L'eradicazione della malattia da Rh(D): a che punto siamo?

The eradication of Rh(D) disease: where do we currently stand?

Francesco Bennardello

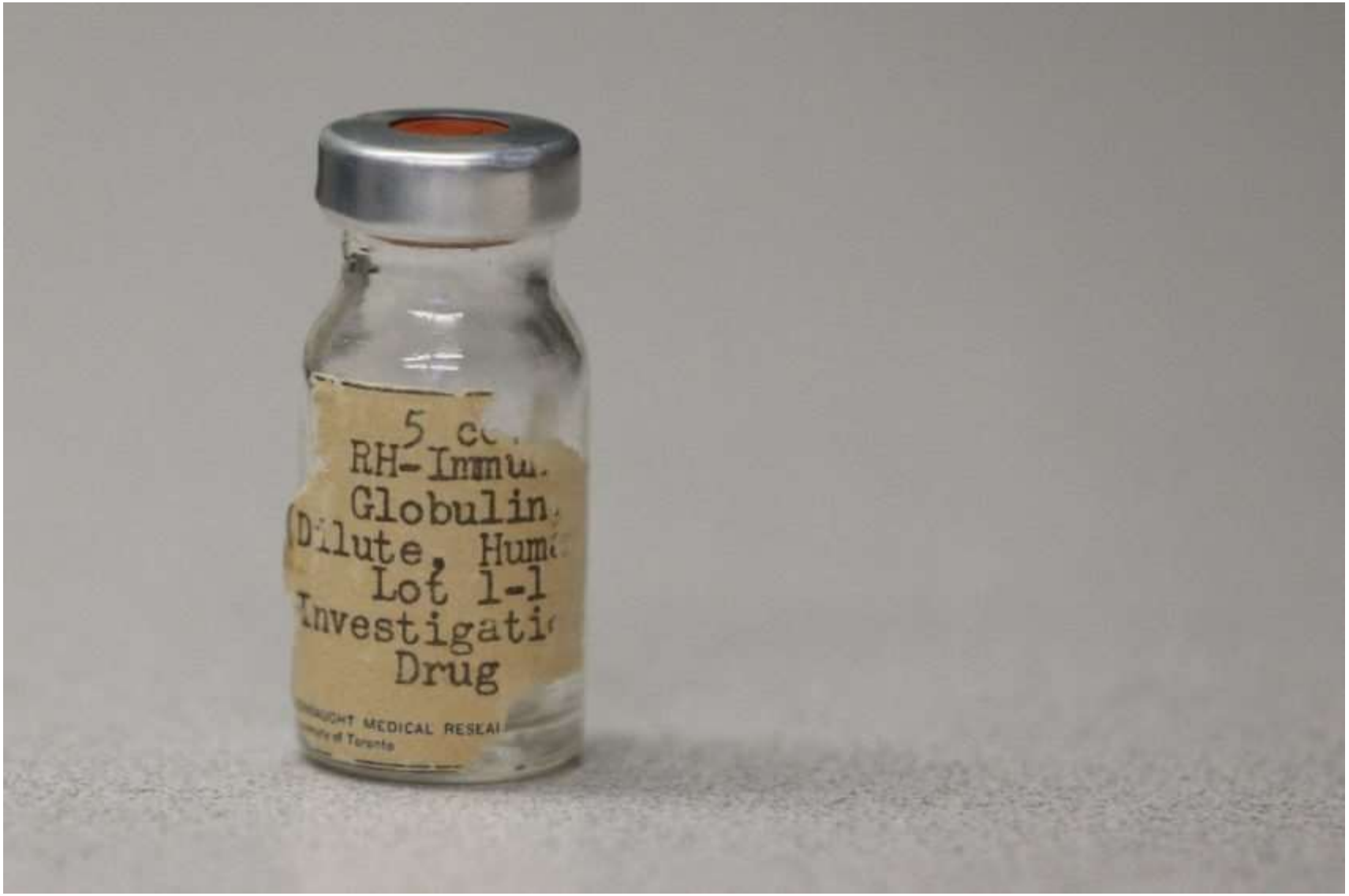
Fifty years of Rh disease prophylaxis
Looking back, looking forth
Roma, 5 Aprile 2018

Il sottoscritto **Francesco Bennardello**,
in qualità di Relatore,
dichiara che
nell'esercizio della Sua funzione e per l'evento in oggetto, **NON E'** in alcun modo portatore di interessi commerciali propri o di terzi; e che gli eventuali rapporti avuti negli ultimi due anni con soggetti portatori di interessi commerciali non sono tali da permettere a tali soggetti di influenzare le mie funzioni al fine di trarne vantaggio.

'My goal? Very modest. Wipe out Rh disease'

Toronto doctor Alvin Zipursky, two decades into retirement, is starting on the biggest challenge of his career.

Dr. Alvin Zipursky, known as "Zip" to his colleagues, was among a group of researchers who developed a cure for rhesus disease, a potentially fatal newborn blood disorder, in the 1960s. (STEVE RUSSELL / TORONTO STAR)



Dr. Alvin Zipursky keeps one of the first vials that held the Rh vaccine, a memento from the early days of research in Winnipeg. (STEVE RUSSELL)

