Seminars in Fetal & Neonatal Medicine 20 (2015) 2–5

Contents lists available at ScienceDirect

Seminars in Fetal & Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Review

# Impact of Rhesus disease on the global problem of bilirubin-induced neurologic dysfunction

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*Keywords:*
Rhesus disease
Bilirubin-induced neurologic dysfunction (BIND)
Minor neurologic dysfunction
Bilirubin
Subtle bilirubin injury

SUMMARY

Clinical experience with Rhesus (Rh) disease and its post-icteric sequelae is limited among high-income countries because of nearly over four decades of effective prevention care. We hypothesized that Rh disease is prevalent in other regions of the world because it is likely that protection is limited or non-existent. Following a worldwide study, it has been concluded that Rh hemolytic disease is a significant public health problem resulting in stillbirths and neonatal deaths, and is a major cause of severe hyperbilirubinemia with its sequelae, kernicterus and bilirubin-induced neurologic dysfunction. Knowing that effective Rh-disease prophylaxis depends on maternal blood-type screening, healthcare afforded to the high-risk mothers needs to be free of bottlenecks and coupled with unfettered access to effective Rh-immunoglobulin. Future studies that match the universal identification of Rh-negative status of women and targeted use of immunoprophylaxis to prevent childhood bilirubin neurotoxicity are within reach, based on vast prior experiences.



## 1. Introduction

The unacceptable occurrence of neonatal Rhesus (Rh) disease and kernicterus are emblematic of a fractured or a fragile maternal–child healthcare system. Such disruptions in healthcare are most likely in low–middle-income countries (LMICs) or in regions in conflict. A safer seamless transition from birthing facility to home, including systems-based prevention of Rh disease, is crucial in preventing stillbirths, perinatal adverse outcomes including brain damage and death [1–5]. Earlier experiences and knowledge of the "know–do" gaps have illustrated the bottlenecks in public health-care systems in emerging markets. The conclusion of these experts is that innovative strategies and affordable technologies can overcome existing social and access barriers in micro- and macro-health environments in order to provide adequate screening for (and in turn prevent) Rh disease [6–11].

Rh-hemolytic disease of newborn infants (referred to herein as Rh disease) occurs in the Rh-positive newborn infants of Rh-negative mothers. The disease has been virtually eliminated in high-income countries by the prophylactic use of Rh immunoglobulin given to the mother during the last trimester of pregnancy and at postpartum. However, we have recently determined that Rh disease is still a major public health problem in developing countries [6], a major cause of severe hyperbilirubinemia as well as a cause of stillbirths and neonatal deaths. These estimates are also corroborated by clinical reports from several nations (see Table 1).

However, there were no significant epidemiological publications describing the incidence of this disease in LMICs. To this end, we developed an indirect method of determining the incidence of Rh disease. It was assumed that Rh disease would occur in countries in which no Rh immunoglobulin prophylaxis was being used. We were assisted in this regard by the Marketing Research Bureau of Orange, CT (USA), which maintains a worldwide inventory of the manufacturing and distribution of all plasma products including Rh immunoglobulin. With the help of Mr Patrick Roberts of that company, we obtained information on the amount of Rh immunoglobulin distributed annually to all countries worldwide. Using those data together with information on the annual number of births and the prevalence of Rh negativity, we determined the number of Rh-negative women who did not receive Rh immunoglobulin and delivered Rh-positive babies, and therefore who were at risk of developing Rh isoimmunization. Their plasma would contain anti-Rh antibodies and their next Rh-positive baby would be at risk of developing Rh disease. An example of the calculations

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http://dx.doi.org/10.1016/j.siny.2014.12.001
1744-165X/

**Table 1**
Reports of Rh isoimmunization (presence of anti-D antibodies in Rh-negative pregnancies).

| Country | Rh-negative pregnancies ($n$ = reported in the study) | No. of women immunized (%) |
|---|---|---|
| India [11] | 2180 | 51 (2.4) |
| India [10] | 305 | 27 (8.9) |
| Czech Republic [8] | 6815 | 181 (2.6) |
| Turkey [12] | 743 | 65 (8.7) |
| Nigeria [13] | 280 | 12 (4.3) |
| Uganda [14] | 72 | 4 (5.6) |
| India [15] | 270 | 35 (13) |
| Thailand [16] | 72 | 7 (10) |
| Nigeria [17] | 67 | 6 (9) |
| Zimbabwe [18] | 629 | 25 (4) |
| Zimbabwe [14] | 85 | 4 (4.7) |
| Mexico [20] | 4857 | 631 (13) |
| Cameroon [21] | 225 | 9 (4) |
| Iraq [22] | 142 | 7 (4.9) |

Percentage of pregnancies that were immunized: 2.4–13%.
Rh-negative pregnancies represent the number of Rh-negative women studied and reported. The number of women isoimmunized (%) represents those women whose blood contains anti-D (anti-Rh) antibodies.

used is shown in Table 2 for Pakistan and India. It indicates that in one year in India and Pakistan, 750,000 and 340,000 mothers, respectively, did not receive protective prophylaxis.

Fourteen percent of these Rh-negative women will develop anti-Rh antibodies evident within the first six months postpartum or during their next Rh-positive pregnancy. Prophylaxis with Rh immunoglobulin delivered within the first 72 h postpartum will reduce the number of women who develop Rh isoimmunization to ~1% (i.e. ~90% protection). In view of these calculations, it would suggest that each year in India and Pakistan, 105,000 and 47,000 women, respectively, would develop anti-Rh (anti-D) antibodies and, accordingly, their next Rh-positive baby would develop Rh disease. These calculations were extended to all countries and the calculated estimate was that each year >350,000 cases of Rh disease would occur worldwide. These calculations are also consistent with our reported estimate as listed in Table 3 (by neonatal mortality rate) and in Table 4 for regions by global designation [6].

