*Biodemography and Social Biology*, 58:116–132, 2012

ISSN: 1948-5565 print / 1948-5573 online
DOI: 10.1080/19485565.2012.720450

Routledge
Taylor & Francis Group

# The Effect of Rh-Negative Disease on Perinatal Mortality: Some Evidence from the Skellefteå Region, Sweden, 1860–1900

ERLING HÄGGSTRÖM LUNDEVALLER[1]
and SÖREN EDVINSSON[2]

[1]Department of Statistics, Umeå University, Umeå, Sweden
[2]Centre for Population Studies, Umeå University, Umeå, Sweden

*The Rh-negative gene is a well-known cause of perinatal mortality. In this article, we analyze the possible role of Rh disease in perinatal mortality and stillbirths in a particular historical setting: the Skellefteå region in northern Sweden between 1860 and 1900. The data used for the study cover 23,067 children born to 4,943 women. The exact impact is not possible to establish using historical data, but the typical pattern of the disease allows us to make estimations. The expected levels based on knowledge of blood group distribution, the risk of sensitization from Rh incompatability, and the risk of perinatal mortality in births by sensitized mothers are compared with the observed levels. The results show that Rh disease was important for perinatal mortality and clustering of deaths within families.*

## Introduction

The decline in mortality in younger age groups has contributed to most of the rapid increases in life expectancy that have taken place during the past centuries. Consequently, many researchers have focused on infant and child mortality in their search for explanations for the prolongation of life expectancy. Studies have provided evidence on the impact of several important factors, such as improved nutrition, sanitary measures, efficient medical treatment, and better child care. It is, however, obvious that one single factor alone cannot explain the mortality transition; instead, the development has been characterized by a complex web of influences.

Recently, several scholars have pointed out that infant and child mortality is unevenly spread across families. Deaths tend to cluster within families. In her study of infant mortality in India during the 1980s, Das Gupta (1990) found that a small proportion of families contributed to a large part of all deaths. Curtis, Diamond, and McDonald (1993) analyzed clustering using a random-effects logistic model and confirmed the significant variation in risks for postneonatal deaths between families in Brazil. However, in a study of family effects on child mortality in Guatemala, Guo (1993) concluded that such effects were relatively unimportant net of household economic status and mother's education. Zaba and David (1996), on the other hand, suggested that clustering of deaths within families is partly explained by a parity effect, either through a voluntary or physiological replacement effect or through higher risks at higher birth orders caused by increased risks of infection

Address correspondence to Erling Häggström Lundevaller, Department of Statistics, Umeå Universitet, SE-90187, Umeå, Sverige. E-mail: erling.lundevaller@stat.umu.se

transmission in households, maternal depletion, or sibling competition. Within historical contexts, Brändström (1984) observed strong concentrations of infant deaths in some families in the nineteenth-century Nedertorneå parish of northern Sweden, which neighbors the Finnish border. Edvinsson et al. (2005) took up the theme of death clustering of infant mortality in a study of the Skellefteå and Sundsvall region, finding that about 10 percent of families contributed to more than half of all infant deaths, while more than half of families with as many as eight children did not experience any infant deaths. Their analysis shows a clear pattern of family clustering and thus a specific group of vulnerable high-risk families. Furthermore, Lynch and Greenhouse (1994) found a strong familial dependence in child mortality, demonstrating that previous infant deaths in the family were one of the main predictors of the death of a newborn child. A study of infant mortality in seventeenth- and eighteenth-century French Canada also showed a strong family component in child mortality risks (Nault, Desjardins, and Légaré 1990). One of the few studies on historical neonatal mortality and stillbirths demonstrated that clustering was stronger in endogenous (measured by deaths in the first month and stillbirths) than exogenous (postneonatal) mortality in early twentieth-century Derbyshire (Reid 2001).

The historical evidence implies that even in a high-mortality regime, many families were successful regarding survival of their children, while other families were severely affected. What, then, characterized these high-risk families? Das Gupta (1990) suggested that clustering was an effect of parental competence. However, alternative factors need to be taken into consideration. Higher risks in some families might be related to biological characteristics, but the fact that siblings share the same home environment and familial socioeconomic position is also a strong determinant of shared risks. Family behavior and child-care practices can also lead to death clustering (Curtis, Diamond, and McDonald 1993:33). Edvinsson et al. (2005) investigated possible characteristics of these high-risk families. However, the characteristics they identified left much of the variation unexplained. Social class had only a marginal effect. The variables that mattered were the mother's remarriages and stillbirths in the family. The former indicates a family crisis, while the latter points to a possible biological component.

In this article, we analyze one such biological determinant as a possible explanation for the clustering of perinatal deaths. Specifically, we look at Rh disease, or HDN (haemolytic disease of the newborn), a disease that appears in newborn children when the mother has developed antibodies against the child because of incompatible blood groups. Rh disease is well known in the medical literature as having been a major cause of perinatal deaths before the discovery of any efficient treatment. However, in earlier studies on death clustering and the historical decline of infant mortality, this factor has largely been neglected. Here, we study the possible effects of Rh disease on perinatal mortality in a society with neither knowledge of nor treatment for the disease. In order to do this, we use historical parish registers and apply simulation methods to the data. The parish registers allow us to observe actual stillbirths and perinatal deaths, and by using gene frequencies and the expected risk levels of Rh disease, we can estimate its share of this mortality. Using observed levels and estimated Rh disease–induced levels of perinatal mortality and stillbirths, we investigate the extent to which Rh disease contributes to higher levels of perinatal mortality with increasing birth orders. Furthermore, we investigate how much of the clustering of perinatal and infant mortality can be attributed to the disease. finally, we discuss the possible effect of reduced fertility on the prevalence of Rh disease.

We argue that this disease had a substantial effect on both the level and the clustering of infant mortality in general and on perinatal mortality in particular, and that this effect is particularly distinguishable in high-pressure demographic regimes with high fertility. Thus, Rh disease must be considered when analyzing family clustering in historical mortality

data. Even when the focus is on social, economic, environmental, medical, or behavioral factors, it is important to control for the effect of Rh disease in populations with a large proportion of Rh-negative genes.

