetalis, or fetal demise.[1,2]

In the United States, a nationwide Rh HDFN estimate of 106 per 100,000 births in 1986 was obtained from analysis of the nationwide Birth Defects Monitoring Program.[3] Since then, alloimmunization rates from 740 to 1200 per 100,000 births and HDFN rates from 3 to 150 per 100,000 births have been estimated from single-center studies of Rh, ABO, or other significant red cell antibodies.[4-6] No recent estimates based on nationwide surveillance data are available.

OBJECTIVES

- To estimate the rate of HDN and the proportion of severe HDN in the United States
- To identify risk factors associated with increased rates of HDN
- To compare clinical outcomes between healthy newborns, newborns with HDN, and other sick newborns

STUDY DESIGN

Data Source. Eligible hospital inpatient medical care visits were selected from the National Hospital Discharge Survey (NHDS), a nationally representative survey of US hospital discharges from non-institutional short stay general hospitals with 6 beds or more conducted by the Centers for Disease Control and Prevention. NHDS sampled 203-480 hospitals per year over the study period. https://www.cdc.gov/nchs/nhds/about_nhds.htm

Study Design. This was a retrospective, observational cohort study of newborn inpatient medical visits involving HDN from 1996 to 2010.

Study Population

- Inpatient newborn visits were identified using the "newborn flag."
- Newborn visits involving HDFN were identified using the *International Classification of Diseases Clinical Modification, 9th Revision* (ICD-9) codes (773.0-773.5).

Variable Definitions

- Patient characteristics included sex, race, and region.
- Hospital characteristics were hospital size and ownership and expected source of payment.
- Treatments were determined using ICD-9 procedure codes (**Table 1**).
- Alloimmunizations were determined using ICD-9 diagnosis codes. Any newborns coded with 773.0 were categorized as "Rh." Any newborns coded with 773.1 and not 773.0 were categorized as "ABO." All other newborns with an HDFN code were categorized as "Other and Unknown."

Table 1. Treatment Codes

Procedure	ICD-9
Phototherapy	99.82-99.83
Simple transfusion	99.04
Exchange transfusion	99.01
IVIG	99.14

ICD-9, International Classification of Diseases Clinical Modification, 9th Revision; IVIG, intravenous immunoglobulin G.

- Disease severity was identified as any newborn coded for hydrops, kernicterus, or late anemia (773.3-773.5) and/or who received intravenous immunoglobulin G (IVIG) or exchange transfusion (99.01, 99.14)
- Clinical outcomes were birth method (**Table 2**), days of care, and discharge status

Table 2. Birth Method Codes

Birth Method	ICD-9
Cesarean birth	V30.01-V39.01
Vaginal birth	V30.00-V39.00, V30.1-V39.1, and V30.2-V39.2

ICD-9, International Classification of Diseases Clinical Modification, 9th Revision.

Statistical Analysis. Simple frequency and weighted percentages were reported for all variables. Logistic regression was used to test for significance of odds ratios between groups. All analyses were completed using SAS® software version 9.4.

CONCLUSIONS

Our study found the estimated rate of HDN to be consistent with those seen in previous studies. This study observed that the frequency of HDN due to Rh alloimmunization decreased over time, likely due to the widespread use of Rh immune globulin prophylaxis. Nevertheless, a low rate of Rh HDN persists, as does severe disease. Additionally, pregnancies involving HDN have a higher rate of cesarean births vs those that result in healthy newborns. Demographic and clinical disparities merit further investigation.

Strengths

- This study is the first nationally representative estimation of the rate of HDN in the United States. The NHDS provides a large and reliable data source obtained through a robust survey of inpatient medical records.
- The study captured medical visits over a 15-year time period. Analyzing data over time provides a larger sample size and allows for analysis of trends.
- Data were obtained from a representative sample of hospitals throughout the United States based on geographic region and hospital size. A robust sampling procedure improved the generalizability of the results to the entire newborn population of the United States.

