PREVENTION OF Rh HEMOLYTIC DISEASE OF THE NEWBORN: AN EVALUATION OF COMPETING STRATEGIES

by

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Prevention of Rh hemolytic disease of the newborn

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STATEMENT OF ORIGINALITY

The work undertaken for this thesis represents original work. Population determinants of Rh disease have never been studied using multivariable regression techniques. As argued elsewhere in this thesis, such techniques are mandatory for the valid quantification of determinant effects. Also, the conditional probability model used for evaluating Rh prophylaxis options has not previously been used for this purpose. Thus, this work represents an original contribution to the medical literature. It should serve to clarify the history of how Rh disease was controlled in the developed world, besides providing a basis for policy decisions in less developed nations. I was primarily responsible for the hypothesis generation, design, search for relevant data sources, analysis and interpretation.

ABSTRACT

Rh hemolytic disease of the newborn, once a major cause of perinatal mortality and long-term disability, is rarely seen in developed countries today. This drastic reduction in the frequency of disease occurrence has followed the widespread postpartum use of Rh immunoglobulin. However, more than half the world's population does not have access to this health care technology.

The objective of this thesis was to study the epidemiology of Rh disease in developed country settings and specifically to quantify the magnitude of Rh disease reduction that occurred secondary to Rh prophylaxis, and to changes in birth order, the quality of medical care and other Rh disease determinants. Another objective was to identify feasible and cost-effective options for Rh disease control in developing countries.

Study methods include Poisson regression modeling of surveillance data from Manitoba, Nova Scotia, Canada and the United States and a model based on conditional probabilities obtained from the medical literature and vital statistics publications. Outcomes considered in these analyses include maternal Rh sensitization, Rh hemolytic disease of the newborn, perinatal deaths from Rh disease and infant deaths from hemolytic disease of the newborn.

The results show that besides Rh prophylaxis, changes in other determinants of Rh disease were responsible for significant reductions in the disease over the last four decades. Changes in the birth order resulted in a 35% reduction in Rh sensitizations, while changes in the quality of medical care were responsible for about 80% of the reduction in perinatal deaths from Rh disease. Rh prophylaxis was found to be responsible for reducing the rate of maternal Rh sensitization (both Rh D and Rh non-D) by 60-69% and the rate of perinatal and infant deaths by 80-90% (estimated effects are independent but not mutually exclusive). Effects of other Rh disease determinants, such as abortion rates, racial composition, race and Rh type-specific blood transfusions, were also quantified. Finally, a decision analysis of various Rh prophylaxis options was modeled with a view to optimizing cost-effectiveness and minimizing cost. The option of administering Rh prophylaxis to first births was found to be the most cost-effective and feasible option. It is recommended as a first step for Rh disease control in countries like India.

RÉSUMÉ

De nos jours, la maladie hémolytique Rh du nouveau-né est rarement rencontrée dans les pays développés bien qu'elle fut, dans le passé, une cause importante de mortalité périnatale et d'invalidité à long terme. Une réduction très importante de la fréquence de cette maladie est survenue à la suite de l'utilisation répandue de l'immunoglobuline Rh juste après l'accouchement (post-partum). Cependant, plus de la moitié de la population du globe n'a pas accès à ce traitement.

L'objectif de cette thèse était d'étudier l'épidémiologie de la maladie Rh dans les pays développés et de quantifier la réduction de la fréquence de cette maladie produite par l'introduction du traitement prophylactique Rh et par les changements dans l'ordre des naissances, dans la qualité des soins médicaux et dans d'autres déterminants de la maladie Rh. Un autre objectif est d'identifier les options faisables qui démontrent un bon rapport coût-efficacité pour contrôler la maladie Rh dans les pays en voie de développement.

Les méthodes d'analyse utilisées au cours de cette thèse sont les suivantes: la modélisation des données de surveillance du Manitoba, de la Nouvelle Écosse, du Canada et des États-Unis par la régression de Poisson et un modèle basé sur des probabilités conditionnelles provenant de la littérature médicale et des publications des statistiques vitales. Les variables dépendantes considérées dans ces analyses sont la sensibilisation Rh maternelle, la maladie Rh du nouveau-né, les décès périnatals causés par la maladie Rh et les décès infantiles associées à la maladie hémolytique du nouveau-né.

Les résultats démontrent qu'en plus du traitement prophylactique Rh, certaines variations dans les déterminants de la maladie Rh sont responsables de la diminution significative de la maladie depuis les quatre dernières

décennies. Le changement de la proportion de la première naissance a produit une réduction de 35% de la sensibilisation Rh, alors que le changement dans la qualité des soins de santé est responsable pour à peu près 80% de la réduction de la mortalité périnatale due à la maladie Rh (les effets estimés sont indépendants mais non mutuellement exclusifs). Les résultats démontrent aussi que le traitement prophylactique Rh est responsable d'une réduction de 60 % à 69 % de la sensibilisation maternelle Rh (Rh D et Rh non-D) et d'une réduction de 80 % à 90 % du taux de mortalité périnatal et infantile. Les effets dus aux changements des autres déterminants de la maladie Rh comme le taux d'avortement, la composition raciale, les transfusions sanguines spécifiques à la race et au type Rh ont aussi été quantifiés. Finalement, une analyse de décision basée sur les différentes options disponibles pour le traitement prophylactique Rh a été effectuée en essayant d'optimiser le rapport coût-efficacité et de minimiser les coûts. L'administration du traitement prophylactique Rh aux premiers-nés est, selon les résultats obtenus, l'option la plus pratique et celle qui a le meilleur rapport coût-efficacité. Dans un pays comme l'Inde, cette option est recommandée comme première étape dans le contrôle de la maladie Rh.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. INTRODUCTION

Rh hemolytic disease of the newborn was once a major cause of perinatal mortality and long-term disability. The condition usually arises as a consequence of anti-D antibody from a sensitized Rh-negative woman crossing the placental barrier and destroying Rh-positive fetal red blood cells bearing the D antigen. The initial sensitizing event usually follows a feto-maternal hemorrhage occurring at the time of delivery. Other events causing sensitization include abortion, invasive procedures such as amniocentesis and feto-maternal transfusion occurring during pregnancy itself. Fortunately, Rh sensitization can be averted by providing the mother with adequate passive antibody so that antigen from an average feto-maternal hemorrhage can be cleared before sensitization occurs. Since the amount of passive antibody administered during pregnancy is small (though adequate for the purpose of clearing a feto-maternal hemorrhage), it does not cause hemolysis in the fetus.

Rh disease is rarely seen in developed countries today. This drastic reduction in the frequency of disease occurrence has followed the widespread postpartum use of Rh immunoglobulin. The discovery and introduction of anti-D immunoglobulin has therefore been hailed as one of the major obstetrical achievements of the past quarter century [1].

Historically, the major breakthrough was the almost simultaneous discovery of anti-D prophylaxis by researchers in

the United Kingdom and the United States [2-4]. By 1971, nine controlled trials of postpartum Rh immunoglobulin prophylaxis had yielded unequivocal results demonstrating Rh immunoglobulin efficacy [5-13]. The said efficacy of postpartum Rh prophylaxis notwithstanding, a residual level of sensitization occurs and 1-2% of Rh-negative women show evidence of antibody production despite such prophylaxis [14]. This is because postpartum Rh prophylaxis protects against sensitizations which are a consequence of feto-maternal hemorrhage occurring during delivery. The residual sensitizations not prevented by postpartum Rh prophylaxis mainly occur secondary to feto-maternal haemorrhage during pregnancy and can be prevented through antenatal prophylaxis. Antenatal prophylaxis involves immunoglobulin administration at 28 and/or 34 weeks of gestation. The efficacy of such antepartum prophylaxis was first proposed and tested in 1967 [15] and subsequently confirmed in several large-scale studies [16-20]. Thus, the combination of postpartum and antenatal administration of anti-D should prevent sensitization in virtually all unsensitized Rh-negative women [21].