## Rh Disease

### *Perinatal Mortality, Rh Disease, and Demography*

The history of perinatal mortality has gone largely unexplored. Few studies have exclusively focused on stillbirths and perinatal mortality. One explanation for this oversight is that perinatal mortality has not been consistently recorded in historical time, and it is not always clear how stillbirths have been treated in official records (Woods, Lokke, and Van Poppel 2006). Hart (1998) argued that one could estimate stillbirths as a ratio of neonatal deaths and thus conclude that stillbirths and perinatal mortality decreased substantially during the early period of industrialization, a decline that she attributes to the improved nutritional status of mothers. This method, however, has clear weaknesses, as there are no well-founded arguments for a stable relation between stillbirths and neonatal mortality. Furthermore, the levels of neonatal mortality deviate considerably from those reported in Sweden, where stillbirths were recorded starting in 1749, although figures for the oldest period are of uncertain quality (SCB 1999:Table 3.1).

Reid's (2001) study of neonatal mortality in early-twentieth-century Derbyshire is one of the few to analyze the issue using individual-level data in a historical context. Her analysis clearly demonstrates that stillbirths are maternally and biologically determined (see also Zenger 1993). She found that a previous stillbirth considerably increased the risk both for another stillbirth and for neonatal death. This relationship underlines the need to look at biological factors as determinants for clustering of deaths in families.

The history of Rh disease is of particular interest if we wish to understand both how the disease impacted a population and the scientific struggle to find cures and preventive measures. Furthermore, even if effective preventive therapies for the disease are available today, the problem remains that many pregnancies still involve incompatible blood groups. Another issue is the possible impact of this disease on demography. A skeptic might argue that this is a marginal phenomenon without any substantial demographic impact. We believe, however, that such a conclusion is wrong.

The actual number of deaths in the pretreatment period can never be exactly known, but an educated estimate made by Zimmerman (1973:48) is five to ten thousand per year in the United States. Looking at Canada in the early 1940s, Bowman (1997) concluded that perinatal mortality occurred in more than 40 births per thousand, of which 10 percent were due to Rh disease. Similar levels are likely to have existed in Europe. Another possible consequence with demographic implications, although uncertain impact, is that Rh-negative women may have avoided having more babies in the period when the disease was understood but no effective treatment existed (i.e., the 1950s and 1960s).

A study of Rh disease can deepen our understanding of historical infant mortality in general and perinatal mortality in particular. The decline of infant mortality in Sweden started in the early nineteenth century, which is earlier than in most other countries (Edvinsson, Gardarsdottir, and Thorvaldsen 2008). Prior to this decline, every fifth child in Sweden died during their first year of his or her life. Within the first year, mortality was highest among the youngest infants (i.e., perinatal and neonatal mortality). Unfortunately, we lack national figures on the age components of infant mortality before 1860, but during the period 1860–1866, neonatal mortality in Sweden was 47 of every 1,000 live births. Mortality during the first week was 21 of ever 1,000, and on the first day 10 of every

1,000 (Berg 1869). Information on stillbirths has been registered since the middle of the eighteenth century, and although we may question how well the clergymen (who were responsible for recording cause of death in death and burial registers) differentiated between stillbirths and early deaths, the figures seem to be quite reliable. The reported number of stillbirths in the 1860s, together with first-week mortality for the period 1860–1866, indicate a rate of perinatal mortality of approximately 50 per 1,000 live births (SCB 1999).

Another reason for studying Rh disease is that it may explain intergenerational transfers of infant and perinatal mortality. Family effects in mortality are not exclusively found among siblings; rather, they have also been observed across generations (Brändström et al. 2007). This is the case even after controlling for socioeconomic position and living environment. As such, Rh disease is a possible cause of intergenerational transfers of mortality. Obviously, Rh-negative children born to Rh-negative mothers (when the father is heterozygous) are more likely to survive than Rh-positive children, in their turn exposing the next generation to the risk.

### *How the Disease Works*

The specific pattern of mortality caused by Rh disease can be understood by considering how the disease works (the following section is largely based on Stockman 2001). In an Rh-positive person, the red blood cells have Rh protein on the surface, whereas an Rh-negative person's red blood cells do not. If an Rh-negative person gets Rh-positive blood in his or her bloodstream, he or she will become sensitized, prompting the immune system to produce antibodies against Rh-positive blood. The most common cause of sensitization for a woman is through a previous pregnancy with an Rh-positive fetus. This sensitization takes place when blood from the fetus enters into the mother's bloodstream, an event that could occur either during delivery or through spontaneous or induced abortion. Sensitization by other causes than recorded pregnancies makes us underestimate the risk of the mother being sensitized; however, this risk is small. Sensitization does not occur in all deliveries. Studies have estimated that up to 16 percent of all deliveries with Rh incompatability between mother and child lead to sensitization (Stockman 2001; Bowman 2008). In the simulations in this article, we have used a figure of 13 percent to produce a slightly conservative estimate of the effect of the disease. If the mother was not sensitized during the first delivery, she again runs the risk with the birth of her second child. Consequently, the more Rh-positive children an Rh-negative woman has, the greater her risk of eventually becoming sensitized. For an Rh-negative woman with a homozygous positive husband, the risk of sensitization is about 50 percent after her fifth pregnancy.

Once a mother has become sensitized, her body will also damage the blood of an Rh-positive fetus. Normally, the pregnancy that sensitizes the mother will damage neither the mother nor the child. However, for all subsequent children born to that mother, the risk of perinatal mortality is about 50 percent. This condition will create a typical pattern in perinatal mortality. The first child will not be affected, because the mother is not yet sensitized. When she finally is sensitized, all subsequent Rh-positive children will run a high risk of dying.

In a child with Rh disease, the immune system attacks and destroys the body's blood cells, leading to complications such as fetal hydrops, jaundice, anemia, and other symptoms. Thus, of all children with Rh disease, every second child either will be stillborn or will die no later than a few days after birth if no effective treatment is available (Bowman 1997:40; Stockman 2001:556). The characteristics of the disease thus create some specific demographic patterns. First of all, the impact of the disease on perinatal mortality increases

with every additional child. This deviates from the typical U-shaped pattern in infant mortality (a pattern that, however, is less clear when corrected for sibship size; see Knodel and Hermalin 1984), where the risk is highest for the first-born, lowest among the second- and third-born, and then increases with every additional birth. An effect of the increasing risks of Rh disease in higher parities is that perinatal mortality is reduced when fertility and the number of siblings decline. An additional effect is that perinatal mortality tends to cluster within families.

