The economic burden of haemolytic disease of the foetus and newborn: A systematic literature review

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Introduction

- Haemolytic disease of the foetus and newborn (HDFN) is an alloimmune condition of pregnancy caused by pathogenic maternal alloantibodies against red blood cell (RBC) antigens of the foetus; it is often unreported and under-recognised.[1,2]
- Maternal alloantibodies attack foetal RBCs leading to the development of haemolytic anaemia in utero often necessitating admission to a neonatal intensive care unit (NICU) if not adequately treated.[2,3]
- Prenatal management of HDFN is limited to invasive intrauterine transfusions (IUTs), which are resource-intensive procedures, whilst postnatal management is focused on managing anaemia and hyperbilirubinemia with exchange transfusions (ET), RBC transfusions and phototherapy if needed.[1-4]

Objective

- The aim of this systematic literature review (SLR) was to identify and summarise data on impact of HDFN on patients and parent, with a particular focus on the economic burden in Europe, Middle East and Africa.

Methods

- The SLR was conducted according to published guidelines.[5-7]
- Full eligibility criteria for the SLR are provided in **Table 1**; the current poster focuses on real-world evidence studies reporting direct and indirect costs or healthcare resource use data in patients with HDFN in Europe, Middle East and Africa.
- Systematic searches of Embase, MEDLINE, MEDLINE Epub Ahead of Print (In-Process & Other Non-Indexed Citations), EBM Reviews and EconLit were conducted on 29th March 2022.
- Electronic database searches were supplemented with interrogation of several recent conference proceedings (2019-2022), reference lists of included publications, Health Technology Assessment (HTA) agencies, and additional databases.
- Screening and data extraction was performed by a single analyst and checked by a second analyst.

Table 1: Eligibility criteria for SLR

CRITERIA	INCLUDE	EXCLUDE
POPULATION	Patients with HDFN	N/A
INTERVENTION & COMPARATOR(S)	No restriction	N/A

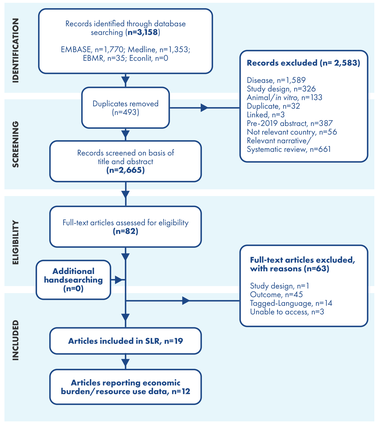
OUTCOMES	• Disease burden (PROs)
	• Patient experience/voice
	• Economic burden/resource use
	  ◦ Presenteeism/absenteeism
	  ◦ Out-of-pocket treatment costs
	  ◦ Hospital/NICU length of stay
	  ◦ Number of outpatient visits
	  ◦ Wider societal impact
	  ◦ Access to specialist care
	  ◦ Impact on family planning, burden on family/day care of other children
		N/A

STUDY DESIGN	• Observational studies:
	  ◦ Epidemiological studies
	  ◦ Cohorts
	  ◦ Cross-sectional studies
	  ◦ Patient surveys
	  ◦ Registries
	  ◦ Case series
	• Government/regulatory reports
	• Reports from other companies
	• Narrative/systematic reviews
		• Studies conducted in a controlled, clinical setting
		• Single case studies/reports

GEOGRAPHY	EMEA	N/A
DATE OF PUBLICATION	No restriction	N/A
LANGUAGE OF PUBLICATION	English language publications or non-English language publications with an English abstract	N/A

Abbreviations: EMEA, Europe, Middle East, and Africa; HDFN, haemolytic disease of foetus and newborn ; N/A, not applicable; NICU, neonatal intensive care unit; PRO, patient-reported outcome; SLR, systematic literature review.