As described in our publication [6], the outcome of pregnancies in which the mother has anti-Rh antibodies is as follows: 33% of the babies will not require treatment; 14% will be stillborn; 24% will result in death during the newborn period due to kernicterus, hydrops fetalis, or related problems. The remaining 29% will develop severe hyperbilirubinemia. Drawing on information from the literature [6], it would appear that ≥50% babies with severe hyperbilirubinemia would develop kernicterus in the absence of sepsis, prematurity, or other perinatal complications that are prevalent in resource-constrained nations. Using these calculations, we estimated that the annual burden of Rh disease worldwide is 41,000 stillbirths, 90,000 neonatal deaths, 97,000 cases of severe hyperbilirubinemia of which at least 48,000 will survive to develop kernicterus. We estimated that annually there were 107,400 cases of severe hyperbilirubinemia due to other causes such as prematurity, glucose-6-phosphate dehydrogenase deficiency, or ABO compatibility. Our data cannot specifically estimate the incidence of bilirubin-induced neurologic dysfunction (BIND) due to co-morbidities of neonatal diseases, which are more likely seen in countries with a neonatal mortality rate (NMR) >15 per 1000 livebirths). These data would be confounded by lack of access to care, suboptimal neonatal care, and other neurologic manifestations. On the other hand, survivors with Rh disease probably confound the unusually high incidence of childhood neurologic burden reported in these nations.

**Table 2**
Reports from India and Pakistan estimating women at risk and disparity on distribution of Rh immunoglobulin (I).[a]

| Country | Population | Women at risk[b] | Rh I units[c] | Untreated (%) |
|---|---|---|---|---|
| India | 1,147,995,904 | 984,979 | 240,000 | 744,979 (75.6%) |
| Pakistan | 172,800,048 | 270,000 | 36,000 | 234,000 (87%) |

[a] Adapted from Bhutani et al. [6].
[b] Rh-negative mothers with an Rh-positive newborn.
[c] Amount of Rh immunoglobulin distributed annually in each country (one unit = one prophylactic dose).

**Table 3**
Estimated burden of Rh disease as categorized by neonatal mortality per 1000 livebirths.[a]

| Neonatal mortality per 1000 livebirths | Rh disease estimated burden | Uncertainty (low to high) |
|---|---|---|
| <5 | <1 | – |
| 5 to <15 | 69,600 | 50,700 to 89,000 |
| ≥15 | 303,600 | 221,000 to 388,000 |
| Worldwide Burden | 373,300 | 271,800 to 477,500 |

[a] Data exclude stillbirths [6].

Rhesus disease is therefore a major problem in many countries of the world. It should be pointed out, however, that the estimates noted above are likely to be underestimations for several reasons. First, we have assumed that in countries in which Rh immunoglobulin is prescribed, compliance with prophylaxis is 100% (this may be an unlikely assumption). Second, postpartum treatment will only be 90% protective; additional protection is required using antenatal injections during the last trimester of pregnancy [7]. Furthermore, maternal Rh isoimmunization following abortions and miscarriages are not calculated in the above estimate. They also represent a risk to the Rh-negative woman [9].

All of the above calculations are based on the assumption that no therapy had been given. Phototherapy may be of help for the lesser forms of hyperbilirubinemia. It is unlikely to be of benefit to the rapidly developing hyperbilirubinemia of Rh disease. Of course, phototherapy would have little effect on babies born with hydrops fetalis or heart failure associated with severe Rh disease; exchange transfusion would be necessary for those cases. Therapy aimed at reducing stillbirths demands intrauterine diagnosis, early delivery, and, for some, intrauterine transfusions. It is unlikely that all these resources will be available in LMICs for some time.

The above calculations were also based on indirect evidence regarding the incidence of Rh hemolytic disease in LMICs. The literature supplies numerous anecdotal reports of the prevalence of Rh isoimmunization [women with anti-Rh (anti-D) antibodies in their blood]. These reports are summarized in Table 1 and provide direct evidence that Rh isoimmunization of pregnancy occurs in

**Table 4**
Global burden of Rh disease among livebirths.[a]

| Global designation | Live-births | Rh disease: mean (IQR) |
|---|---|---|
| South East Asia/Pacific Islands | 29,000,000 | 16,600 (370) |
| South Asia | 37,000,000 | 143,400 (43,577) |
| East Europe/Central Europe | 5,400,000 | 28,350 (895) |
| Hi-income Countries | 11,700,000 | 300 |
| Latin America/Caribbean | 9,900,000 | 34,200 (1697) |
| North Africa/Middle East | 9,700,000 | 26,900 (2252) |
| Sub-Saharan Africa | 32,000,000 | 123,500 (2462) |
| Worldwide | 134,700,000 | 373,300 (1479) |

IQR, interquartile range.
In infants born in high-income nations, estimates for impairment are based on the following information. It is predicted that among infants with Rh disease alone, 29% will develop, if untreated, hyperbilirubinemia of which 50% will develop kernicterus. Risk estimates in Table 3 of our previous publication [6] provided the percentage of cases with each of the neurologic handicaps. These were used to calculate the total number of cases with neurologic handicap. Impairment data in remainder nations cannot be estimated with reasonable accuracy.
[a] Data exclude stillbirths [6].