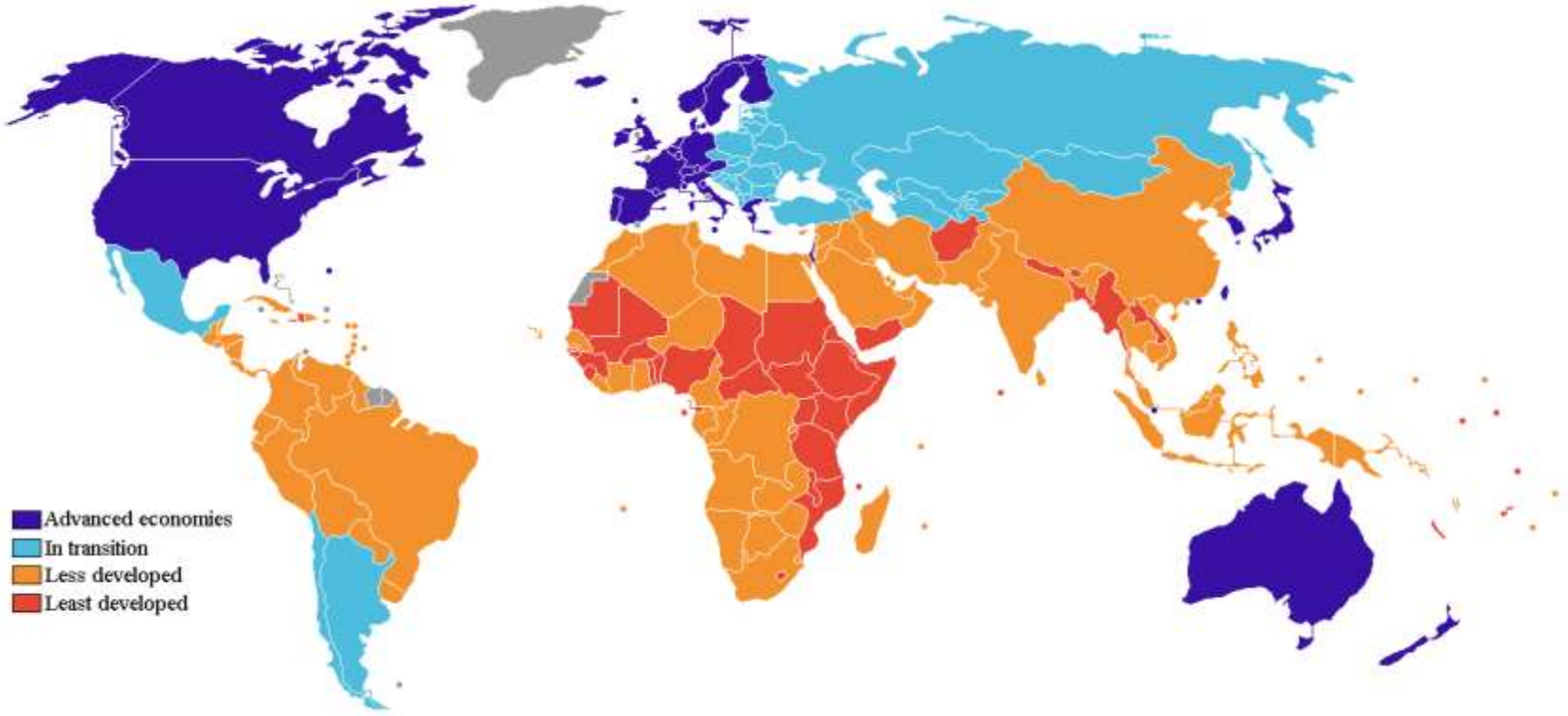
Neo Natal Mortality Rate (NMR) (per 1000 live births)

- High-income countries, with NMR <5

- Emerging countries with lower NMR (5 to <15)

- Countries with higher NMR (≥15)

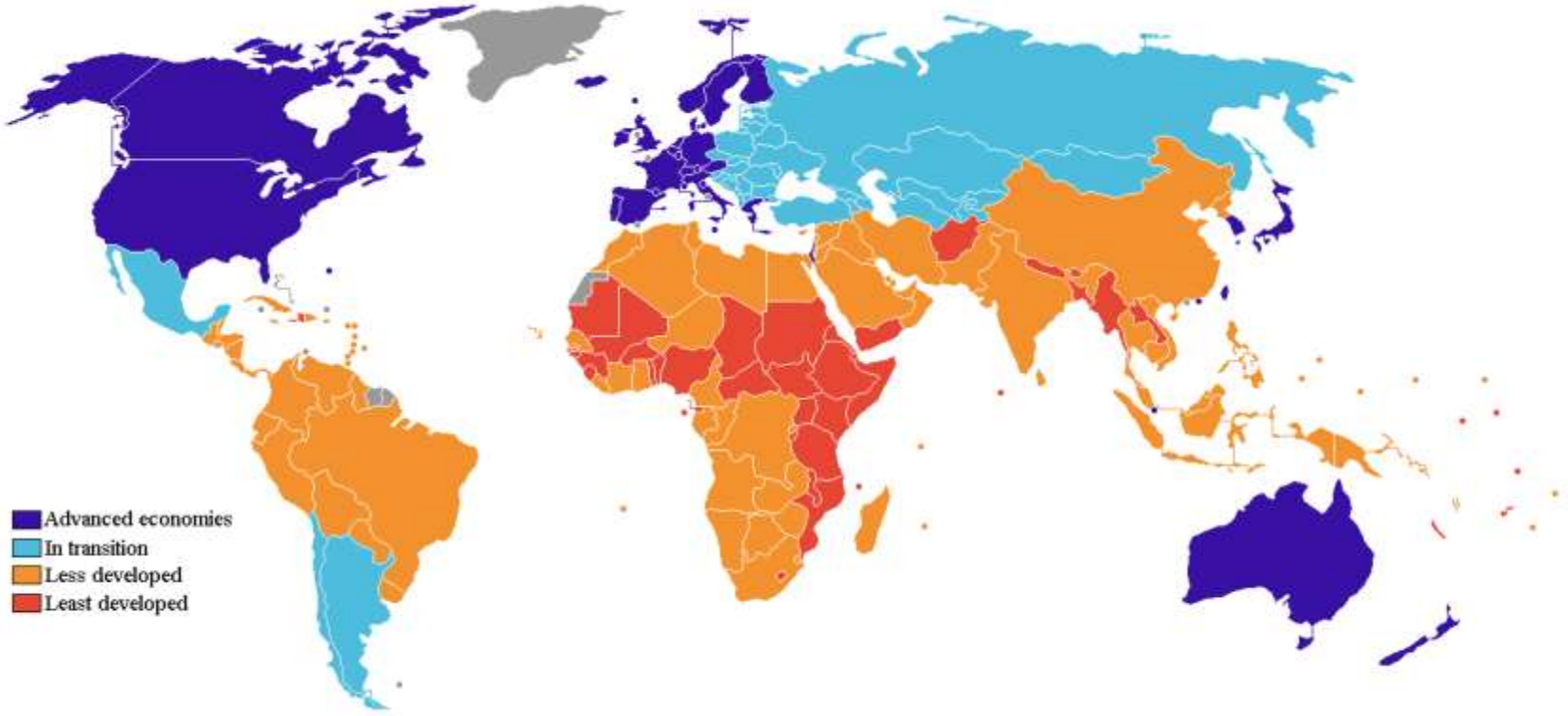
NMR < 5



- Countries with a neonatal mortality rate (NMR) <5 were therefore presumed to have good Rh prophylaxis and strong health systems, with very few cases of Rh disease.

- Rh hemolytic disease has been virtually eradicated by coordinated obstetrical and neonatal care. It is likely that there are lapses in universal immunoprophylaxis in some of these countries.