Figure 1: PRISMA flow diagram



Abbreviations: HDFN, haemolytic disease of the foetus and newborn; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

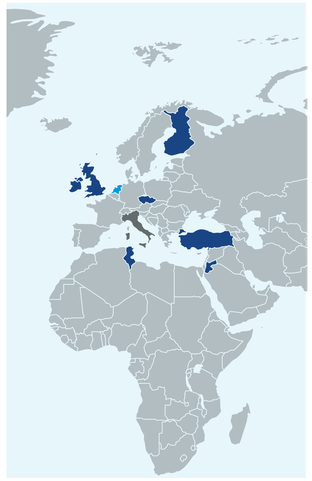
Results

- After screening and supplementary searches, 12 studies were identified reporting economic burden/resource use outcomes in patients with HDFN conducted in Europe, the Middle East or Africa (**Figure 1, Table 2**).[8-19]
- Eleven post-2010 studies were included[8-13, 15-19] plus a single study published in 1997;[14] the latter may be of limited relevance to current clinical management.
- Study designs were primarily retrospective cohorts (n=9)[8-10, 12-17, 19] with two prospective cohorts[9, 18] and one cross-sectional study[11] also being reported.
- Evidence for the following countries was identified (**Figure 2**): The Netherlands (n=3),[14-16] Italy (n=2),[11, 13] Czech Republic (n=1),[18] Finland (n=1),[17] Ireland (n=1),[19] Jordan (n=1),[8] Tunisia (n=1),[10] Turkey (n=1),[9] and UK (n=1).[12]
- Data were limited to neonatal healthcare resource use outcome data only; no direct medical/non-medical cost data on prenatal management of HDFN were identified.
  - NICU visits
    - Admissions (n=2)[9, 17]
    - Readmissions (n=1)[8]
  - Average hospital length of stay (ALOS) (n=10).[8-10, 12-16, 18, 19]
  - Access to care (n=1)[11]

Table 2: List of included studies (n=12)

STUDY, COUNTRY	STUDY DESIGN	POPULATION	OUTCOMES: NEONATAL VISITS	OUTCOMES: ALOS	OUTCOMES: ACCESS TO CARE
AL-LAWAMA 2019,[8] JORDAN	Retrospective cohort	Neonates with HDFN admitted to the neonatal unit and treated with postnatal phototherapy +/- IVIG[1] • +IVIG (n=94) • -IVIG (n=108)	✓	✓	×
ALTUNYURT 2012,[9] TURKEY	Prospective cohort	Neonates with severe HDFN (RhD), previously treated with IUTs (n=19)	✓	✓	×
BEL HADJ 2019,[10] TUNISIA	Retrospective cohort	Neonates hospitalised for HDFN (ABO) (n=98)	×	✓	×
BENNARDELLO 2013[11], ITALY	Cross-sectional	Survey conducted by the SIMTI in Italian Transfusion Structures (n=176)	×	×	✓
BIRCHENALL 2013,[12] UK	Retrospective cohort	Neonates with HDFN, previously treated with IUTs[1] • 1999–2004 (n=44) • 2004–2009 (n=45)	×	✓	×
CORVAGLIA 2012,[13] ITALY	Retrospective cohort	Neonates admitted to NICU for HDFN (RhD) and treated with postnatal phototherapy +/- IVIG[1] • +IVIG (2005–2009) (n=54) • -IVIG (1999–2002) (n=34)	×	✓	×
JANSSENS 1997,[14] THE NETHERLANDS	Retrospective cohort	Neonates with severe HDFN, previously treated with ultrasound-guided IUTs (n=75)	×	✓	×
RATH 2010,[15] THE NETHERLANDS	Retrospective cohort	Neonates with HDFN due to Rh D, C, c, or E antibodies[1] • 2000–2005 (n=156) • 2006–2008 (n=27)	×	✓	×
REE 2021,[16] THE NETHERLANDS	Retrospective cohort	Neonates with severe HDFN admitted to NICU[1] • 2000–2005 (n=156) • 2006–2015 (n=181) • 2015–2020 (n=101)	×	✓	×
SAINIO 2015,[17] FINLAND	Retrospective cohort	Neonates with HDFN, previously treated with IUTs (n=99)	✓	×	×
SIMETKA 2014,[18] CZECH REPUBLIC	Prospective cohort	Neonates with mild or moderate HDFN • Mild (n=14) • Moderate (n=9)	×	✓	×
WALSH 2008,[19] IRELAND	Retrospective cohort	Neonates with HDFN requiring postnatal IVIG & intensive phototherapy over study period (n=11)[1]	×	✓	×