In historical times, nothing could be done when a child contracted Rh disease. Although cases of the disease were observed and described early on, physicians did not connect the different symptoms to a specific disease, and it was thus not understood as an entity in itself. The history of how medical science began to understand the disease and find effective treatment commenced in the early 1930s, when American pediatrician Louis Diamond identified the different symptoms as belonging to the same disease (Zimmerman 1973:26). When the Rh blood group was discovered around 1940, progress toward understanding the disease began. During the following years, researchers found that the disease was caused by immunization when Rh-positive blood entered the mother's bloodstream. From that point onwards, therapies were developed, first through blood transfusion and later using anti-D immunoglobulin prophylaxis. It has now become standard practice to check the blood status of the parents during pregnancy in order to take the right measures. The disease is almost extinct in contemporary Europe, but it was a very common cause of perinatal mortality in earlier periods.

### *The Distribution of the Gene and Rh Disease*

The appearance of the disease is dependent on the frequency of the blood group Rh negative in the population in general and in mothers in particular. Without such mothers, there would be no risks of Rh disease. The blood group, however, is not equally distributed over the world; instead, there are large geographical differences in its incidence. This blood group occurs primarily among white populations. In the United States, it is present in 15 percent of the Caucasian population, while it occurs in only 1 percent of the Asian or native population. Some groups in Europe have a very large proportion of Rh negative in their populations. One example is the Basques, who have an occurrence of the blood group of around 50 percent. In other parts of Europe, the proportion is around 15 percent (Cavalli-Sforza 1988).

Some parts of Sweden have been identified as having comparatively large numbers of Rh-negative persons. In a study of blood groups in Västerbotten, Beckman et al. (1972) found that Rh-negative individuals were quite common in the northern parishes along the coast of the county-the area also under investigation here. The presence of the Rh-negative allele (gene variant) was about 48 percent in this region's population, and for those born in the early twentieth century, approximately 23 percent were Rh negative. These levels of incidence make the Skellefteå region an interesting study area. The proportion of Rh-negative individuals is likely to be similar several generations back, as the region had rather small migration streams and the selective pressure acting for or against the Rh gene is weak, since the affected children are all heterozygous, with both a negative and a positive gene.

## Data

We performed our analysis using data covering the nineteenth-century Skellefteå region. This region has many advantages that make it interesting to study. As mentioned previously, the Rh-negative gene occurs frequently in the region. The region is also one of the areas

for which the Umeå Demographic Data Base (DDB) has entered all information from the parish registers for the period 1699–1900. The database thus covers a long period, giving us excellent possibilities to follow individuals throughout their entire life course, as well as to reconstruct families as long as they stayed in the region. The effects of migration on the data were limited, partly because the population remained fairly stable and partly because much of the movement took place within the parish, an effect of its large geographical size.

Death records prior to 1815 are missing, and stillbirths are probably severely under-registered before 1860, according to available information. We thus chose to study only mothers born during the period 1840–1882, whose children were born in the year 1900 at the latest. We identified every woman observed in the region at age 18 and followed her until death, her first migration out of the region, or the end of registration. The mothers included have no gaps in observation longer than one year. In that way, we were able to check each mother's childbearing history from the start of her fertile period to the date of censoring. For all mothers, we collected information on all recorded stillbirths and perinatal deaths. Unfortunately, we lack cause-of-death data on infants in most cases. However, this absence is of minor importance, because Rh disease could not have been diagnosed at that time, and related symptoms could not be diagnosed today with certainty.

In total, our study includes 4,943 women and the 23,067 children born to them. The children are recorded until 1900, so many mothers born during this period had later-born children who are not included in the study. Consequently, our study exhibits an underrepresentation of higher parities. This does not cause any problems for our analysis, because only preceding pregnancies can have an effect on succeeding ones. It is thus only necessary to have complete childbearing histories from the first birth up until some parity, and if the mother had more children later in life, this did not bias our analysis. The distribution of different sibship sizes is shown in Figure 1. In approximately 900 cases, the mother had only one child included in the analysis. There were only a few cases in which mothers had 13 or more children.

## Methods

In the following section, we try to assess how Rh disease affected a society—nineteenth-century Skellefteå—with high fertility, high levels of the Rh-negative allele (gene variant), and no access to treatment. To do so we need some estimates of the effects of the disease. Obviously, the optimal situation would be if we had blood types of the individuals and information on their causes of death that could be related to Rh disease. Unfortunately,

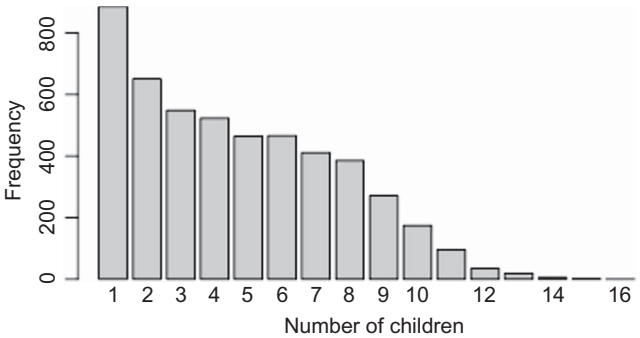


**Figure 1.** Sibship size of families, Skellefteå, 1859–1900.

we have neither. Instead we used estimates for the proportion of Rh-negative alleles in the population of the early-twentieth-century Skellefteå region (Beckman et al 1972), together with risk estimates reported in current medical literature. Parish records provide information about all births in the region and whether the infants were stillborn, died perinatally, or survived. Knowing the risks, the frequency of the Rh allele, and the number of children born to each mother, an estimate of expected number of deaths can be calculated according to parity and family. Thus, we can obtain a theoretical level of clustering induced by Rh disease, as well as estimations of the level of increase at each parity. In principle, these levels could be calculated mathematically, but as this would be very cumbersome, we chose to use simulations instead. These estimated levels were then compared with the actual levels of mortality recorded in the parish register to assess how much the disease contributed to the total mortality.