However, in spite of the fact that disease prevention is possible, two major obstacles hinder the global conquest of Rh disease. First, although the cost-effectiveness of postpartum Rh immunoprophylaxis is not questioned, more than half the world's population does not have access to it. The economic realities within developing countries preclude

the routine postpartum use of Rh immunoglobulin. A similar dilemma also arises with regard to antepartum prophylaxis in developed countries, where despite its demonstrated efficacy in clinical trials, its acceptance and use have not been universal.

The major concerns in the debate (regarding antenatal prophylaxis) have revolved around the increases required in anti-D production and cost considerations [22-26]. Rh immunoglobulin is produced by boosting sensitized men and women, extracting the anti-D by plasmapheresis and sending the extract for centralized pooling, packaging and distribution. Current production of anti-D in most countries cannot meet the demands of antenatal and postnatal prophylaxis. For instance, only two of eight regional immunoglobulin production centres in England are able to meet local demands [27]. While countries like Canada and the United States manufacture enough product to meet their needs, there is currently a global shortage of Rh immunoglobulin [28]. With decreasing numbers of sensitized volunteers available today and increasing fears of disease transmission through repeated boosting with blood products [29,30], the supply of human anti-D is unlikely to increase drastically. Increasing the supply with monoclonal anti-D (derived from Epstein-Barr virus-transformed lymphocytes [31] or from heterohybridomas obtained by fusing transformed lymphocytes with mouse myelomas [32]) appears to be the alternative offering the greatest hope, but this

solution seems some years away. Experimental studies on the efficacy of monoclonal anti-D in suppressing endogenous anti-D are being carried out presently, but clinical trials to assess the clinical benefits have yet to be planned [27].

Besides limits on production, the other significant factor in the debate regarding the use of antepartum Rh immunoglobulin prophylaxis involves the question of cost. Antepartum prophylaxis is not nearly as cost-effective as postpartum prophylaxis for various reasons, including the fact that in the former instance prophylaxis has to be administered without knowledge of the fetus's Rh status. Also, the AIDS epidemic and related tainted blood scandals worldwide have led to more stringent quality control requirements in the manufacturing process for anti-D. Since the implementation of different tests for viral contaminants, costs of production have increased [28,33]. Health care technology is coming under much closer scrutiny, because burgeoning health care costs require that choices be made between several effective, yet expensive, options.

Even though issues of Rh disease control command attention in the medical literature of the 1990's [27,34-36], risk factors for the disease have not been fully studied in epidemiologic terms. Specifically, the concepts of confounding and effect modification, have not been adequately addressed in relation to determinants of Rh disease (see below). Perhaps because the theoretical conquest of Rh disease (through the

demonstration of Rh immunoglobulin prophylaxis) occurred decades ago, this disease has escaped close epidemiologic scrutiny.

This point is highlighted in recent publications. While Rh immunoglobulin prophylaxis is hailed as one of the major achievements of the past quarter century, it is accepted that the observed decline in Rh disease over the last few decades was also a consequence of trends towards smaller family size i.e., a shift to the left in birth order distribution [1]. Nevertheless, the relative contributions of the two alternate mechanisms responsible for disease reduction are not discussed, mainly because the contributions have never been quantified. A closely related issue is highlighted in a recent paper by Baskett and Parsons [34], which attempted to evaluate the cost-benefit of the Rh prophylaxis program in Nova Scotia, Canada. The authors reasoned that since the observed prevalence of Rh sensitization was 1.3 per 1000 total births (Nova Scotia, 1982-86) in contrast to an expectation of 10 per 1000 total births (the rate observed in Manitoba in 1963 before anti-D prophylaxis was introduced [37]), the program was responsible for an 88% decline in the occurrence of Rh sensitization. An identical calculation was used by the group in an earlier paper [38]. The cost-benefit estimate was based on this reasoning, with no attempt made to correct for the reduction in Rh sensitization rates that occurred secondary to changes in birth order distribution since 1963

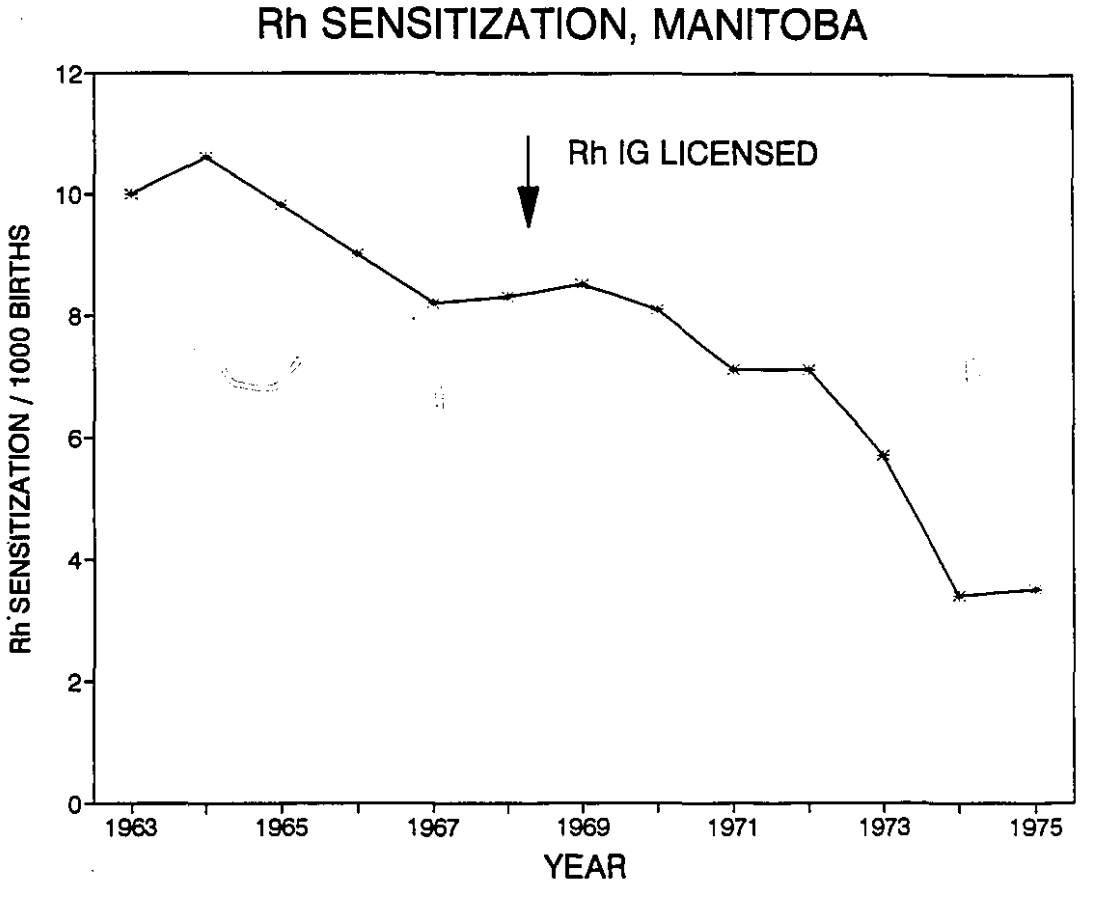
(in particular, an increase in the proportion of first births, see Figure 1).

In a similar vein, Chavez et al [36] estimated the relative risk for Rh hemolytic disease of the newborn across categories of race/ethnicity in the United States in 1986. Incidence rates of Rh hemolytic disease were used in this computation with no correction made for the varying birth order distributions across racial categories. These unadjusted estimates of the relative risk thus served as the basis for drawing conclusions about the effect of Rh immunoglobulin across racial/ethnic groups.