Limitations

- The sample size was too small to conduct some subgroup analyses.
- Maternal–fetal care for earlier-onset HDFN and cases resulting in fetal loss are not captured in this study. Additionally, the less than 1.2% of births that occurred outside of the hospital in any given year during this time period were not captured.[7]
- Severity is not currently well defined in any peer-reviewed materials. The definition of "severe" HDN was created through clinical literature and validated by experts. Severity was inferred from diagnostic and procedure variables, so it could not be analyzed with those variables.
- This study relied on ICD-9 codes for the identification of HDN. ICD-9 codes lack detail, and few additional clinical details were available. Imputation error was possible.

Areas for Future Research

- Possible racial disparities leading to the different rates of HDN between White and Black newborns.
- Validation of using HDN treatment and diagnosis as a marker for severity.
- Clinical markers for increased risk of requiring HDN treatment, cesarean birth, and greater length of stay.

RESULTS

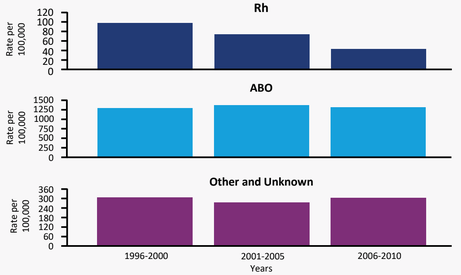
NHDS Newborn Dataset. A total of 480,245 newborn visits were identified and assumed to represent a single newborn delivery visit. The largest proportion of total newborns were White (53.8%) and from the South (36.7%). The largest proportion of visits were to nonprofit hospitals (76.4%) and paid for using Private insurance (45.9%). Most births were vaginal births (73.5%) and resulted in routine discharge (95.8%) (**Table 3**).

Table 3. Total Newborn Characteristics

Characteristic	n (visits/newborns)	Percentage of category
Total	480,245	
Race		
White	233,395	53.8 (53.5-54.0)
Black	59,677	12.1 (11.9-12.3)
Asian or Hawaiian & Pacific Islander	9516	3.0 (2.9-3.1)
Other	34,166	4.8 (4.7-4.9)
Not stated	143,476	26.4 (26.2-26.6)
Region		
Northeast	91,691	18.0 (17.8-18.2)
Midwest	132,176	21.1 (20.9-21.3)
South	170,319	36.7 (36.4-36.9)
West	86,044	24.3 (24.0-24.5)
Birth method		
Vaginal birth	351,020	73.5 (73.3-73.7)
Cesarean birth	129,210	26.5 (26.3-26.8)
Discharge status		
Discharged home	460,063	95.8 (95.7-95.9)
Not discharged home	6122	1.6 (1.5-1.7)
Alive, disposition not stated	10,736	1.6 (1.5-1.7)
Dead	1684	0.3 (0.3-0.4)
Not stated or not reported	1625	0.7 (0.6-0.7)

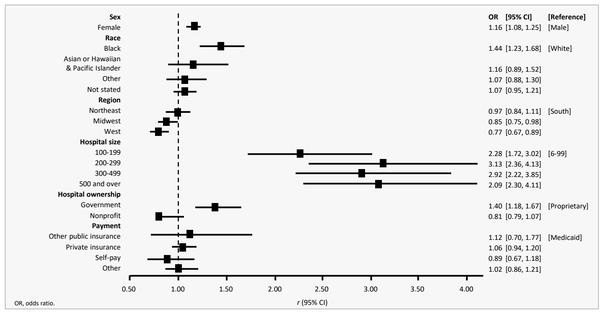
HDN Rate, Severity and Alloimmunization. The rate of HDN was estimated to be 1695 cases/100,000 newborns based on identification of 9810 HDN newborns amongst 480,245 total newborns. Severe HDN represented 0.6% of cases (46 severe cases out of 9810 HDN newborns). The majority of alloimmunizations were ABO (78.1%). Rates of Rh alloimmunization have been decreasing, while no apparent trend was seen with other alloimmunizations (**Figure 1**).