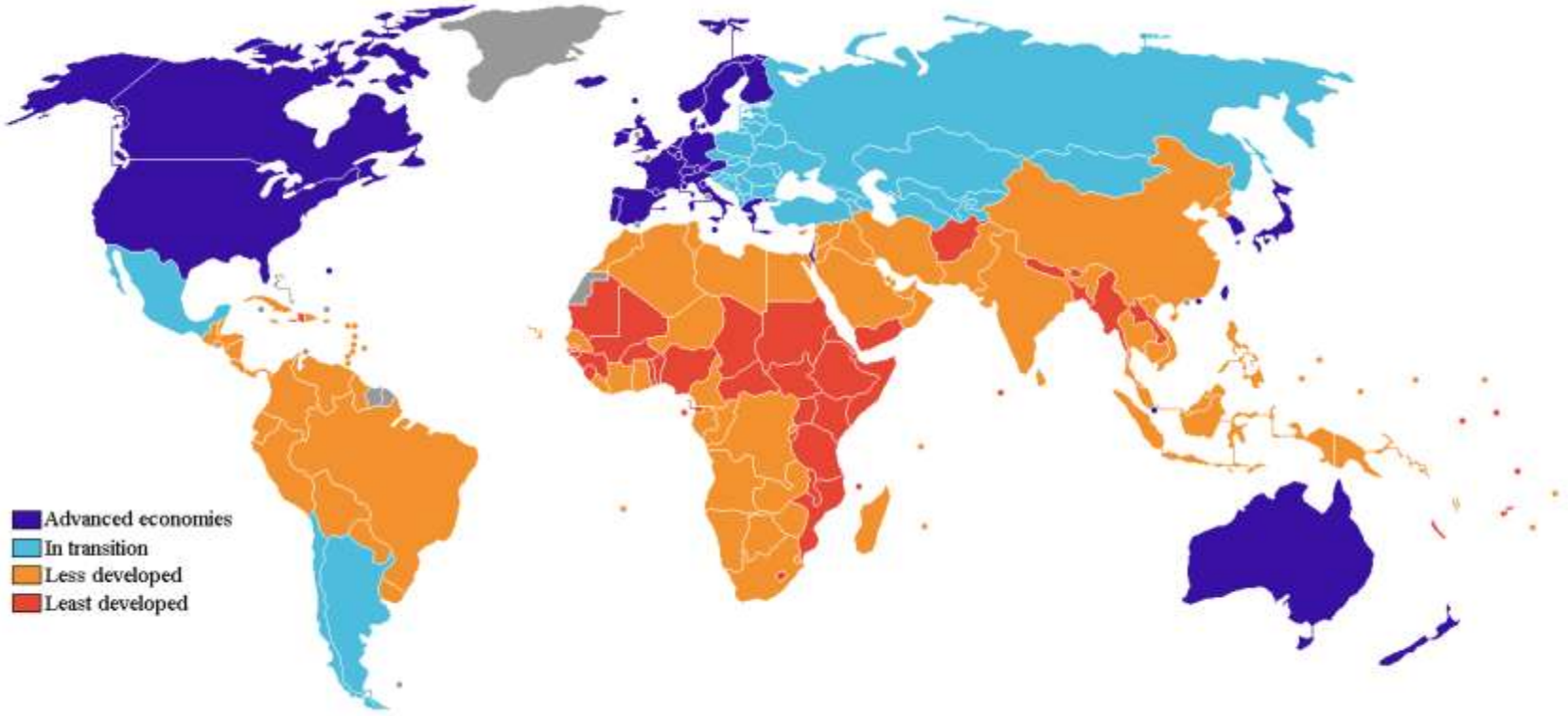
NMR 5 TO < 15



- Emerging countries with NMR > 5 to < 15 that exhibit variations in the quality of care, with variable approach for maternal and newborn care, including for Rh disease and EHB management.

- The management and prevention of Rh sensitization appears to have penetrated clinical practice, but it does not seem to be universal.

NMR ≥ 15



- Countries with higher NMR (≥15) are at the highest risk for neonatal mortality due to Rh disease. Here, reduction in Rh sensitization and better care of every newborn, including management of Extreme Hyper Bilirubinemia (EHB) when needed, are an urgent implementation priority.
- The challenge is to provide unfettered access to Rh immunoprophylaxis and reach remote regions or areas of conflict and postconflict settings.

Neonatal hyperbilirubinemia and Rhesus disease of the newborn: incidence and impairment estimates for 2010 at regional and global levels

Vinod K. Bhutani[1,2], Alvin Zipursky[1], Hannah Blencowe[3], Rajesh Khanna[4], Michael Sgro[5], Finn Ebbesen[6], Jennifer Bell[1], Rintaro Mori[7], Tina M. Slusher[1,8], Nahed Fahmy[9], Vinod K. Paul[10], Lizhong Du[11], Angela A. Okolo[12], Maria-Fernanda de Almeida[13], Bolajoko O. Olusanya[14], Praveen Kumar[15], Simon Cousens[4] and Joy E. Lawn[16,17]

BACKGROUND: Rhesus (Rh) disease and extreme hyperbilirubinemia (EHB) result in neonatal mortality and long-term neurodevelopmental impairment, yet there are no estimates of their burden.

METHODS: Systematic reviews and meta-analyses were undertaken of national prevalence, mortality, and kernicterus due to Rh disease and EHB. We applied a compartmental model to estimate neonatal survivors and impairment cases for 2010.

RESULTS: Twenty-four million (18% of 134 million live births ≥32 wk gestational age from 184 countries; uncertainty range: 23–26 million) were at risk for neonatal hyperbilirubinemia-related adverse outcomes. Of these, 480,700 (0.36%) had either Rh disease (373,300; uncertainty range: 271,800–477,500) or developed EHB from other causes (107,400; uncertainty range: 57,000–131,000), with a 24% risk for death (114,100; uncertainty range: 59,700–172,000), 13% for kernicterus (75,400), and 11% for stillbirths. Three-quarters of mortality occurred in sub-Saharan Africa and South Asia. Kernicterus with Rh disease ranged from 38, 28, 28, and 25/100,000 live births for Eastern Europe/Central Asian, sub-Saharan African, South Asian, and Latin American regions, respectively. More than 83% of survivors with kernicterus had one or more impairments.

CONCLUSION: Failure to prevent Rh sensitization and manage neonatal hyperbilirubinemia results in 114,100 avoidable neonatal deaths and many children grow up with disabilities. Proven solutions remain underused, especially in low-income countries.

The majority of the total EHB and Rh disease (80%) occurred in those born in countries with NMR >15 that account for 60% of the global live births.