The failure to adjust for confounding is surprising, because the effects of birth order and other determinants were first discussed many years ago [39]. One possible reason for this omission is that since the effect of changing birth order has not been quantified, its contribution to Rh disease reduction tends to be ignored.

Although studies on the cost-effectiveness of both postpartum and antepartum prophylaxis have been carried out repeatedly using various methodologies, such estimates have invariably tended to be location- and time-specific. Adequate attention has not been paid to the manner in which cost-effectiveness/cost-benefit estimates are modified by the determinants of disease incidence. For instance, since the prevalence of the Rh-negative phenotype in a population affects the rate at which Rh disease occurs, this factor could

Figure 1. Rate of Rh sensitization (per 1000 total births) in Manitoba between 1963 and 1975. The declining trend in the rate is seen to precede the introduction of Rh prophylaxis. (Source: Bowman et al [37]).



serve to modify the cost-effectiveness equation. For instance, post-abortion prophylaxis may prove expensive for a third world country with a low prevalence of the Rh-negative phenotype. Similarly, other determinants of disease frequency such as birth order distribution and quality of medical care could also affect the cost-effectiveness of Rh prophylaxis.

Given the economic realities faced by developing countries, it may be worth considering and modifying tactical options once explored by developed nations. For instance, researchers in developed countries once proposed restricting antepartum prophylaxis to primiparous women with a view towards maximising the benefit:cost ratio of antepartum Rh prophylaxis [40-41]. Restricting postpartum prophylaxis to primiparous women in developing countries with limited resources for health care may be a way of making the prophylaxis option more affordable and feasible. Such an option would also address the issue of limits to immunoglobulin production.

1.1 OBJECTIVES

1. To quantify the impact of Rh immunoglobulin prophylaxis, changing birth order pattern and quality of medical care on the decline in the occurrence of Rh sensitization, Rh hemolytic disease and deaths from Rh disease.
2. To quantify the risk of Rh sensitization in relation to other known factors which affect disease occurrence.
3. To determine how variations in the prevalence of determinants of Rh sensitization influence the cost -effectiveness of Rh immunoglobulin prophylaxis.
4. To evaluate the options for Rh prophylaxis in developing countries, so as to identify the prevention program that maximizes feasibility and cost-effectiveness.

This thesis is organised into seven chapters. This first introductory chapter has discussed the rationale and stated the objectives of the study. The second chapter reviews the pertinent literature on Rh disease. Chapter 3 presents the methods employed in this study; the first section details the regression methodology employed for the epidemiologic part of the study, while the second section discusses the conditional probability model. The results are presented in Chapter 4 which is also subdivided in two sections corresponding to the regression analysis and the conditional probability modeling, respectively. A discussion of the results and the conclusions drawn are presented in Chapter 5, while Chapter 6 is an appendix which contains information and results of lesser import.

2. REVIEW OF THE LITERATURE

An understanding of the pathophysiologic basis underlying Rh hemolytic disease of the newborn began with the discovery of the Rh blood group system in 1940. Since then, striking advances have been made in obstetric and neonatal services which have increased the survival rate of the affected fetus and newborn several-fold. The revolution in the control of Rh disease, however, occurred with the discovery and introduction of Rh immunoglobulin prophylaxis.

Rh hemolytic disease and hemolytic disease of the newborn in general have been the subject of clinical research for more five decades. Various reviews and texts describe these related diseases and their history [1,42-44]. The following review is a brief summary of the Rh blood group system, the clinical manifestations, treatment and prevention of Rh hemolytic disease, historical developments in the conquest of the disease and finally an overview of the sparse literature on the population determinants of Rh disease.

2.1 THE Rh BLOOD GROUP SYSTEM

The clinical importance of the Rh blood group system stems from the fact that the D antigen of the Rh system is highly immunogenic. Rh-negative mothers of Rh D-positive infants become sensitized to the antigen following minor feto-maternal transfusions which sometimes occur at delivery and less commonly during pregnancy itself. Transfusion with D-positive

blood and invasive procedures on mothers of D-positive fetuses (amniocentesis, therapeutic abortion etc.) provoke a similar immunogenic response. Subsequent pregnancies in such Rh D-sensitized mothers carry the risk of hemolytic disease for D-positive infants.

2.1.1 NOMENCLATURE OF Rh ANTIGENS

Until recently, categorizing human beings into Rh-positive and Rh-negative was considered sufficient at least for most clinical purposes. This distinction was made by testing red cells with the commonest kind of Rh antibody, which in Fisher's nomenclature is known as anti-D. According to Fisher's original theory, the presence of the D antigen is determined by a gene D which has an allele d so that there are three possible genotypes DD (homozygous, D positive), Dd (heterozygous, D positive) and dd (homozygous, D negative). Fisher's complete scheme for the nomenclature of all Rh blood antigens is discussed below, as are current concepts regarding the recessive allele d.

FISHER'S SCHEME [45]: Under the scheme proposed by Fisher in 1943, the Rh system is composed of three closely linked allelic genes: C and c, D and d and E and e. Individuals inherit a set of 3 alleles (a haplotype) from each parent: (i) C or c (ii) D or d (iii) E or e. For example, a person may inherit CDe from one parent and cde from the other.

Although it was originally assumed that each allele would determine a corresponding antigen only C, c, D, E and e antigens have been recognized, whereas d antigen is thought to be amorphic. Recent work [46] using Southern blot analysis suggests that there may be only 2 Rh genes, one determining D status and the other determining C, c, E and e status. D-negative individuals are found to have only the latter gene with no allelic counterpart for the D gene.

WIENER'S NOMENCLATURE [47]: In 1951 Wiener proposed an alternative scheme for the classification of Rh antigens which postulated Rh antigen inheritance based on a single gene with multiple alleles. Under this scheme the inheritance of CDe is determined by the allele R^1 of a singe gene rather than by specific alleles of three different genes.

A World Health Organization expert committee on biological standardization [48] has recommended the universal adoption of Fisher's scheme in the interest of simplicity and uniformity. Although valid criticisms regarding the deceptive simplicity of Fisher scheme have been voiced [49], recent work [50,51] showing differences between D, C/c and E/e polypeptides (antigens) has provided support for the CDE terminology.

2.1.2 RELATIVE IMPORTANCE OF THE D ANTIGEN

The Rh D antigen is at least 20 times more immunogenic than c,

the next most potent Rh antigen. In most clinical situations, D is the only Rh antigen taken into account and "Rh-positive" commonly implies Rh D-positive unless otherwise specified. However, this practice is currently under revision [42] with greater importance being attached to the non-D antigens. This change has been motivated by the greatly reduced frequency with which anti-D sensitized individuals are encountered. The introduction of Rh D-specific blood transfusion and routine Rh D immunoglobulin prophylaxis for susceptible mothers have been responsible for this drastic reduction in the numbers of D-sensitized patients encountered in clinical practice.

2.1.3 Rh GENOTYPES AND PHENOTYPES

The commonest Rh haplotypes in an English population are CDe and cde [52]. Thus the commonest three Rh genotypes are CDe/cde (frequency 32%), CDe/CDe (frequency 16%) and cde/cde (frequency 15%). The D-negative phenotypes also include Cde/cde and CdE/cde etc. and total 17%. The frequency of different Rh antigens varies widely according to race, with the frequency of D-negative individuals ranging from 20-40% (Basques) to 0-1% (Japanese, Chinese, American Indians and Eskimos [53,54] (see Table 1A, Appendix).

2.1.4 Rh D SENSITIZATION FOLLOWING BLOOD TRANSFUSION

Transfusion of large amounts of D-positive red cells into D-negative individuals leads to the production of serologically

detectable anti-D in more than 90% of recipients [55,56]. Almost all D-negative subjects who fail to respond to a first large injection of D-positive cells will fail to respond to subsequent injections of D-positive cells [57]. The reasons for this immunologic non-response are unknown.