In the following calculations, we have used the following figures: 48 percent Rh-negative alleles in the region, a 13 percent risk of sensitization in every risk pregnancy, a 50 percent risk of perinatal death, and a 16.7 percent risk of stillbirth in a risk pregnancy. A risk pregnancy is defined here as a pregnancy with an Rh-negative mother and a fetus with the Rh-positive trait. Because the Rh-negative gene is recessive, both parents need to provide an Rh-negative allele to a child for it to inherit the Rh-negative trait. If the Rh-negative frequency is 48 percent, about 23 percent of all individuals will be Rh negative if alleles are randomly mixed (the probability can be calculated as $0.48 \times 0.48 = 0.23$). The frequency of the Rh-negative allele is taken from Beckman et al. (1972). The estimated risk of sensitization varies in the literature (Eklund and Nevanlinna 1973; Ascari, Levine, and Pollack 1969). According to Zimmerman (1973), risk is between 5 and 20 percent. Here, we chose a middle value. The suggested proportions of perinatal deaths and stillbirths may be an underestimation, as they do not refer to the historical context we are analyzing here (Bowman 1997:40; Stockman 2001:556). No attention was paid in the calculations to the possible effects of family decisions on additional children, given the outcome of previous births. Families during our period of investigation had no knowledge about the mechanisms causing the disease, thus decisions about avoiding more births for this reason are improbable at this time. To reflect this behaviour in the simulations, the total number of children in a simulated family was set to the total number of children in a real family. Thus, no adjustment was made in the number of children depending on the outcome of earlier children. Neither did we take into account that the disease becomes more lethal at higher parities when the mother can become "re-sensitized." The reason for this effect is analogous to why many vaccines are given on several occasions to increase the immunization effect.

The simulations were made by reconstructing every family's childbearing history. First, the husband and wife were randomly assigned Rh-negative and Rh-positive genes according to the frequencies occurring in the area. This assignment produced couples with three different risk levels. If the mother is Rh positive or both the mother and father are Rh negative, there will be no risk for Rh disease. If the mother is Rh negative and the father Rh positive with two Rh-positive alleles (homozygous), all pregnancies will be risk pregnancies. If the mother is Rh negative and the father is Rh positive but with one Rh-negative allele, 50 percent of the pregnancies will lead to high risk, namely when the father passes on his positive allele to the fetus.

We then reconstructed the set of children born to the couple by simulation, exposing the mother to a 13 percent risk of becoming sensitized at each risk pregnancy. For each subsequent pregnancy of the sensitized mother, the child was exposed to a 50 percent risk of perinatal death, of which a third would be stillbirths. This was done for all 4,943 families 1,000 times, thus giving us an estimate of how Rh disease is likely to have affected this

population. Based on these figures, the patterns of mortality according to parity and clustering within families as a result of Rh disease could be analyzed, using the means of these figures from the 1,000 simulations as estimates.

## Nineteenth-century Skellefteå: Demography and Socioeconomic Conditions

The nineteenth-century Skellefteå region consisted of the parish of Skellefteå and, somewhat later, the parish of Byske. Two other parishes, Norsjö and Jörn, belonged to Skellefteå until 1813 and 1834, respectively, when they broke free from the old home parish. Data from these parishes, however, are available in digitized form for research even for years after the separation and are included in the data files analyzed here. The region is situated in the province of Västerbotten in the northern part of Sweden on the Gulf of Bothnia. Skellefteå was one of the largest parishes in Sweden both in area and in population. The population began to increase during the seventeenth and eighteenth centuries, and by the turn of the nineteenth century, about 6,900 inhabitants lived in the region. During the following century, the region experienced rapid population growth. In 1850, the region had approximately 14,000 inhabitants and by 1900 nearly 30,000 (Alm Stenflo 1994).

Fertility was high, not only by Swedish standards but also compared to many other parts of Europe. The total fertility rate was around five live births per woman throughout the entire nineteenth century (Alm Stenflo 1994; Coale and Watkins 1986). Indeed, the fertility transition in Västerbotten first occurred during the second decade of the twentieth century, making it one of the last provinces in Sweden to adopt family limitation on a wide scale. Although the total fertility rate fluctuated prior to the transition, women in Skellefteå gave birth to about five children on average. Because illegitimate births were not as common as in the rest of northern Sweden, the region's high birth rates were mainly the result of high marital fertility. Mortality was relatively low (Edvinsson et al. 2005), and thus population growth was the result of natural increase rather than migration gains. The region experienced some net migration losses in conjunction with the nineteenth-century population increase. On the whole, migration to and from the region was moderate, resulting in a fairly homogeneous population (Egerbladh 1995). Animal husbandry was the mainstay of the local economy, and although crofters and rural landless groups were not uncommon, the population consisted mainly of freeholding peasants. There were no large estates and industrial development was limited. The town of Skellefteå, founded in 1845, was of minor importance, with a population of only 1,300 in 1900 (Fahlgren 1956).

## Perinatal Mortality and Rh-Negative Disease in Nineteenth-Century Skellefteå

Eva Lena Lindholm, a farmer's wife, had her first child in 1873, a daughter who survived into adulthood. During the next twelve years she had five more children, all surviving the perinatal period, although two died in childhood. However, Eva Lena's seventh child, born in 1888, was stillborn, and following that birth she had four more children, all of whom were also stillborn. Although we cannot prove it conclusively, there is good reason to believe that this was a case of Rh-negative disease. The symptoms follow the typical pattern of a mother ultimately becoming sensitized, which leads to the stillbirth of many of her subsequent children. The childbearing patterns of mothers provide us with good indicators of possible Rh disease.