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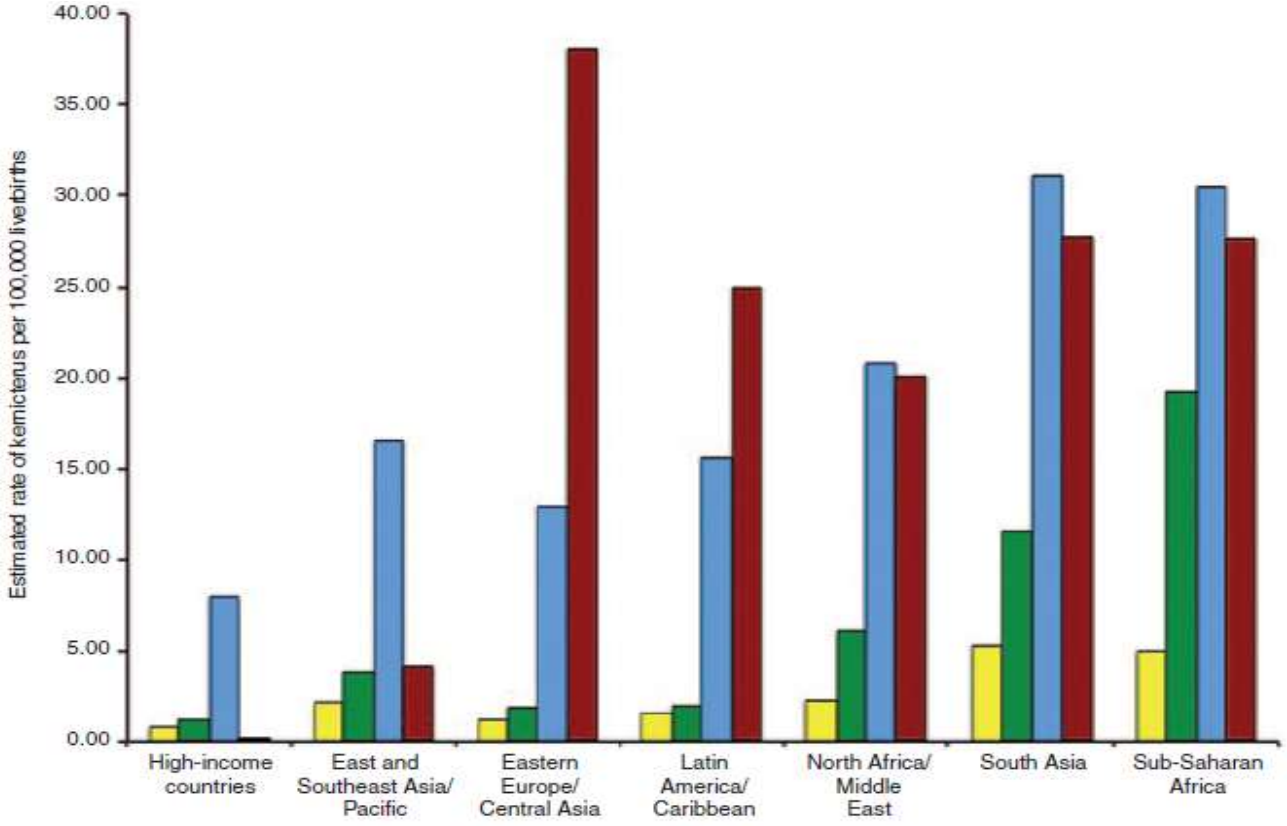

Figure 4. Estimated rates of kernicterus (per 100,000 live births). Data are presented and attributed to cause of hyperbilirubinemia due to prematurity by yellow bars; G6PD deficiency by green; hemolytic and idiopathic conditions by blue; and Rhesus (Rh) disease by red. These are shown for regional geographic distribution worldwide using global burden of diseases (GBD) categorization (54,55).

Management of haemolytic disease of the foetus & newborn: Steps to improve the outcomes

Before the 1970s, haemolytic disease of the foetus and newborn (HDFN) was a major obstetric problem, with a large impact on foetal and neonatal morbidity and mortality. However, with the long-standing established use of anti-D in Rhesus (Rh) negative women for post-natal prophylaxis, together with its increasing routine use for antenatal prophylaxis, the incidence of Rh-(D) sensitization has dramatically fallen[1]. Nevertheless, Rh-D alloimmunization together with sensitization against other red cell antigens still affects a large number of pregnancies every year, with significant health and financial implications[2]. Without an appropriate antenatal detection and treatment programme, up to 50 per cent of untreated HDFN cases will result in neonatal death or damage. In developing countries, especially those lacking an efficient prophylaxis progamme, this will cause a big public health problem and costs. It has been estimated that more than 50,000 foetuses could be affected by this condition every year in India[3]. On the other hand, if anaemia is diagnosed and treated with intrauterine blood transfusions in a timely manner, survival rates can exceed 90 per cent[4]. Women with rising red cell antibody levels are usually referred to tertiary foetal medicine units for specialized management. The main

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REVIEW

Unexpected red blood cell antibody distributions in Chinese people by a systematic literature review

Chunxia Chen, Jinzhe Tan, Lixin Wang, Bing Han, Wei Sun, Li Zhao, Chunyan Huang, Bin Tan, and Li Qin

TABLE 1. Distribution of common Rh blood group system antibodies

	Anti-D	Anti-C	Anti-E	Anti-c	Anti-e
N	2846	707	3929	643	283
F_d	0.000043	0.000006	0.000051	0.000008	0.000001
F_p	0.000270	0.000098	0.000578	0.000074	0.000039
F_h	0.119751	0.015474	0.052941	0.015707	0.014085
F	0.191251	0.047510	0.264028	0.043209	0.019018