Responses to small injections of D-positive cells elicit a similar immunologic response with some distinct features. In particular, the rate of sensitization is lower than with larger exposures. Also, some individuals with no serologically detectable antibody show a secondary immune response to a second injection of D-positive cells, suggesting that primary sensitization had occurred with the first injection. Finally, a small proportion of subjects who do not have demonstrable antibodies after the first injection respond to a second injection with a rapid clearing of the injected cells. These subjects demonstrate detectable antibody subsequently. The phenomenon of primary sensitization occurring in the absence of serologically detectable antibody has been termed 'sensibilization' [58].

RESPONDERS AND NON-RESPONDERS: Some 8% of Rh-negative subjects fail to produce anti-D in spite of repeated injections of D-positive cells and are termed non-responders [55,56]. Despite the presumption that responsiveness to Rh D is genetically determined, this has not been demonstrated to date.

INFLUENCE OF ABO INCOMPATIBILITY: The effect of ABO-incompatibility in protecting against Rh D sensitization was first discovered from analyses involving the ABO status of parents of infants with Rh hemolytic disease [59,60]. This effect has been demonstrated through the experimental injection of ABO compatible or incompatible D-positive red cells into D-negative subjects [61]. The protection observed in ABO incompatible situations is thought to occur because rapid clearance of the A/B red cells (by anti-A and anti-B antibodies) prevents immunologic processing of Rh antigens.

2.1.5 RH D SENSITIZATION FOLLOWING TRANSPLACENTAL HEMORRHAGE

2.1.5.1 DELIVERY

Transplacental hemorrhage is a relative common occurrence during childbirth and fetal red cells have been detected in 30% of women immediately after delivery [62]. Large studies have shown that about 1% of recently delivered women have 3 ml or more of fetal red cells in their circulation and 0.3% have 10 ml or more [43,63-65].

Estimates of the incidence of anti-D in D-negative women who have delivered a D-positive infant vary depending on various factors including the ABO status of the pregnancy and time at which serological testing is done. Also, primary sensitization may have occurred without demonstrable antibody in the plasma. Estimates of the incidence made 6 months after delivery vary from 2-13% in ABO compatible pregnancies

[6,10,11,44,66-68]. However, in one study [44] where 8.2% of the D-negative mothers had anti-D in the plasma 6 months after delivery, follow up revealed that 17% had anti-D by the end of a second pregnancy with a D-positive fetus. This 9% excess is thought to represent women with primary sensitization but no detectable antibody who required the stimulus of the second D-positive pregnancy to produce detectable antibody. A small proportion of this 9% could represent women who became sensitized by the second pregnancy.

INFLUENCE OF ABO INCOMPATIBILITY: The influence of ABO-incompatibility in experimentally induced Rh sensitization (following blood transfusion) has already been discussed (see Section 2.1.4). The fact that ABO incompatible pregnancies protect against Rh sensitization was first noted in 1943 [59]. It has been estimated that in whites, group A-incompatibility between infant and mother gives 90% protection against Rh D sensitization while B-incompatibility provides 55% protection [69].

2.1.5.2 ABORTION

Some evidence suggests that significant transplacental hemorrhage occurs only after curettage and not after either spontaneous or threatened abortions. The older belief that spontaneous abortion in the first trimester leads to primary Rh D sensitization has hence been challenged [42], although

some authorities quote this rate to be about 2% [25]. The overall risk of Rh D sensitization following medical termination of pregnancy in D-negative women, on the other hand, seems to be at least 4% [42]. This figure is estimated from studies on whites with no direct information on proportions of fetuses who are Rh-positive. The rate of post-abortion sensitization is therefore likely to be slightly higher in Rh-negative women from races with a higher prevalence of the Rh-positive phenotype.

2.1.5.3 PREGNANCY

The rate of Rh D sensitization in women tested at the end of the first pregnancy with a D-positive infant has been determined to be about 0.7 to 0.9 percent [66,70,71]. Higher rates are reported from studies using more sensitive methods of testing for the presence of anti-D antibodies. Autoanalyser or enzyme methods show a sensitization rate of 1.2% in primiparae by the end of the first pregnancy [72].

2.2 HEMOLYTIC DISEASE OF THE NEWBORN

An interesting perspective on hemolytic disease was proposed and reviewed by Billingham and Kirby [73,74], who conceptualized pregnancy as a homograft and the occurrence of hemolytic disease as a limited form of 'rejection'. While the placental barrier generally prevents fetal antigenic material from entering the maternal circulation, anatomic breaches

occasionally occur and lead to a potent immunologic response from the mother. Some of the antibodies produced cross the placenta and enter the fetal circulation. Since the Rh antigens are virtually confined to circulating red cells, maternal rejection thus produces a hemolytic anemia.

Hemolytic disease of the newborn is a condition in which the lifespan of the infant's red cells is shortened by the action of specific maternal antibodies. The disease begins in intrauterine life and in severe cases can lead to stillbirth. Red cell destruction is maximal at the time of birth and diminishes subsequently as the concentration of maternally acquired antibody in the infant's circulation falls.

The clinical manifestations of Rh hemolytic disease vary widely, depending on the severity of the illness. All abnormalities are a consequence of red cell destruction secondary to coating of fetal red cells with maternal anti-Rh antibody. In the mildest of cases, tests reveal antibody coating of red cells but no red cell destruction. This is usually seen when maternal antibody titres are low, for instance, in a first pregnancy when the D-positive infant was responsible for maternal sensitization.

When red cell destruction occurs, hemoglobin falls more rapidly than normal in the first few days of life. Jaundice develops in the first or second day of life as bilirubin levels rise (*icterus gravis neonatorum*). The signs

of moderate to severe hemolytic disease are natural consequences of these two phenomena, i.e., anemia and hyperbilirubinemia. In fetuses with a severe hemolytic process, profound anemia develops and signs of cardiac failure become apparent (*hydrops fetalis*). Severe *hydrops fetalis* is complicated by intravascular coagulation with pulmonary hemorrhage and subarachnoid hemorrhage. Infants may die in utero at any time from about the seventeenth week of gestation in severe cases.

The serious consequences of hyperbilirubinemia arise owing to deposition of bilirubin compounds in parts of the brain including the basal ganglia. This leads to kernicterus, a syndrome characterized by signs of brain damage. Infants who develop kernicterus suffer a high mortality, and survivors have permanent cerebral damage characterized by spasticity and choreoathetosis. Milder cases of kernicterus may show high-frequency deafness as the only sign.

2.3 TREATMENT OF HEMOLYTIC DISEASE

It is recommended that sera of all D-negative women be tested for anti-D at the time of their first antenatal visit and subsequently again at 20 and 28 weeks [42]. Given Rh sensitization, antenatal assessment of the severity of hemolytic disease will have to be made. Maternal antibody concentration (autoanalyser) is correlated with severity and provides a simple and useful index for assessing severity.

Estimation of the amount of bilirubin in amniotic fluid (obtained by amniocentesis) can be performed by appropriate optical density measurements. Repeated examination of the fetus by ultrasonography can detect early signs of cardiac decompensation like a small pericardial effusion or cardiac dilatation. Assessment of severity can be most reliably carried out by fetal blood sampling, although the procedure carries a small risk to the fetus.

Antenatal treatment of hemolytic disease may consist of premature delivery even as early as 30-32 weeks or depending on the severity, transfusion of the fetus in utero. This latter procedure was first attempted in 1963, with red cells being injected into the peritoneal cavity of the fetus. Current practice consists of intravascular transfusion though a needle inserted into the umbilical vein under sonographic guidance.