The yearly levels of perinatal mortality and stillbirths in the area are presented in Figures 2 and 3. Perinatal mortality varied between 3 and 6 percent, except for some outliers

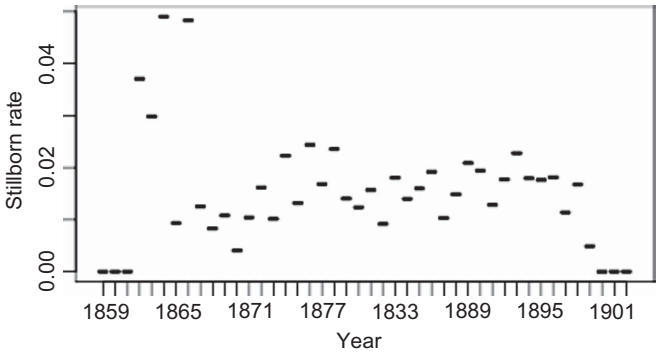


**Figure 2.** Stillbirth rate, Skellefteå, 1859–1900.

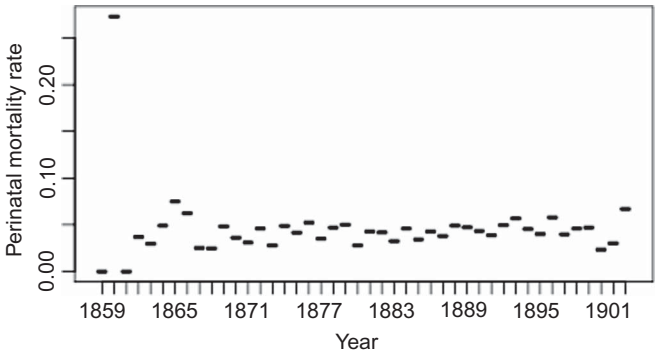


**Figure 3.** Perinatal mortality, Skellefteå, 1859–1900.

in the first years of the study as a result of small numbers. There is no trend of declining rates in either perinatal mortality or stillbirths. In comparison with Swedish national rates, Skellefteå's rates are roughly at the same level, except we see a slight tendency toward higher mortality in the Skellefteå region as we near the end of the century. Stillbirths varied between 1 and 3 percent, a rate somewhat lower than the national level. This could be an effect of the underrepresentation of higher parities in the dataset.

## Perinatal Mortality and Parity

One of the effects of Rh disease is the increased risk with parity. In the following section, we compare the observed levels of perinatal mortality and stillbirths, respectively, to the theoretical level of deaths resulting from Rh disease, based on the assumptions and as described in the Methods section, in order to assess the possible impact of the disease. We chose to exclude the highest parities (17 and higher) in the figures because of the small numbers.

In Figure 4, the observed perinatal deaths in the Skellefteå region are presented in the dotted line, with the theoretical level of perinatal deaths resulting from Rh disease indicated by the solid line. The observed perinatal mortality shows the often encountered U-shape, with rather high mortality at parity one, and in this case lowest mortality in parities three to five, after which the mortality levels rises again. The recorded levels fall in between 3 and 8 percent in parities up to 12 (at higher parities, the total number of births was so low as

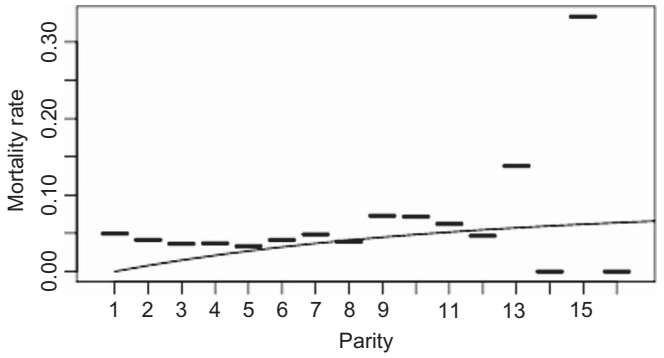


**Figure 4.** Perinatal mortality and parity compared to theoretical levels, Skellefteå, 1859–1900.

to make calculations more sensitive to random fluctuation). The expected deaths from Rh disease increase with parity, but that increase levels off in the higher parities. The increase derives from the fact that more and more mothers become sensitized over time, and the leveling off is the result of fewer mothers at risk of becoming sensitized at higher parities. From Figure 4, we can establish that Rh disease contributed to a large part of the observed increase in mortality with parity. From about parity five and higher, the expected level of perinatal mortality is rather similar to the level observed.

These results may be compared to the figures obtained for stillbirths shown in Figure 5. The proportion of stillbirths goes from less than 1 percent to more than 4 percent. The curve for the expected level of stillbirths follows the observed increase quite well, indicating that most stillbirths at higher parities may have been caused by Rh disease. The results make it highly plausible that the disease accounts for a large proportion of perinatal deaths, particularly stillbirths. It also explains a substantial proportion of the increase in mortality among higher parities.

## Stillbirths and Clustering within Families

One consequence of Rh disease is that stillbirths and mortality during the first days of life become clustered within families, especially in a society characterized by high fertility. If the disease is prevalent, perinatal mortality and stillbirths in particular are not randomly

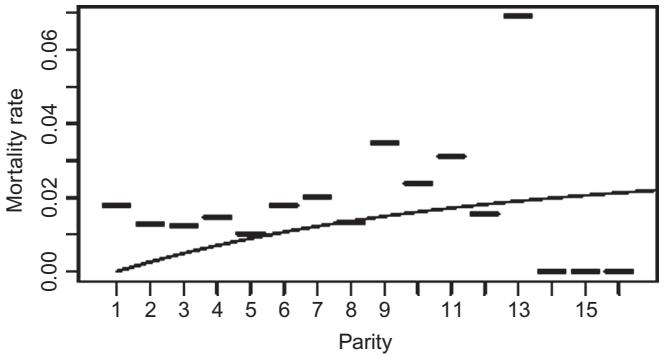


**Figure 5.** Stillbirths and parity compared to theoretical levels, Skellefteå, 1859–1900.

distributed across families, but should instead be heavily concentrated within some families. In this section, we focus on stillbirths in order to investigate whether the assumption of strong clustering was fulfilled in the Skellefteå region and to demonstrate the possible effects of Rh disease.

Table 1 reports the observed frequencies of specific numbers of children and numbers of stillborns for mothers in the Skellefteå region and indicates in brackets the frequencies of specific numbers of children and expected numbers of stillborns, assuming no clustering. The expected numbers were calculated under the assumption that every child has the same risk of being stillborn. Whether a child is stillborn or not is assumed to be independent of the mother or the parity of the child. The main conclusion to be drawn from the table is that having more than one stillborn child is unusual assuming independence, but is in practice often observed. This is in line with the Rh disease hypothesis and indicates a strong effect of clustering. Another interesting observation is the high risk for the first and only birth, where $26/(860 + 26) = 2.9$ percent were stillborn, a percentage that is much larger than the overall risk for the total of firstborns. For these children, there was probably an overrepresentation of complicated deliveries and maternal deaths.