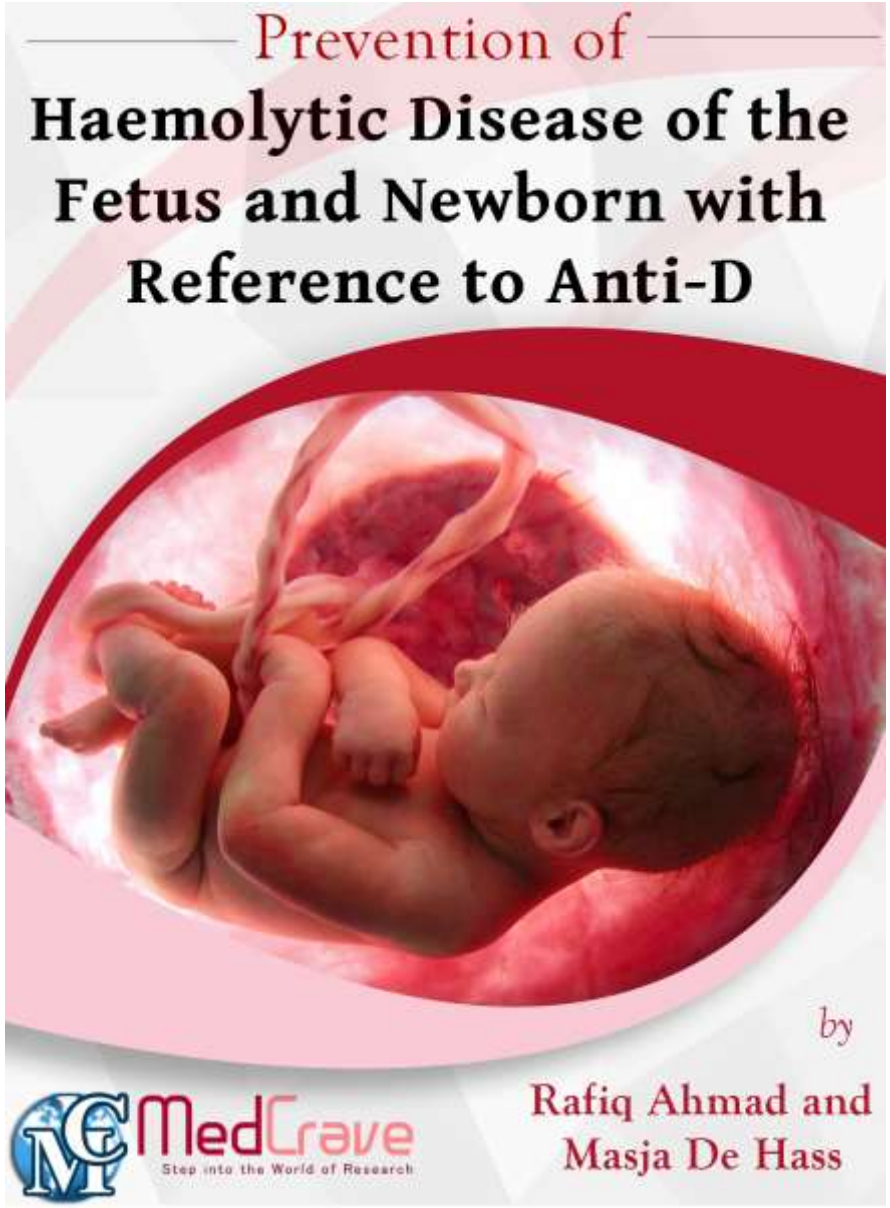
N = total number of certain specified antibody in all extracted data; F_d = frequency in blood donors; F_p = frequency in patients; F_h = the highest frequency reported in special population (for its reference please see Table S1, available as supporting information in the online version of this paper); F = frequency as a percent of all antibodies, F = N/14,881.

TABLE 4. Distribution of unexpected antibodies with HTRs or HDFN*

Blood group system	Antibody	HTR	HDFN
Rh	Anti-D	119 (4.99%)	949 (39.81%)
	Anti-C	53 (2.22%)	70 (2.94%)
	Anti-E	300 (12.85%)	367 (15.39%)
	Anti-c	64 (2.68%)	75 (3.15%)
	Anti-e	34 (1.43%)	5 (0.21%)
	Anti-Ce	8 (0.34%)	27 (1.13%)
	Anti-DC	0	24 (1.01%)
	Anti-CE	2 (0.08%)	3 (0.13%)
	Anti-Ec	27 (1.13%)	46 (1.93%)
MNS	Anti-M	30 (1.26%)	49 (2.06%)
	Anti-N	5 (0.21%)	8 (0.34%)
	Anti-S	5 (0.21%)	4 (0.17%)
	Anti-Mur	8 (0.34%)	9 (0.38%)
p	Anti-P_1	6 (0.25%)	0
Lewis	Anti-Le^a	18 (0.76%)	1 (0.04%)
	Anti-Le^b	5 (0.21%)	0
	Anti-Le^x	1 (0.04%)	0
Kidd	Anti-JK^a	10 (0.42%)	3 (0.13%)
	Anti-Jk^b	18 (0.76%)	9 (0.38%)
Duffy	Anti-Fy^a	0	2 (0.08%)
Diego	Anti-Di^a	2 (0.08%)	9 (0.038%)
	Anti-Di^b	0	2 (0.08%)
Kell	Anti-K	2 (0.08%)	0
Lutheran	Anti-Lu^a	0	1 (0.04%)
Others	H_m	1 (0.04%)	0

* Number in parentheses is F, frequency as a percentage of all antibodies involving HTRs or HDFNs.

- A total of **6,102,361** subjects were included in the 1228 articles.
- The prevalence of unexpected antibodies was around 0.23% (14,095/6,102,361), of which antibodies of the Rh blood group system were the most.
- The prevalence of D antibodies among D-negative people was **15%**



Published By: MedCrave Group LLC July 05, 2017

This retrospective study was undertaken from January, 2012 to December, 2013 to assess the frequency of all immunization in a retrospective review cohort of Rh D negative and RhD-positive pregnant women in a region of Saudi Arabia

1179 pregnant women investigated

Overall prevalence of anti-D **8.03%** among RhD-negative pregnant women

TABLE 1. Distribution of alloantibody specificities*

Antibody	No.†	Percentage‡
Rhesus	587	48.8
E	228	19.0
D	150	12.5
c	93	7.7
C	62	5.2
Cw	45	3.7
e	8	0.7
f	1	0.1
MNS	255	21.2
M	233	19.4
S	16	1.3
s	4	0.3
N	2	0.2
Kell	98	8.1
K	98	8.1
Lewis	76	6.3
Le(a)	57	4.7
Le(b)	19	1.6
Kidd	46	3.8
Jk(a)	39	3.2
Jk(b)	7	0.6
Duffy	35	2.9
Fya	35	2.9
Other	106	8.8
Lu(a)	12	1.0
P1	9	0.7
Kp(a)	7	0.6
Nonspecific	78	6.5
Total	1203	

* The number of affected pregnancies per antibody and the percentage of all alloimmunizations are indicated. Nonspecific antibodies were only included when accompanied by another specific alloantibody.

† Numbers indicate all cases in which specificity for each antibody was detected.

‡ Values indicate the proportion of each antibody among all antibodies.

Red blood cell alloimmunization in pregnancy during the years 1996-2015 in Iceland: a nation-wide population study

Gunnar Bollason,[1] Hulda Hjartardottir,[2] Thorbjorn Jonsson,[1,3] Sveinn Gudmundsson,[3] Sveinn Kjartansson,[4] and Anna Margret Halldorsdottir [1,3]

Anti-D represented only 12.5% of all alloantibodies, being detected in only 16.4% of pregnancies.

The prevalence of D antibodies among D-negative women giving birth was **1.13%** during the study period.