Postnatal assessment of severity at the earliest possible moment is mandatory, since management can vary greatly depending on severity. Cord blood hemoglobin and serial measurements of hemoglobin and bilirubin are used to decide among the various forms of treatment. Mild cases with only antibody coating of red cells may not require any treatment. Mild cases of hyperbilirubinemia are treated with phototherapy to reduce the level of serum bilirubin. Exchange transfusions are the mainstay for the treatment of severe cases. The procedure corrects anemia, lowers serum bilirubin

and removes antibodies as well. It has been shown to greatly improve survival rates and reduce the risk of kernicterus.

2.4 SUPPRESSION OF Rh D SENSITIZATION

Suppression of Rh D sensitization by anti-D in male volunteers was first demonstrated in 1963/64 [2-4,75] using an immunoglobulin concentrate of IgG anti-D delivered intramuscularly. Subsequently, the suppression of Rh D sensitization was demonstrated in women by the administration of anti-D soon after delivery [76-78].

Today it is well established that Rh D sensitization can be prevented by giving 20 μg or more of anti-D immunoglobulin for every 1 ml of D-positive cells introduced into the circulation. Failure to prevent the Rh D sensitization that follows delivery occurs either if the dose of anti-D administered is insufficient in relation to the size of the transplacental hemorrhage or if the administration of anti-D is delayed beyond 72 hours after delivery. Thus, the administration of anti-D postnatally will reduce the rate of Rh D sensitization (in Rh-negative women with D-positive infants) from 17% to 1.5% by the end of a second D-positive pregnancy [42].

Antenatal administration of anti-D immunoglobulin reduces this rate of Rh D sensitization even further. Studies have shown that administration of anti-D immunoglobulin at 28 and/or 34 weeks of gestation leads to a rate of Rh

sensitization of 0.1-0.2% by the end of the first pregnancy [42]. This figure is likely to have been slightly higher had the estimates been made early in the second pregnancy.

FAILURE RATES FOLLOWING POSTPARTUM PROPHYLAXIS: Administration of 100-300 μg of anti-D immunoglobulin immediately after delivery reduces the rate of Rh D sensitization to 0.1-0.5% when women are tested 6 months after delivery [79-81]. When failure rates are estimated at the end of a second D-positive pregnancy these rates increase to between 1.5 and 1.9% [79-81]. These latter rates have been attributed to a combination of sensitization that occurred during the first pregnancy (0.7%), sensitization that occurred during the second pregnancy (0.7%) and failure of anti-D (0.2%) due to a large transplacental hemorrhage at the time of the first delivery [42].

2.5 HISTORICAL LANDMARKS IN Rh DISEASE CONTROL

The developments in medicine which affected the occurrence and prognosis of Rh disease began in 1939 with a serendipitous finding by Levine and Stetson [82]. They showed that antibody derived from the serum of a recently delivered woman reacted with the red cells of the father but not with her own cells. The antibody also reacted with red cells of approximately 80 percent of white subjects. The authors suggested that, as the woman had not been previously transfused, she might have been

sensitized by a paternally derived fetal antigen. Landsteiner and Weiner discovered the Rh blood group system in 1940 [83], and the hypothesis of Levine and Stetson was soon confirmed in the now classic paper of Levine, Burnam, Katzin and Vogel published in 1941 [84].

In 1946 Coombs and colleagues described the anti-human globulin test for the detection of incomplete antibodies, and in 1954 Chown provided evidence for the occurrence of feto-maternal transfusion by demonstrating the presence of fetal hemoglobin in maternal circulation. Exchange transfusion as a therapeutic postnatal procedure was introduced into clinical practice in the mid and late 1940's and led to a significant improvement in prognosis in comparison with simple transfusion using the father's blood. Early delivery based on the results of clinical history and maternal antibody titre was introduced in the mid 1950's, and early delivery based on amniotic fluid spectrophotometry was used in the late 1950's and popularized by Liley in the early 1960's. Intrauterine peritoneal transfusions were first introduced into clinical medicine by Liley in 1963 at about the same time as the first demonstration of Rh prophylaxis for preventing Rh sensitization. Rh immunoglobulin was licensed for postpartum use during the years 1968-1970 and antenatal prophylaxis followed 5-10 years later. Intravascular transfusions were first attempted in the mid 1980's, first by fetoscopy and subsequently under sonographic guidance.

2.6 POPULATION DETERMINANTS OF Rh DISEASE

Few studies have attempted to relate the rate of Rh disease in populations to levels of population determinants. Knox addressed this issue in a 1976 paper [39] using registered data from England and Wales. Stillbirths and deaths from hemolytic disease for the years 1961 to 1973 constituted the outcome of interest. Standardization techniques were used to attribute observed changes in stillbirths and deaths from hemolytic disease to changes in birth rank distribution, care of infants, Rh prophylaxis, abortions and the racial composition of the population.

The most effective component in reducing infant deaths from hemolytic disease of the newborn was found to be improved care of the liveborn infant, which was responsible for 62% of the reduction. 38% of the reduction was attributed to changes in birth order. Control programs (Rh prophylaxis) were shown to have had a marginal effect on the stillbirth rate while changes in abortion rates and racial composition of the population did not appear to have been significantly responsible for disease reduction.

The statistical methods used in this study consisted of standardization and other techniques which are not conducive to the simultaneous adjustment of multiple confounders. Also, the last year for which data were then available was 1973, at which point the effect of Rh prophylaxis was only beginning to be discernable. The above-

mentioned shortcomings notwithstanding, Knox's paper represents the first and only attempt to quantify the contributions of the multiple factors responsible for the decline in hemolytic disease of the newborn. This thesis is an attempt to fill this lacuna in medical knowledge using appropriate methods (Poisson regression and conditional probability modeling) and data from a period 15-20 years after the introduction of Rh prophylaxis.

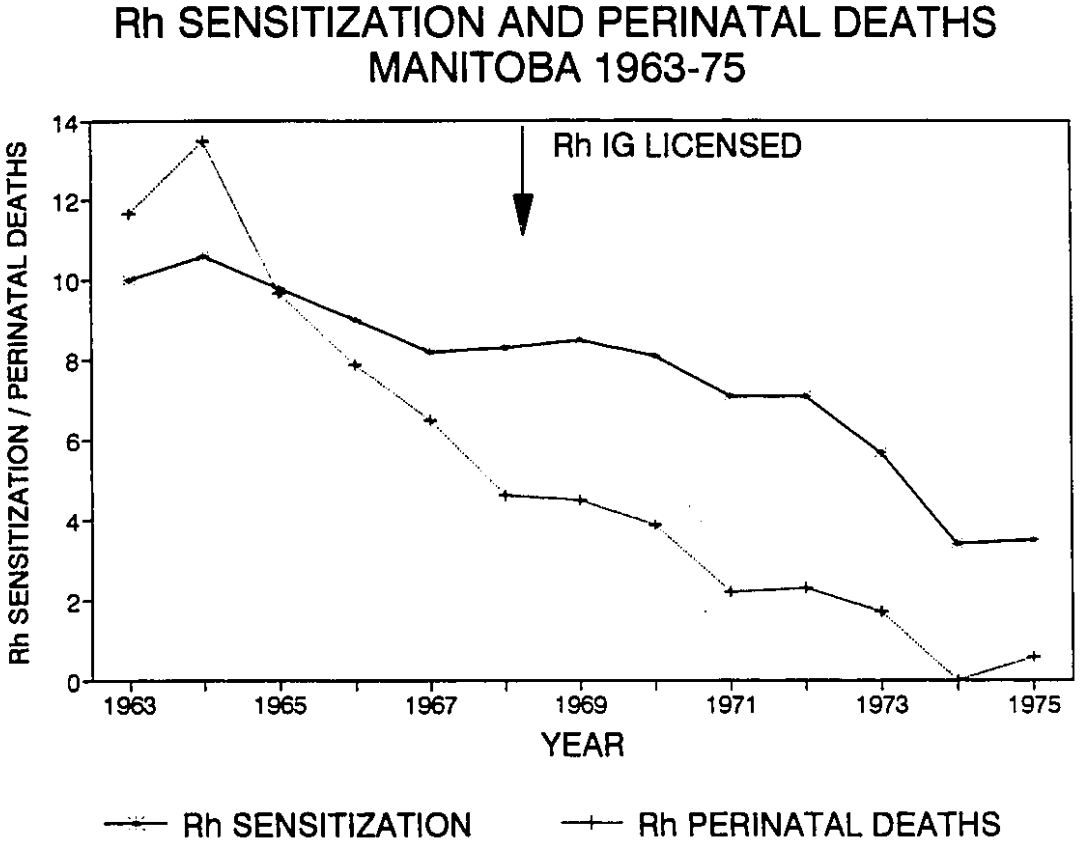
2.7 Rh DISEASE-RELATED TRENDS IN MANITOBA