Figure 1. HDN Alloimmunization



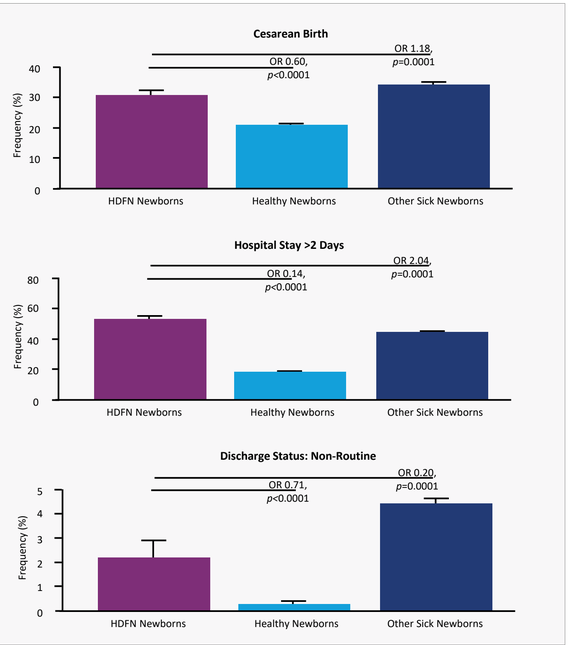
HDN Patient Characteristics. Newborns with HDN were more likely to be Black (vs White), female (vs male), and from the South (vs Midwest and West). Newborns with HDN were more likely to be born in larger hospitals (100-199, 200-299, 300-499, and 500 and over vs 6-99 beds) and government hospitals (vs proprietary) (**Figure 2**).

Figure 2. HDN Patient Characteristics



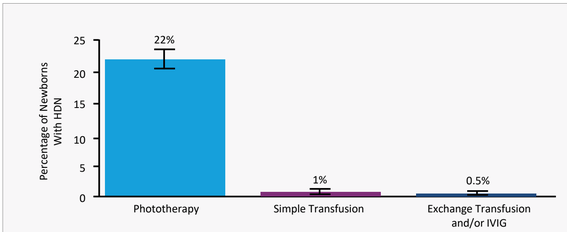
Clinical Outcome. Newborns with HDN were 1.4 times as likely to be delivered by cesarean birth, 1.8 times as likely to require more than 2 days of stay compared with healthy newborns and 1.86 times as likely to experience non-routine discharge (**Figure 3**).

Figure 3. Clinical Outcome



HDN Treatment. Phototherapy was common among patients with HDN (22%), while simple transfusion and exchange transfusion/IVIG were used in only 1% and 0.5% of patients with HDN, respectively (**Figure 4**).

Figure 4. HDN Treatment



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Disclosures

Tjoa ML, Yu D, and Ling LE are employees of Janssen Global Services, LLC and may own stock or stock options in Johnson & Johnson. Moise Jr KJ receives research funding from Momenta Pharmaceuticals, Inc., for participating in a multicenter drug trial, and receives an honorarium for membership of the Steering Committee of this trial.

References

1. Moise KJ, Argoti PS. *Obstet Gynecol.* 2012;120(5):1132-1139. **2.** de Haas M, Thurik FF, Koelewijn JM, van der Schoot CE. *Vox Sang.* 2015;109(2):99-113. **3.** Chávez GF, Mulinare J, Edmonds LD. *JAMA.* 1991;265(24):3270-3274. **4.** Delaney M, Matthews DC. Hematology *Am Soc Hematol Educ Program.* 2015;2015:146-151. **5.** Smith HM, Shirey RS, Thoman SK, Jackson JB. *Immunohematology.* 2013;29(4):127-130. **6.** Moinuddin I, Fletcher C, Millward P. *J Blood Med.* 2019;10:283-289. **7.** MacDorman MF, Declercq E. *Birth.* 2019;46(2):279-288.

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