The rate of anti-D alloimmunization in D-negative women is comparable to the rate in other countries before the introduction of routine antenatal anti-D prophylaxis but higher than published rates after the implementation of antenatal prophylaxis.

Survey on the prevention and incidence of haemolytic disease of the newborn in Italy

Francesco Bennardello[1], Giuseppe Curciarello[2]

[1]Service of Immunohaematology and Transfusion Medicine, Provincial Health Authority n. 7, Ragusa; [2]Service of Immunohaematology and Transfusion Medicine, Florence Health Authority, S.M. Annunziata Hospital, Florence, Italy

Background. In 2010, the Italian Society of Immunohaematology and Transfusion Medicine (SIMTI) carried out a survey of the incidence of haemolytic disease of the newborn (HDN) and the prevention of HDN caused by anti-Rh(D) in Italian Transfusion Structures (TS).

Materials and methods. A questionnaire divided into the following five sections was administered: (i) types of services provided and maintenance of legally required registers, (ii) immunoprophylaxis (IP), (iii) red cell typing and searches for irregular antibodies, (iv) evaluation of foetal-maternal haemorrhage (FMH), and (v) incidence of HDN in 2010. Of the 280 TS sent the questionnaire, 176 (63%) replied.

Results. A HDN register was available in 55.5% of the TS (n =91). Immunoprophylaxis with a dose of anti-D IgG was given to all Rh(D) negative and Rh(D) variant puerpera with Rh(D) positive newborns: in more than 93% of cases the dose was between 1,500 IU (300 µg) and 1,250 IU (250 µg). Antenatal IP between the 25th and 28th week was proposed by 42 TS (26%). Seventy percent of the TS (n =115) did not make any evaluation of FMH. The number of births surveyed in 2010 was 203,384, the number of Rh(D) negative pregnancies was 13,569, while anti-D antibodies were present in 245 pregnancies. There were 111 cases of HDN due to anti Rh(D) incompatibility and in 40 of these, intrauterine transfusion (n =) or exchange transfusion (n =32) was necessary. In 94 cases HDN was due to other irregular anti- 4 of these cases intrauterine transfusion was needed and in 11 other recourse was made of e ge transfusion. Finally, there were 1,456 newborns with ABO HDN of whom 13 unde sion.

Discussion. The da re of the incidence of HDN in Italy and of the methods of managing IP and c r an update of the SIMTI recommendations on the management and preve

1.8 %

45 %

TRANSFUSION MEDICINE
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Transfusion Medicine | GUIDELINES

BCSH guideline for the use of anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn

H. Qureshi,[1] E. Massey,[2] D. Kirwan,[3] T. Davies,[4] S. Robson,[5] J. White,[6] J. Jones[7] & S. Allard[8]

Prior to the availability of anti-D immunoglobulin (anti-D Ig), the incidence of Rh D alloimmunisation in D negative women following two deliveries of D positive, ABO-compatible, infants was approximately 16%, and haemolytic disease of the fetus and newborn (HDN) due to anti-D was a significant cause of morbidity and mortality (Urbaniak & Greiss, 2000). Following routine post-partum administration of anti-D Ig, the rate of alloimmunisation dropped to approximately 2%. A further reduction in the sensitisation rate ranging from 0·17 to 0·28% was achieved by introducing routine antenatal prophylaxis during the third trimester of pregnancy (Tovey *et al.*, 1983a,b; Huchet *et al.*, 1987; Mayne *et al.*, 1997; MacKenzie *et al.*, 1999). Associated with this reduction in sensitisation is a reduction in mortality associated with HDN, from 46/100 000 births to 1·6/100 000 births (Pilgrim *et al.*, 2009).

Hemolytic disease of the fetus and newborn (HDFN)

Developed countries

Despite advances in prenatal and postnatal care, alloimmunization during pregnancy is still a problem and Rh-D alloimmunization still affects a large number of pregnancies every year, with significant health and financial implications.

Hemolytic disease of the fetus and newborn (HDFN)

Main causes of anti Rh (D) immunization

- Immunization during pregnancy
- Errors in administration of prophylaxis and in Rh (D) typing
- Inadequate dose prophylaxis
- Mismtached tranfusion

Recommendations for the prevention and treatment of haemolytic disease of the foetus and newborn

Francesco Bennardello[1], Serelina Coluzzi[2], Giuseppe Curciarello[3], Tullia Todros[4], Stefania Villa[5], as Italian Society of Transfusion Medicine and Immunohaematology (SIMTI) and Italian Society of Gynaecology and Obstetrics (SIGO) working group

[1]Immunohaematology and Transfusion Medicine Centre, Provincial Health Authority n. 7, Ragusa; [2]Immunohaematology and Transfusion Medicine Centre, "La Sapienza" University, Rome; [3]Immunohaematology and Transfusion Medicine Centre, "S. Maria Annunziata" Hospital, Florence; [4]Obstetrics and Gynaecology Unit, "Sant'Anna" OIRM Hospital, Turin; [5]Immunohaematology and Transfusion Centre, IRCCS Ca' Granda Foundation, Milan, Italy

Table IX - Recommendations on systematic antenal immunoprophylaxis.

Rec. n.	Recommendation	GoR
21	It is **recommended** that all non-immunised RhD negative women are offered IP at 28 weeks of gestation with a dose of anti-D Ig of 1,500 IU (300 μg). IP at 28 weeks of gestation should be proposed even if IP was given in the preceding weeks because of a potentially immunising event.	*1B*

Blood Transfus 2015; 13: 109-34 DOI 10.2450/2014.0119-14

L'immunoprofilassi anti-Rh (D) deve essere offerta di routine alla 28^ settimana a tutte le donne in gravidanza Rh (D) negative non sensibilizzate

Novembre 2010

The role of antenatal immunoprophylaxis in the prevention of maternal-foetal anti-Rh(D) alloimmunisation

Giancarlo Maria Liumbruno[1,2], Angelo D'Alessandro[1], Federica Rea[3], Vanessa Piccinini[1], Liviana Catalano[1], Gabriele Calizzani[1], Simonetta Pupella[1], Giuliano Grazzini[1]

Table II – Recommended antenatal anti-D prophylaxis in the main international recommendations

	Recommended dose	Week
Canada (SOGC)[20]	300 (or 100-120)	28 (or 28 and 34)
Italy (SIMTI-SIGO)[21]	250-300	28
USA (ASCP)[16]	300	28-30
USA (ACOG)[51]	Not specified	28
USA (USPSTF)[52]	300	24-28
UK (NICE)[53]	100	28 and 34
UK (BCSH)[54]	100	28 and 34
Australia (NHMRC)[56]	125	28 and 34
Australia (RANZCOG)[57]	125	28 and 34
France (CNGOF)[58]	300	28
The Netherlands (CHI)[59]	200	30
Spain (SETS-SEOG)[60]	300	28

in the 28th week is the dose most commonly indicated in international recommendations[16,20,52,58].