This section presents a brief review of the Rh surveillance program of Manitoba, Canada. The surveillance program, which routinely screens post-delivery maternal and cord blood samples (to detect maternal Rh sensitization and affected infants), was initiated in November 1962. Data collection has been ongoing and statistics are presented in annual reports issued by the Rh Laboratory of the Winnipeg Health Sciences Centre in Winnipeg. The surveillance program is unique because it was initiated well before routine Rh prophylaxis was instituted and also because unlike other surveillance programs (for instance, the Rh surveillance program of Connecticut, U.S.A.), it continues to monitor the population for Rh disease-related outcomes. Surveillance programs like the currently ongoing Rh surveillance program of Nova Scotia, Canada, on the other hand, began functioning in the early nineteen-eighties and therefore lack data on pre-Rh-

prophylaxis disease rates.

Trends in the rates of maternal Rh sensitization and perinatal death from Rh disease between 1963 and 1975, as documented and published by the program [37], offer insights into some of the risk factors responsible for the declining trends in Rh disease (see Figure 2). The decline in the frequency of maternal Rh sensitization and perinatal death from Rh disease clearly preceded the introduction of Rh prophylaxis in late 1968. Changing birth order distribution is possibly the sole explanatory factor responsible for the reductions in maternal Rh sensitization rates seen in the nineteen-sixties. The decline in perinatal death from Rh disease, however, probably occurred as a consequence of changes in both the perinatal care of affected infants and in birth order distribution. The magnitude of disease reduction attributable to each of the factors needs to be quantified. This is necessary from the point of view of medical history and also because the absence of such quantification has led to a misapprehension about the magnitude of the effect of Rh prophylaxis. Further, the implications of these findings need to be extended to populations of third world countries (where Rh prophylaxis is not routine) with suitable modifications to account for racial differences.

Figure 2. Rate of Rh sensitization (per 1000 total births) and perinatal death from Rh disease (per 10,000 total births) in Manitoba between 1963 and 1975. (Source: Bowman et al [37]).



3. METHODS

The analytic methods used to characterize the epidemiology of Rh disease consisted of regression techniques and conditional probability modeling. The two methodologies were intended to complement each other, although potential advantages of one method over the other were also considered and explored.

The data for regression were obtained from Rh disease surveillance programs and national vital statistics publications. These data (which either covered an entire province/state or the national population of Canada or the United States) extended from a period during which no program of Rh prophylaxis existed, to more recent years.

The use of the model based on conditional probabilities was possible because of the unique nature of Rh disease. Unlike other diseases, the probabilities associated with events that lead to disease predisposition and occurrence are well delineated and quantified. This permits the construction of a simple model for predicting disease behaviour in populations. The model was also used to evaluate the cost-effectiveness of various alternative strategies for the delivery of Rh immunoglobulin and in this context the modeling represented bonafide decision analysis.

3.1 EPIDEMIOLOGIC ANALYSIS

Non-experimental studies of intended effects are generally considered infeasible because of the difficulties associated

with controlling for confounding by indication [85]. This general principle does not apply in this situation, however, because the indication for Rh prophylaxis is an absolute one i.e., it is of the all-or-none type [85]. An Rh-negative mother with an Rh-positive baby represents an indication for Rh prophylaxis and no gradations of disease severity/indication exist which can modify recommendations with regard to Rh prophylaxis. Clinical practice over the last few decades has been unequivocal in this regard. Thus, the non-experimental assessment of the effect of Rh prophylaxis is free of bias secondary to confounding by indication in spite of a lack of randomization in study design.

The design of the study was ecological, with the annual experience of a population representing a unit of observation. The rate of Rh disease (or other related outcome) in the population in any given year was studied as a function of determinant levels in that population at that time.

3.1.1 CHOICE OF REGRESSION MODEL

Regression analysis of the various data sets was possible under two different regression models – the Poisson regression model (logarithmic transform of the dependant variable, Poisson error) and the logistic regression model (logit transform of the dependant variable, binomial error). The two generalized linear models are specified below:

Poisson regression model (log-linear)

$$\ln E(c_i) = \ln (n_i) + B_0 + \mathbf{B}\mathbf{X}_i$$

where $E(c_i)$ = mean value of the Poisson variable, namely, the number of cases with the given outcome in the stratum defined by the subscript i

n_i = the denominator for the i^{th} stratum, i.e., the number of births in the i^{th} stratum

B_0 = the intercept

$\mathbf{B}$ = vector of beta coefficients associated with the vector of independent variables $\mathbf{X}_i$.

Logistic regression model

$$\ln (P_i/(1-P_i)) = B_0 + \mathbf{B}\mathbf{X}_i$$

where P_i = outcome risk in the i^{th} stratum

B_0 = the intercept

$\mathbf{B}$ = vector of beta coefficients associated with the vector of independent variables $\mathbf{X}_i$.

Both models fall into the generalized linear model category i.e., the mean of the dependent variable is expressed as a linear combination of the independent parameters, namely B_0, B_i etc. The difference between the two models arises because the transformation of the mean of the dependent variable differs between the two models. In the Poisson regression model, the dependent variable is the natural logarithmic

transformation of the outcome count, while the logit (natural logarithm of the odds) of the outcome risk serves as the dependent variable in the logistic regression model [86].

Given the large number of study subjects (pregnancies/births) and low probability for outcome events (e.g., Rh disease), the two models were expected to yield similar results in terms of the effects of independent variables. Under the Poisson regression model, the beta coefficient for any independent variable represents an estimate of the (natural) log of the risk ratio for a unit increase in the independent variable, while under the logistic regression model the beta coefficient represents an estimate of the (natural) log odds ratio for unit increase in the independent variable. Since the rare disease assumption is satisfied for all outcomes under consideration, the odds ratio obtained from logistic regression was expected to approximate the risk ratio obtained from Poisson regression. The direct interpretability of the risk ratio and previous work suggesting a lack of effect modification of the risk ratio by the background level of disease [35] made the Poisson regression model marginally more attractive. Thus, the analytic method adopted was Poisson regression; the expectation of its equivalence with logistic regression (in terms of the estimated effects of the independent variables) was checked nevertheless.

3.1.2 SOURCES OF DATA

Sources of study data included the following:

1. Annual reports [87] and past publications [37] of the Rh surveillance program of Manitoba in conjunction with vital statistics reports of the province of Manitoba [88-91].
2. Annual reports of the Rh surveillance program of Nova Scotia [92] in conjunction with vital statistics reports of the province of Nova Scotia [88,89,93].
3. Annual vital statistics publications of Canada, including those detailing causes of death, numbers of live births, birth order distribution and infant mortality rates [88,89].
4. Annual vital statistics publications of the United States, including those detailing causes of death, numbers of live births, birth order distribution and infant mortality rates [94,95].

The validity of the information obtained from these data sources is discussed elsewhere (see Sections 3.1.12 and 4.1.8).