Table 2 illustrates clustering within the family, disregarding family size. The first column shows the expected frequencies of different numbers of stillbirths, assuming random occurrences of stillbirths. The middle column shows the observed numbers.

A chi-2 test to see whether the observed data tend to follow the expected distribution, assuming independence, produced an observed value of the test statistic 77.1 with two degrees of freedom (stillborn groups with expected value of less than 5 merged),

**Table 1**
Frequencies of families with both stillborn and total births, Skellefteå, 1859–1900

| | Number of stillborn | | | | | |
|---|---|---|---|---|---|---|
| Number of births | 0 | 1 | 2 | 3 | 4 | 5 |
| 1 | 860 (872.2) | 26 (13.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 2 | 637 (630.9) | 12 (19.9) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 3 | 526 (523.8) | 20 (24.8) | 2 (0.4) | 1 (0.0) | 0 (0.0) | 0 (0.0) |
| 4 | 497 (491.2) | 23 (31.1) | 2 (0.7) | 1 (0.0) | 0 (0.0) | 0 (0.0) |
| 5 | 437 (429.9) | 26 (34.0) | 1 (1.1) | 1 (0.0) | 0 (0.0) | 0 (0.0) |
| 6 | 429 (424.1) | 29 (40.2) | 4 (1.6) | 1 (0.0) | 1 (0.0) | 2 (0.0) |
| 7 | 384 (369.2) | 25 (40.9) | 2 (1.9) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| 8 | 351 (339.6) | 29 (43.0) | 2 (2.4) | 2 (0.1) | 1 (0.0) | 0 (0.0) |
| 9 | 237 (235.3) | 28 (33.5) | 5 (2.1) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| 10 | 160 (149.6) | 12 (23.7) | 2 (1.7) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| 11 | 82 (80.8) | 9 (14.0) | 2 (1.1) | 0 (0.1) | 2 (0.0) | 1 (0.0) |
| 12 | 30 (29.0) | 4 (5.5) | 1 (0.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 13 | 15 (16.3) | 4 (3.4) | 0 (0.3) | 0 (0.0) | 1 (0.0) | 0 (0.0) |
| 14 | 6 (4.8) | 0 (1.1) | 0 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 15 | 2 (1.6) | 0 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 16 | 1 (0.8) | 0 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

*Note:* Expected values (assuming no clustering) in brackets.

**Table 2**
Frequency of number of stillbirths, Skellefteå, 1859–1900

| Number of stillbirths | Independent | Observed | Rh only |
|---|---|---|---|
| 0 | 4,599 | 4,654 | 4,850 |
| 1 | 329 | 247 | 66 |
| 2 | 14 | 25 | 21 |
| 3 | 0 | 9 | 5 |
| 4 | 0 | 5 | 1 |
| 5 | 0 | 3 | 0 |
| Total deaths | 357 | 359 | 127 |

which gives us a *p*-value close to zero. Thus, there seems to be a strong clustering of stillbirths.

The next question is how much of the clustering within families can be explained by Rh disease. The third column of Table 2 shows the expected frequencies of stillbirths within families, assuming that they are exclusively caused by Rh disease. These frequencies were estimated by simulation using the same figures as earlier: 48 percent Rh-negative genes, 13 percent risk of sensitization, 50 percent risk of perinatal mortality, and a third of these deaths being stillbirths. The estimated number of cases of Rh disease–related deaths is 127 of a total of 359, or about 35 percent of all stillbirths. The "Rh only" column indicates a pattern for the higher numbers of stillbirths that, especially for two and three stillbirths, coincides with the observed pattern. The rather low values for "Rh only" for four or five stillbirths might be due to chance or to other factors responsible for these clusters. Another alternative is that the risk of stillbirths attributed to a sensitized mother in the simulations, $16.7 = (0.5 \times (1/3))$, is a bit too low. It is clear, however, that the Rh gene can explain a large proportion of all stillbirths and especially the clustering effect.

The clustering of perinatal mortality is shown in Table 3. The number of deaths per mother are a bit high for the expected frequency caused by Rh disease (Rh only column) for number of deaths above three. The observed clustering is thus less pronounced for perinatal deaths than for stillbirths, similar to the findings of Reid (2001) . The calculations of the expected values are also very sensitive to the assumed death risk and which might be less than 0.5 assumed here.

**Table 3**
Frequency of perinatal deaths, Skellefteå, 1859–1900

| Number of deaths | Independent | Observed | Rh only |
|---|---|---|---|
| 0 | 4,062 | 4,211 | 4,773 |
| 1 | 781 | 554 | 65 |
| 2 | 91 | 120 | 46 |
| 3 | 8 | 46 | 30 |
| 4 | 1 | 5 | 17 |
| 5 | 0 | 5 | 8 |
| 6 | 0 | 2 | 3 |
| Total deaths | 989 | 989 | 385 |

### *The Effect of Reduced Fertility on Stillbirths*

Rh disease causes a higher risk of perinatal death for higher parities. It may therefore be part of the explanation that the number of perinatal deaths has dropped as fertility has gone down, as suggested by Joseph and Kramer (1998) in relation to the twentieth-century decline: "In summary, changes in birth order distribution and in the quality of perinatal care have been responsible for an important fraction of the decline in incidence and mortality from Rh hemolytic disease of the newborn. These results provide a historical perspective on the conquest of a once major cause of perinatal mortality and long-term disability" (Joseph & Kramer, 1998, p. 214).

Because mortality of later siblings does not affect the perinatal mortality of previously born siblings, a good picture of how reduced fertility influences perinatal mortality can be found by pretending that later siblings will not be born.

In this section, we apply this method to stillbirths to illustrate the hypothetical effects of lowered fertility (see Table 4). The illustration does not closely mimic the actual fertility decline process but rather gives an assessment of its potential impact. For each column to the right, the last child among a set of siblings is removed, and the resulting number of stillborns per family is recorded. We restricted this procedure to cases in which the number of remaining siblings exceeds two. The first column labeled "0" displays the actual distribution of stillbirths. There were thus 4,654 families with no stillbirths, 247 families with one stillbirth, and so on. The last row in the table shows the percentage of stillbirths of all pregnancies in the dataset before reduction: 1.56 percent. In the next column, the last-born sibling in each family with more than two children is removed from the dataset. Continuing this process of reducing family sizes mimics a fertility decline toward one or two children. The percentage of stillbirths holds rather stable throughout, at around 1.5 percent. This may seem surprising, as the high mortality amongst higher parity children is removed from the dataset. However, most of this effect vanishes, because mortality in the low parities is equally high or even higher and thus compensates for stillbirths in the highest parities.