It is not, however, possible to completely eliminate the risk of sensitisation because, despite increased adherence to antenatal immunoprophylaxis[65], and although most foeto-maternal haemorrhages able to cause immunisation occur in the last trimester of pregnancy, sensitisation does occur before the 28th week in a small percentage of women; alternatively, there may be cases in which intramuscular administration of the anti-D IgG is insufficient to provide passive prophylaxis.

Blood Transfus 2010; 8:8-16

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Table V - Antenatal prophylaxis in the third trimester.

Antenatal IP between the 25th and 28th weeks	26% yes	
	62% no	
	12% no response	
Dose used	71.4%	300 µg
	14.3%	250 µg
	11.9%	100 µg - 200 µg
	2.4%	no response

Blood Transfus 2013; 11: 518-27 DOI 10.2450/2013.0179-12

TRANSFUSION MEDICINE
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British Blood Transfusion Society
Transfusion Medicine | CONFERENCE REPORT

SHOT conference report 2016: serious hazards of transfusion – human factors continue to cause most transfusion-related incidents

P. H. B. Bolton-Maggs

Serious Hazards of Transfusion Office, Manchester Blood Centre, Manchester, UK

cases with serious outcomes still occur. A baby died following exchange transfusion for haemolytic disease of the foetus and newborn (HDFN) (second pregnancy). Maternal anti-D had been identified in the first pregnancy, but misunderstanding and miscommunication followed so that the first baby was born with unexpected HDFN requiring exchange transfusion. This information was not fully transmitted or understood in the second pregnancy. The anti-D detected in the booking blood sample in the second pregnancy was thought to be due to prophylaxis (although too early in pregnancy at 10 weeks), and the same wrong assumption was made at 28 weeks. There were at least 10 errors across these two pregnancies in the clinical and laboratory management that contributed to the tragic outcome.

In addition to this, there were 350 reports of adverse incidents associated with anti-D Ig, 271 (77·4%) related to late administration or omission. Nurses or midwives were responsible for 227 (83·8%) of these, doctors for 24 (8·8%) and errors in the laboratory for 20 (7·4%). Three women developed anti-D in the current pregnancy as a result of this. In 50 cases, the women did not receive routine antenatal prophylaxis, 27 of these in the community. Anti-D Ig can cause anaphylaxis, so it usually may not be given in the patient's home. Although anti-D Ig should be given within 72 h of a potentially sensitising event, guidelines note that this may be of benefit for up to 10 days (Qureshi *et al.*, 2014). These (and other) guidelines may be used as 'rules', but there is evidence in the literature that the anti-D response may be suppressed by giving anti-D Ig later than this, up to 14 days (Samson and Mollison 1975), so that there is room for some clinical judgement and flexibility.

Many of these reports demonstrate poor communication and misunderstanding. The request may not clearly identify whether or not the woman has received prophylactic anti-D Ig, and laboratory staff may misinterpret the findings, resulting in misleading reports or reports that are not understood by the

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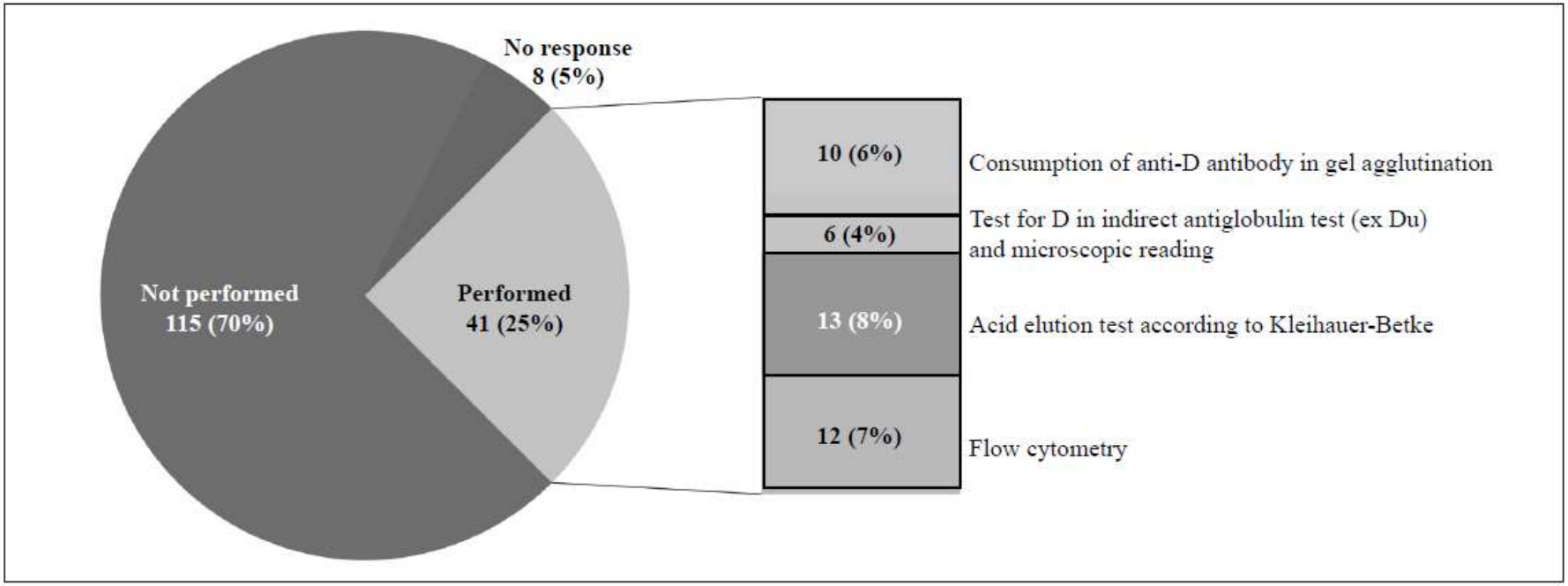

Figure 2 - Evaluation of foetal-maternal haemorrhage and the methods used.

Blood Transfus 2013; 11: 518-27 DOI 10.2450/2013.0179-12

What do we have to do?

Primary prevention

- Identification of all Rh(D)-negative women during pregrancy
- Rh immunoprophylaxis postpartum and ideally at the 28th week

Secondary prevention

- Care of affected pregnancies and neonates
- Implementation of affordable and proven-effective technologies for identification of and improved newborn care.