3.1.3 CONTENT OF THE MODEL

STUDY PERIOD

Each annual experience of the population represented one unit of observation. For the purposes of the primary analysis, the pre-prophylaxis years included in the study spanned the period 1963 to 1968. Data for years prior to this period were not

documented under the surveillance program in Manitoba. Although vital statistics records from Canada and the United States did provide information on infant deaths from hemolytic disease of the newborn for the period prior to 1963, data from these years were not included in the primary analysis. The reason for their exclusion was that the declining trend seen in hemolytic disease infant deaths in both Canada and the United States in the 1950's was explained, at least in some part, by the introduction of Rh-specific blood transfusions in the late 1940's [96]. The proportion of pregnant women whose Rh sensitizations were a consequence of incompatible blood transfusion had decreased to zero by about the year 1960 [96]. Thus, with the data set restricted to the years 1963-68 for the pre-prophylaxis information, the analysis was not affected by changes in Rh sensitization rates which occurred secondary to the introduction of Rh type-specific blood transfusions.

Analyses with data for the years 1951-54 were also performed, however, with the addition of an independent variable which served to characterize the effect of introducing Rh-specific blood transfusions. This independent variable was assigned a value of 0 for the period 1951-54 and a value of 1 for subsequent years. While this is not literally true (blood transfusions in the early 1950's were Rh type-specific), it is assumed that the effect (perhaps even the peak) of past incompatible transfusions was still present during this period.

The period from 1969 to 1981 was also excluded from the regression model, because the effect of Rh immunoglobulin prophylaxis was only partially apparent during these years. The years immediately following Rh immunoglobulin licensing were marked by partial population coverage with anti-D. Also, rates of Rh sensitization, Rh disease and death from Rh disease during these years were driven by sensitizations that had occurred in the pre-prophylaxis era. For these reasons, the comparison period chosen was the period between 1982 and 1988. Thus, the years included in the regression analysis were clearly distinguished by the absence/presence of an Rh prophylaxis program.

DEPENDENT VARIABLES

Data from Manitoba included information on three Rh disease-related outcome variables, namely, Rh sensitization (maternal), Rh hemolytic disease and perinatal deaths from Rh disease. Data from the Nova Scotia surveillance program also included information on these three variables for the post-prophylaxis years. The Canadian and U.S. national statistics provided information on another Rh disease-related outcome, namely, infant deaths from hemolytic disease of the newborn (ICD code 770 under the Sixth and Seventh Revisions, 774 and 775 under the Eighth Revision and 773 and 774 under the Ninth Revision, see Appendix Table 2A). This outcome differs from the third outcome available from Manitoba (perinatal deaths

from Rh disease) in that:

1. Affected stillbirths are included in perinatal deaths but not in infant deaths. This is an important difference, because stillbirth was a common outcome of serious Rh hemolytic disease, especially in the pre-prophylaxis years. Although the numbers of perinatal deaths from hemolytic disease of the newborn were published routinely some decades ago, this practice has been discontinued. Therefore, it was not possible to identify the number of perinatal deaths from hemolytic disease of the newborn for recent years.
2. Infant deaths include deaths occurring through the first year of life, while perinatal deaths are restricted to those that occur in the first week of life.
3. The outcome, infant deaths from hemolytic disease of the newborn, encompasses all fatal cases of hemolytic disease of the newborn among infants irrespective of etiology, whether Rh or non-Rh. The Manitoba outcomes, on the other hand, were all Rh hemolytic disease-specific. ICD codes specific for Rh hemolytic disease (774.0 and 775.0) were introduced with the Eighth Revision and adopted for use by the United States and Canada in 1968 and 1969, respectively. Since Rh immunoglobulin was also licensed during this period, no information is available for this category for the pre-prophylaxis years. Also, this category does not include all cases, because some Rh hemolytic

disease deaths were coded as hemolytic disease of the newborn, without mention of cause, under ICD codes 774.3 and 775.3 [101].

INDEPENDENT VARIABLES

When Rh sensitization or Rh hemolytic disease of the newborn is the outcome variable, the independent variables used in the model are the proportion of first-order births in the population (BO1) and the presence/absence of a program of Rh prophylaxis (PRG). Conceptually, the entire birth order distribution of a population has a bearing on the occurrence of Rh disease-related outcomes. However, the introduction of all birth order proportions into a regression model would lead to a completely collinear system, since for any given year, the proportion of first order births, second order births .... nth order births adds up to 100%. The strong correlations which exist between the various birth orders would lead to problems of collinearity even when only an incomplete list of terms is entered into the model. For instance, first-order births are highly correlated (negatively) with high-order births (for instance, eighth or greater). For this reason, only the proportion of first-order births in the population was entered into the model. The choice of first-order births was based on the belief that it is the proportion that drives the rate of Rh sensitization to the greatest extent. This reasoning was tested with the data from Manitoba to determine

whether alternative characterization of the birth order distribution would alter the results of the regression analysis.

For the models employing deaths of any sort as outcome events, a 'quality of medical care' variable was added as a third independent variable in the model, because the quality of medical care is known to affect the rate of death/survival from Rh disease. It was not included in the models with Rh sensitization and Rh disease, because the quality of medical care (other than prophylaxis with Rh immunoglobulin) is not considered to be a determinant for the occurrence of these outcomes.

When perinatal deaths from Rh disease was the outcome variable, this 'quality of medical care' term was intended to capture changes in prognosis of Rh disease which occurred secondary to improvements in obstetric and neonatal services. When infant deaths from hemolytic disease was the outcome variable, this variable was intended to capture improvements which affected prognosis and survival during the first year of life. Since the quality of medical care is known to have improved over the period during which Rh prophylaxis was introduced and became routine, and since quality of medical care is a determinant of death/survival given Rh hemolytic disease, it was viewed as a confounding factor. With the confounder (quality of medical care) thus defined in conceptual terms, its operationalization was attempted based

on information available in the context of each data set. In the case of the data from Manitoba (and Nova Scotia), this was simply and ideally achieved by using the rate of perinatal survival given Rh disease. However, for analysis of the data from Canada and the United States, a similar index was unavailable. Infant survival rate (the complement of infant mortality rate) was used to represent the changes in the quality of infant care in hemolytic disease over the study period. Such a representation assumes that improvements in the care of infants with hemolytic disease occurred at a rate commensurate with overall improvements in infant care.

3.1.4 POISSON REGRESSION OF MANITOBA DATA

Outcome data were obtained from the Rh surveillance program of Manitoba, Canada. The data, documented in regular annual reports [87] and past publications [37], are the product of a screening program covering all pregnant women in Manitoba. Post-delivery maternal and cord blood samples are screened at the Rh laboratory of the Winnipeg Health Sciences Centre, and this allows the compilation of statistics related to maternal Rh sensitization and perinatal deaths from Rh disease. The surveillance program, initiated in 1962, also documents the results of antigen tests and Coombs tests on the babies of sensitized women. The number of babies positive for the antigen to which their mothers are sensitized is also documented in the reports. The reports published by the

surveillance program cover the calendar period between the first day of November for any given year and the last day of October of the succeeding year. Thus, the 1963 annual report in fact includes outcome information for the period November 1, 1962 to October 31, 1963.

One feature of the annual reports which is relevant to this study pertains to the exclusion criteria used for calculating rates of Rh sensitization for any given year. Reports first list the number of pregnant women who tested positive during that year (sensitized women). Non-residents of Manitoba are then excluded from the statistics. Subsequently, a variety of other exclusion criteria are applied, and the number of sensitized women is reduced to yield a group which represents "true" or "relevant" cases of sensitization. For instance, 7 of the Manitoba residents who tested positive in 1988 were excluded because their antibodies were subsequently confirmed to be due to passive Rh immunoglobulin administered prior to the blood test. Similarly, 9 women were excluded on account of abortion. Table 3A (Appendix) gives a list of the exclusion criteria used in the annual reports for computing the number of women positive for any of the Rh disease-related outcomes.