Figure 2: Countries reporting relevant evidence



Abbreviations: ABO, blood groups; ALOS, average length of stay; ET, exchange transfusion; HDFN, haemolytic disease of the foetus or newborn; IVIG, intravenous immunoglobulin; IUT, intrauterine transfusion; NICU, neonatal intensive care unit; NR, not reported; Rh, Rhesus; SD, standard deviation; SIMTI, Italian Society of Immunohaematology and Transfusion Medicine.
[1] Postnatal treatment.
[2] Subgroups based IUT guideline amendment.
[3] Subgroups based on ET guideline amendment.

Neonatal intensive care unit admissions and readmissions

- Limited data were identified for neonatal visits; three publications reported NICU admissions (n=2)[9, 17] or readmissions (n=1)[8] in patients with HDFN (**Table 3**).
  - Across the included studies, the size of the HDFN populations ranged from 19[9] to 202[8] patients and no data were reported from African countries.
  - Five studies exclusively included neonates that had been admitted to hospital or the NICU.[8, 10, 13, 16, 19]
- The proportion of patients with HDFN admitted to the NICU was high (78.0% and 79.8%) in studies conducted in Turkey[9] and Finland,[17] respectively.
- A retrospective study in Jordan reported low NICU readmission rates for blood transfusion or phototherapy (<4%) regardless of whether adjunct postnatal intravenous immunoglobulin (IVIG) infusion had been received.[8]

Average length of stay (ALOS)

- ALOS was the most frequently reported outcome, with relevant data from 10 publications[8-10, 12-16, 18, 19] (**Table 3**). However, a high degree of inter-study heterogeneity was observed regarding the relevant populations and reason for hospitalisation, making robust synthesis of data challenging.
- Across the included studies, the size of HDFN populations ranged from 11[19] to 438[16] patients.
- ALOS was generally between 6–7 days across eight post-2010 publications.[8-10, 12, 13, 15, 16, 18] However, a single study, published in 1997, reported a mean ALOS of 17.9 days in neonates with severe HDFN that had previously been treated with ultrasound-guided IUTs.[14]
- Six studies reported comparative data based on postnatal treatment (n=2),[8, 13] postnatal ET guidelines (n=2),[15, 16] IUT guidelines (n=1),[12] or severity of HDFN (n=1).[18]
  - One study reported significantly higher ALOS in neonates with moderate HDFN versus mild HDFN (p<0.01).[18]
  - One study reported significantly higher ALOS in neonates receiving postnatal adjunct IVIG with phototherapy versus phototherapy alone (p<0.001).[13]
  - However, no significant differences in ALOS were reported between postnatal ET (n=2),[15, 16] postnatal IVIG (n=1)[8] or IUT (n=1)[12] regimen subgroups in the remaining four studies, suggesting limited improvement in treatment management over time.

Access to care

- Bennardello and Curciarello (2013) reported an overview on the management and prevention of HDFN in Italy, based on survey data from 55.5% of Italian transfusion centres.[11]
- Of the responding centres, 46% reported only performing immunohaematological tests on the mother and newborn with 29% recording that immunoprophylaxis had been given. In total, 64 of the 1,661 cases (3.8%) of clinically relevant HDFN required transfusion treatments, such as intrauterine transfusion and exchange transfusion.
- The survey identified gaps in types of services and legally required registers across centres, which, if addressed, could improve the clinical and economic burden of the disease.