Tertiary prevention

- Early identification and care of affected survivors exposed to severe hyperbilirubinemia to address long-term impairments

Improved data and use of data

Survey on the prevention and incidence of haemolytic disease of the newborn in Italy

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The Italian law n. 219 of 21 October 2005, *New regulations on transfusion activities and national production of blood derivatives*[14], sets out the essential levels of health care with regards to transfusion activities, including among these that Transfusion Structures (TS) carry out all the antenatal investigations aimed at preventing immunohaematological problems and HDN. Furthermore, the TS are obliged to keep a register of individuals to be given prophylaxis. Unfortunately, a considerable number of TS often cannot meet these obligations in full because of organisational problems resulting from the frequent lack of collaboration with birthing centres (private or public), which are the centres which actually administer the prophylaxis in almost all cases.

Table I - Types of services provided and legally required registers.

Only immuno-haematological tests on mother and newborns (A)	46%
(A) + indication for giving IP (B)	25%
(A) + (B) + record of IP having been given	29%
Existence of a register of Rh(D) negative women who have undergone IP	57%*
Paper records	58%
Electronic records	42%
*Typology of records	
Record of IP having been given	74%
Evaluation of FMH	27%
Record of partner's blood group	24%
Evaluation of efficacy of IP	22%

Blood Transfus 2013; 11: 518-27 DOI 10.2450/2013.0179-12

CONCLUSIONS (1)

- The Rh disease has been known for more than 6 decades and the means for its prevention have been established for more than 50 years.

- In the more recent years, combined strategy of routine postnatal and antenatal prophylaxis and additional anti-D Ig in high-risk conditions during pregnancy, has become the standard care for D-negative women in and has substantially decreased RhD immunisation to 0.1-0.3% in **many developed countries .**

- The global burden of Rh disease is disproportionately heavy for **the poorest countries**: 11-fold higher for infants born in countries with NMR > 15 compared with those with NMR <5 (prevalence of 480 vs. 42 per 100,000 live births).

CONCLUSIONS (2)

- It is not current practice **in many countries** to provide D-negative women with antenatal anti-D Ig prophylaxis, although there are tendencies to do so.

- The programme of antenatal prophylaxis in some countries is applied to all RhD-negative women while in other countries the administration of anti-D Ig to RhD-negative women is restricted to those without a living child, because of the scarcity of anti-D Ig.

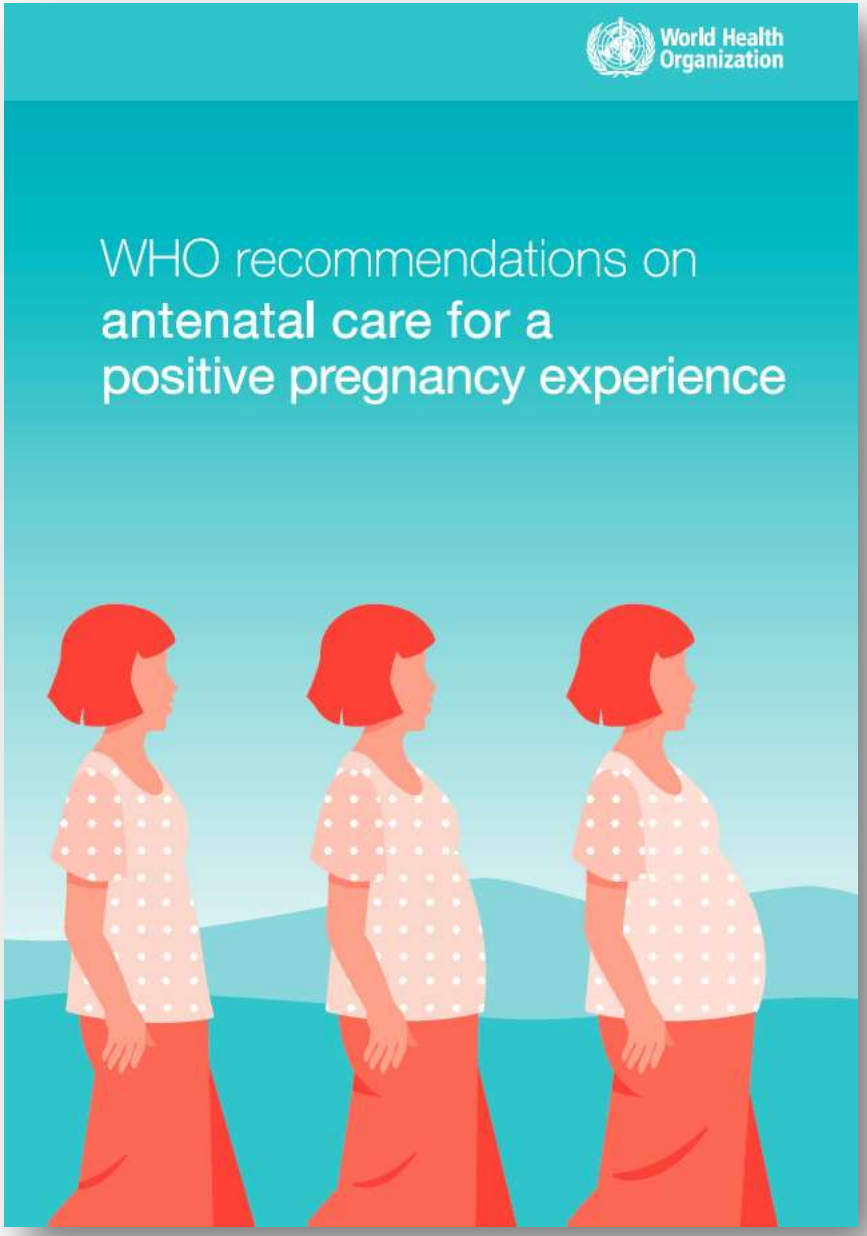
- There has been a failure to prevent Rh sensitization and its adverse consequences worldwide, most heavily on the world's poorest countries, especially in South Asia and sub-Saharan Africa.

CONCLUSIONS (3)

- Barriers include low attention to this issue, poor dissemination of evidence-based tools for effective Rh disease prevention, and high cost for the currently available immunoprophylaxis.

- Strict compliance with the guidelines for the development of a national program is the best strategy for managing this perinatal disease.

- Global and national leadership is needed to mobilize policies and programs to substantially and sustainably reduce newborn deaths and disability related to Rh disease.



« To achieve the Every Woman Every Child vision and the Global Strategy for Women's, Children's and Adolescents' Health, we need innovative, evidence-based approaches to antenatal care. I welcome these guidelines, which aim to put women at the centre of care, enhancing their experience of pregnancy and ensuring that babies have the best possible start in life. »

Ban Ki-moon, United Nations Secretary-General

Thank you for your kind attention :)