Table 5 displays the corresponding theoretical pattern of stillbirths as a result of Rh disease. These numbers are calculated to illustrate the likely contribution of Rh disease to changes in the number of stillbirths with a reduction of fertility. These values are calculated by simulation, applying the same method used previously. The percentage of pregnancies resulting in an Rh disease–related stillbirth drops from 0.55 to 0.11 percent when the nine

**Table 4**
Number of families with a specific number of stillborn mimicking reduction of fertility by removing the highest parities and percent stillborn of all births, Skellefteå, 1859–1900

| | Number of children romoved from the highest parities | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Number of stillborn | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| 0 | 4,654 | 4,688 | 4,716 | 4,756 | 4,774 | 4,789 | 4,802 | 4,807 | 4,807 |
| 1 | 247 | 220 | 199 | 168 | 155 | 146 | 134 | 130 | 130 |
| 2 | 25 | 23 | 19 | 16 | 14 | 8 | 7 | 6 | 6 |
| 3 | 9 | 6 | 8 | 3 | | | | | |
| 4 | 5 | 5 | 1 | | | | | | |
| 5 | 3 | 1 | | | | | | | |
| Percent of stillbirths | 1.56 | 1.57 | 1.58 | 1.44 | 1.45 | 1.45 | 1.45 | 1.48 | 1.53 |

**Table 5**
Number of families with a specific number of stillborn mimicking reduction of fertility by removing the highest parities, expected values if Rh disease is the only cause of death, Skellefteå, 1859–1900

| | Number of children removed from the highest parities | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Number of stillborn | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| 0 | 4,850 | 4,872 | 4,889 | 4,903 | 4,914 | 4,922 | 4,927 | 4,930 | 4,932 | 4,933 |
| 1 | 66 | 53 | 41 | 32 | 24 | 19 | 15 | 12 | 11 | 10 |
| 2 | 21 | 15 | 10 | 6 | 4 | 2 | 1 | 0 | 0 | 0 |
| 3 | 5 | 3 | 2 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| 4 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Percentage of stillbirths | 0.55 | 0.49 | 0.40 | 0.32 | 0.28 | 0.21 | 0.17 | 0.12 | 0.12 | 0.11 |

highest parities are removed from the dataset. The analysis shows that if fertility is high, Rh disease causes a large proportion of all stillbirths, while the numbers are considerably reduced if fertility is low. This means that in the high-fertility case, more than a third ($0.55/1.56 = 0.35$) of all stillbirths are expected to be due to Rh disease. If we reduce sibship size by one child, 31 fewer cases of the disease occur; if we reduce sibship by two children, 60 fewer cases occur; and so on.

There is no sign of a fertility transition during the period under study in the Skellefteå region. According to our estimates, the fertility decline, which is considered to have started in the 1910s, should have resulted in fewer deaths caused by Rh disease. This corresponds well with the development of perinatal mortality and stillbirths in our observed period, when the levels were quite stable throughout the century (see Figures 2 and 3).

## Conclusions

In this study, we have looked at the role of a specific type of mortality: perinatal mortality. A substantial proportion of all infant deaths take place during the first week, both today and historically. Before or during the mortality transition, neonatal deaths as well as stillbirths were frequent. In earlier research, there have been indications that biological factors played an important role in the clustering of deaths within families (Edvinsson et al. 2005). Reid (2001) found that previous stillbirths were strong indicators of stillbirths in particular, but also of neonatal mortality. Here we have been able to highlight a possible mechanism that contributes to the clustering of perinatal mortality and stillbirths. Our knowledge about the distribution of the Rh factor in this area, together with qualified estimates on the risks of sensitization and the mortality risks for those who acquire the disease, enabled us to estimate the expected number of cases in the studied region. After comparing the expected numbers to the observed numbers, we draw the conclusion that Rh disease caused a substantial proportion of all stillbirths and perinatal deaths. This is especially true with regard to higher parity children. Without Rh disease, the stillbirth rate would have been about a third lower, and in higher parities lower still.

The increased risk at higher parities thus implies that a decline in fertility would lower the frequency of Rh disease in particular, but also of perinatal mortality in general. During

the period under study, there was no sign of declining fertility. This decline did not take place until the twentieth century. The effect of Rh disease had a strong impact in Skellefteå, because of both the large proportion of Rh-negative mothers and the very high fertility in the region. Families with ten or more children were common in Skellefteå. If Rh-negative mothers have that many children, it is likely that most of them will be sensitized in higher parities.

We cannot establish the exact level of Rh disease in Skellefteå; we can only estimate its probable impact through simulations. It is possible, however, that we underestimate its impact if mothers who lose their children shortly after delivery have a shortened birth interval to the next child. This could be due to compensation, but it is usually an effect of no lactation after the death of a child and consequently earlier onset of ovulation. Women in historical populations experiencing high infant mortality, especially perinatal and neonatal mortality, thus had more children and more children of higher parities. Mothers who had become sensitized could be expected to have more children as a result of shorter birth intervals after perinatal deaths, which would lead to more children with Rh disease. It is possible to include this effect in the model, but we have not considered it here.

Without Rh disease, infant mortality would certainly have been lower, and the effect would have been even stronger in perinatal mortality. Nevertheless, a large proportion of infant mortality cannot be explained by Rh disease. We are not arguing that the disease explains all or even most of the death clustering among infants. Rh disease is only one component in the risk panorama of newborn infants at this time. Mother's age, for example, can also explain the parity effect. Pregnancies at higher ages entail higher risks for stillbirths, spontaneous abortions, ectopic pregnancies, preterm births, and other complications (Schmidt et al. 2012). However, Rh disease is a factor with a significant impact and therefore needs to be considered in the analysis of infant mortality. Our estimates indicate a considerable number of cases related to the disease. We can thus safely conclude that it had a substantial impact on children's survival at that time. Even if it was a rather small part of the risks for the fetus, Rh disease killed many children and was experienced by many families.