Table 3: Studies reporting hospital/NICU admission data or ALOS in patients with HDFN

STUDY, COUNTRY, STUDY DESIGN	NICU ADMISSIONS OR READMISSIONS	ALOS (VARIANCE), DAYS
AL-LAWAMA 2019,[8] JORDAN RETROSPECTIVE COHORT (n=202)	Readmitted for blood transfusion[§] • +IVIG[†], 3.2% • -IVIG, 2.7% **p=0.86** Readmitted for phototherapy[§] • +IVIG[†], 2.1% • -IVIG, 2.7% **p=0.7**	Mean (SD)[‡] • +IVIG, 6.7 (4.1) • -IVIG, 6.9 (6.9) **p=0.8**
ALTUNYURT 2012,[9] TURKEY PROSPECTIVE COHORT (n=19)	Admitted to NICU, 78%	Median (range), 4 (1–77)
BEL HADJ 2019,[10] TUNISIA RETROSPECTIVE COHORT (n=98)	[Admitted to hospital, 100%][§]	Median (range), 5.48 (2–12)
BIRCHENALL 2013,[12] UK RETROSPECTIVE COHORT (n=89)	NR	Median (range) • 1999–2004, 7 (0–94) • 2004–2009, 8 (0–43) **p=0.957**
CORVAGLIA 2012,[13] ITALY RETROSPECTIVE COHORT (n=88)	[Admitted to NICU, 100%][§]	Median (range) • +IVIG, 10 (3–29) • -IVIG, 6 (3–25) **p=0.000**
JANSSENS 1997,[14] THE NETHERLANDS RETROSPECTIVE COHORT (n=75)	NR	Mean (SD) [range], 17.9 (13.6) [0–69]
RATH 2010,[15] THE NETHERLANDS RETROSPECTIVE COHORT (n=183)	NR	Median (SD) • 2000–2005, 6.0 (3.3) • 2006–2008, 6.3 (3.9) **p=0.47**
REE 2021,[16] THE NETHERLANDS RETROSPECTIVE COHORT (n=438)	[Admitted to NICU, 100%][§]	Median (SD) • 2000–2005, 6 (3) • 2006–2015, 7 (3) • 2015–2020, 7 (2) **p=NR**
SAINIO 2015,[17] FINLAND RETROSPECTIVE COHORT (n=99)	Admitted to NICU, 79.8%	NR
SIMETKA 2014,[18] CZECH REPUBLIC PROSPECTIVE COHORT (n=23)	NR	Median (range) • Mild HDFN, 0 (0–6) • Moderate HDFN, 6 (2–23) **p=<0.01**
WALSH 2008,[19] IRELAND RETROSPECTIVE COHORT (n=11)	[Admitted to hospital, 100%][§]	Range of inpatient days, 4–23

Abbreviations: ALOS, average length of stay; HDFN, haemolytic disease of the foetus or newborn; IVIG, intravenous immunoglobulin; NICU, neonatal intensive care unit; NR, not reported; SD, standard deviation.
[†] Postnatal treatment.
[‡] Reported as 'length of hospital stay'; assumed to be the initial hospital stay rather than readmission.
[§] Five studies exclusively included neonates that had been admitted to hospital or the NICU.

Conclusions

- As a rare disease, the economic burden associated with HDFN from both a global and local perspective is poorly understood.
  - The total economic burden, including a robust assessment of costs associated with HDFN, remains to be elucidated. However, data presented in the current SLR show that a substantial proportion of HDFN patients are admitted to NICU.
    - Information relating to the economic burden of HDFN identified in the current SLR was limited to heterogeneous healthcare resource utilisation outcomes.
    - Details of the direct and indirect costs incurred by patients and parents or caregivers as a result of HDFN were not reported.
    - Additional studies investigating aspects such as out-of-pocket treatment costs, work capability, and the burden on family/day care of other children would provide a greater understanding of the patient experience of HDFN.
- In addition to the inherent heterogeneity between real-world evidence publications and evident data gaps, the robustness of conclusions within the included studies is impacted by small recruited patient populations. Evidence is primarily limited to European territories.
  - Further well-powered and representative observational studies using well-defined outcome measures are therefore required to address the evidence gaps highlighted.
- Limited reported comparative data or aligned outcomes between studies makes it difficult to draw notable conclusions, suggesting that further research on the economic burden of HDFN is warranted.

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