Rh disease is furthermore an important factor in explaining some of the clustering of mortality we have found. If a sensitized mother continued to give birth to further children, these sibships would often constitute a cluster. Without the disease, clustering would have been less significant.

As far as we know, the role of Rh disease has not been discussed in historical contexts, partly because it is difficult to establish the extent to which the disease occurred and partly because we lack data on cause of death. Furthermore, we can easily ignore its potential role, because so many studies have demonstrated the impact of socioeconomic conditions such as poverty, overcrowding, or behavioral factors such as artificial feeding or neglect. We argue that we need to know more about the role of Rh disease in societies with a potential risk for this disease. We hope our results have convincingly illustrated the potential impact of the disease in historical settings.

## References

Alm Stenflo, G. 1994. Demographic description of the Skellefteå and Sundsvall regions during the 19th century. Report Series: Information from the Demographic Data Base, 1103–6974, Demographic Data Base.

Ascari, W., P. Levine, and W. Pollack. 1969. Incidence of maternal Rh immunization by ABO compatible and incompatible pregnancies. *Br Med J* 1:399–401.

Beckman, L., B. Cedergren, E. Collinder, and M. Rasmuson. 1972. Population studies in northern Sweden. iii. Variations of ABO and Rh blood group gene frequencies in time and space. *Hereditas* 72(2):183–200.

Berg, F. T. 1869. Om dödligheten i första lefnadsåret [About mortality in the first year of life]. *Statistisk tidskrift*, 3, 435–493.

Bowman, J. 1997. The management of hemolytic disease in the fetus and newborn. *Semin Perinatal* 21(1):39–44.

———. 2008. Alloimmune hemolytic disease of the fetus and newborn (erythroblastosis fetalis): diagnosis, management and prevention. Global Library of Women's Medicine. doi 10.3843/GLOWM.10201.

Brändström, A. 1984. De kärlekslösa mödrarna [The unloving mothers]. Ph.D. diss., Umeå University.

Brändström, A., S. Edvinsson, M. Lindkvist, and J. Rogers. 2007. Clustering across generations: a comparative analysis of infant mortality in 19th century Sweden. Paper presented at the annual meeting of the Social Science History Association, Chicago, 15–18 November, 2007.

Cavalli-Sforza, L. L. 1988. The Basque population and ancient migration in Europe. *Munibe (Antropologia y Arqueologia) Supplemento* 6:129–137.

Coale, A. J., and S. C. Watkins. 1986. *The decline of fertility in Europe*. Princeton, NJ: Princeton University Press.

Curtis, S., I. Diamond, and J. McDonald. 1993. Birth interval and family effects on postneonatal mortality in Brazil. *Demography* 30(1):33–43.

Das Gupta, M. 1990. Death clustering, mothers' education and the determinants of child mortality in rural Punjab. *Popul Stud* 44(3):489–505.

Edvinsson, S., A. Brändström, J. Rogers, and G. Broström. 2005. High-risk families: the unequal distribution of infant mortality in nineteenth-century Sweden. *Popul Stud* 59(3):321–337.

Edvinsson, S., O. Gardarsdottir, and G. Thorvaldsen. 2008. Infant mortality in the Nordic countries, 1870–1930. *Contin Chang* 23(3):457–485.

Egerbladh, I. 1995. Flyttningar på landsbygden i 1800-talets Norrland [Migrations in rural 19th Century Norrland]. In *Då, nu och sedan* [Before, now and beyond]. *Kungliga Skytteanska samfundets handlingar*, ed. I. Layton, 31–47. Kungliga Skytteanska Samfundet, Umeå.

Eklund, J., and H. Nevanlinna. 1973. Rh prevention: a report and analysis for a national programme. *J Med Genetics* 10:1–7.

Fahlgren, K. 1956. *Skellefteå stads historia*. Uppsala: Uppsala Wahlström & Widstrand.

Guo, G. 1993. Use of sibling data to estimate family mortality effects in Guatemala. *Demography* 33(1):15–32.

Hart, N. 1998. Beyond infant mortality: gender and stillbirth in reproductive mortality before the twentieth century. *Popul Stud* 52(2):215–229.

Joseph, K. S., and M. S. Kramer. 1998. The decline in Rh hemolytic disease: should Rh prophylaxis get all the credit? *Am J Public Health* 88:209–215.

Knodel, J., and A. I. Hermalin. 1984. Effects of birth rank, maternal age, birth interval, and sibship size on infant and child mortality: evidence from 18th and 19th century reproductive histories. *Am J Public Health* 74(10):1098–1106.

Lynch, K. A., and J. B. Greenhouse. 1994. Risk factors for infant mortality in nineteenth-century Sweden. *Popul Stud* 48(2):117–133.

Nault, F., B. Desjardins, and J. Légaré. 1990. Effects of reproductive behaviour on infant mortality of French-Canadians during the seventeenth and eighteenth centuries. *Popul Stud* 44:273–285.

Reid, A. 2001. Neonatal mortality and stillbirths in early twentieth century Derbyshire, England. *Popul Stud* 55(3):213–232.

Statistiska Centralbyrån (SCB) [Statistics Sweden]. 1999. *Befolkningsutvecklingen under 250 år Historisk statistik för Sverige* [The population trend over 250 years: Historical Statistics of Sweden]. Vol. 2 of *Demografiska rapporter*, Statistics Sweden.

Schmidt, L., T. Sobotka, J. G. Bentzen, and A. Nyböe Andersen 2012. Demographic and medical consequences of the postponement of parenthood. *Hum Reprod Update* 18(1):29–43.

Stockman, J. A. III. 2001. Overview of the state of the art of Rh disease: history, current clinical management, and recent progress. *J Pediatr Hematol Oncol* 23(8), 554–562.

Woods, R. I., A. Lökke, and F. van Poppel 2006. Two hundred years of evidence-based perinatal care: late-fetal mortality in the past. *Arch Dis Child Fetal Neonatal Ed* 91(6):F445–F447.

Zaba, B., and P. H. David 1996. Fertility and the distribution of child mortality risk among women: an illustrative analysis. *Popul Stud* 50:263–278.

Zenger, E. 1993. Siblings' neonatal mortality risks and birth spacing in Bangladesh. *Demography* 30(3):477–488.

Zimmerman, D. R. 1973. *Rh: the intimate history of a disease and its conquest*. New York: Macmillan.