For the purpose of this study, the exclusions were accepted *in toto* under the premise that the data represent a product of identical exclusions applied across all the years. Thus, the exclusion of the 9 Rh sensitized women with

abortions in 1988 is justified on account of similar exclusions made for the years 1963-68. Similarly, the exclusion of very weakly sensitized individuals, detected by the better methods of testing available in recent years, is mandatory if no bias is to be introduced secondary to changing modalities of case detection.

OUTCOME VARIABLES

Outcome information was available from 1963 onwards on the number of

1. Rh sensitized deliveries (Rh D and Rh non-D combined)
2. Babies affected by Rh hemolytic disease (mother Rh sensitized and baby positive for corresponding antigen).
3. Perinatal deaths from Rh disease.

Although the reports allow outcome counts for the later years to be stratified as Rh D and Rh non-D, this feature is not present for the data from the pre-prophylaxis years. This limitation meant that outcome rates for all years included the combined total of Rh D and Rh non-D outcomes.

Denominators used in estimating rates were based on the number of total births (live births and stillbirths over 28 weeks gestation) that occurred in the province for the given surveillance year. Data on the number of total births in Manitoba for each year were obtained from Dominion Bureau of Statistics [88] and Statistics Canada publications [89]. Since these publications provide details of live births and

stillbirths for each province by month, it was possible to obtain the number of total births that occurred in Manitoba during the above-mentioned surveillance year (November to October).

INDEPENDENT VARIABLES

FIRST BIRTH ORDER (BO1): The publications of the Dominion Bureau of Statistics provided information on birth order changes among Manitoba residents for the years 1963 to 1968 [88]. Birth order information for subsequent years was obtained from the Manitoba Bureau of Statistics [90] and the Canadian Centre for Health Information [91]. Birth order information was available only for the regular calendar year and not for the surveillance-year (November to October) according to which outcome information was documented.

PERINATAL CARE QUALITY (PCQ): This variable was used in the model in which perinatal deaths from Rh disease constituted the outcome of interest. The rate of perinatal survival given Rh disease was computed for each year based on the mortality and morbidity information and used as the measure of the quality of Rh-specific perinatal care.

PRESENCE/ABSENCE OF A PROGRAM OF Rh PROPHYLAXIS (PRG): The Rh prophylaxis program was introduced in late 1968 and considered established in Manitoba by 1971 [37]. By 1982 the routine

program had been in effect for more than a decade. Further, those women sensitized during the pre-prophylaxis years would have aged sufficiently by 1982 so as to cease childbearing. This assumes that reproductive events in a woman's life are unlikely to be separated by a period of 14 years or greater. Since the early years following the commercial licensing of Rh immune globulin were not included in the regression analysis, the necessity of quantifying immune globulin coverage rates did not arise. The presence or absence of an established program of Rh screening and Rh immune globulin prophylaxis was thus indicated with a dichotomous variable with values of 0 or 1.

3.1.5 POISSON REGRESSION OF DATA FROM NOVA SCOTIA

This analysis was undertaken mainly for the purpose of duplicating, in a multivariate manner, previous analyses [34,38] which estimated the crude effect of Rh prophylaxis. The rational for this approach has been discussed previously (see Section 1). In these previous analyses [34,38], the expected rate of Rh sensitization (for Nova Scotia 1982-86) was based on observed rates of Rh sensitization in Manitoba in 1963. The effect of Rh prophylaxis was then assessed by comparing this pre-prophylaxis rate from Manitoba with the rate observed in Nova Scotia between 1982-84 [38] or 1982-86 [34]. This assumes that Nova Scotia experienced the same pre-prophylaxis rate of Rh sensitization as Manitoba did during

1963. While the racial composition of the two populations differs with respect to the proportion of native Indians (3% of the Manitoba population consisted of native Indians in 1961 while the proportion in Nova Scotia was <0.5% [102]), this small difference is unlikely to have caused a major violation of the assumption regarding equivalence of the rates of Rh sensitization in the two provinces.

The outcome variables in the combined data set from Manitoba-Nova Scotia were identical to those in the data set from Manitoba alone (Section 3.1.4.). These included Rh sensitization (maternal), Rh disease and perinatal deaths given Rh disease. Information for the years 1982-88 was obtained from the annual reports of the Rh surveillance program of Nova Scotia [92].

The independent variables for this analysis included proportion of first-order births and presence/absence of an Rh prophylaxis program for the models with Rh sensitization and Rh disease as the outcome variables. With perinatal deaths from Rh disease as the outcome, perinatal care quality (perinatal survival given Rh disease) was added as a third variable in the model. Birth order information for Nova Scotia was obtained from provincial vital statistics publications [93], while data on quality of perinatal care were obtained from the annual reports of the surveillance program of Nova Scotia [92]. The data set used for Poisson regression thus included data for the years 1963-68 from Manitoba and for the

years 1982-88 from Nova Scotia.

3.1.6 POISSON REGRESSION OF DATA FROM CANADA

Canadian data were obtained for the years 1963-68 and 1982-88 from various publications documenting vital statistics information [88,89].

OUTCOME VARIABLE

The outcome variable for which information was available was infant deaths from hemolytic disease of the newborn. This information was abstracted from vital statistics publications of Canada. The number and details of the ICD codes for hemolytic disease of the newborn has undergone some change over the decades, but the overall category can be identified across revisions (see Appendix, Table 3A for the ICD codes across revisions 6, 7, 8 and 9, also Section 3.1.12). The outcome rate for each year was obtained by using the annual number of live births that occurred in Canada in that year as the denominator.

INDEPENDENT VARIABLES

The independent variables included in the model were proportion of first births in Canada, quality of infant care and the presence/absence of a program of Rh prophylaxis. Infant survival rate was used as the measure of the quality of infant care.

FIRST BIRTH ORDER: These proportions were estimated from data on birth order published by the Dominion Bureau of Statistics and Statistics Canada [88,89]. The data do not include birth order information for births occurring in the province of Newfoundland. The exclusion of this province is unlikely to have seriously affected the estimates of birth order for Canada as a whole, given the relatively small size of the province and the fact that no serious departures from the national trend (in terms of birth order distribution) are expected specifically for this region. (Note: Information on infant deaths from hemolytic disease of the newborn was obtained for all Canadian provinces, including Newfoundland).

INFANT CARE QUALITY: Information on infant survival rate given hemolytic disease of the newborn was not available from routine records. We therefore decided to use the infant survival rate (ISR, the complement of the infant mortality rate) to estimate the changes in the quality of infant care.

PRESENCE/ABSENCE OF Rh PROPHYLAXIS: As with the two previous data sets, the years 1963-68 were assigned a value of 0 for this variable to indicate the absence of Rh prophylaxis, while the years 1982-88 were assigned a value of 1.

OTHER ANALYSES

Analysis of the Canadian data was repeated after including

data for the years 1951-54. For this analysis, a dichotomous variable indicating the introduction of Rh type-specific blood transfusions was added to the model. This variable was assigned a value of 0 for the years 1951-54 and a value of 1 for the later years. Although such transfusion services were introduced in the late 1940's, the effects of such incompatible transfusions were evident (perhaps even peaked) during the early 1950's [96]. Given this expectation of a latent period, some fraction of hemolytic disease deaths observed during this period (1951-54) were assumed to have occurred as a consequence of past incompatible transfusions. The above-mentioned dichotomized variable was intended to measure the effect of introducing Rh type-specific blood transfusions.

3.1.7 POISSON REGRESSION OF DATA FROM THE UNITED STATES

Data for the United States were obtained from the vital statistics publications of the United States [94,95]. Regression analysis was first performed on the data for the entire population. This analysis was identical to that performed on data from Canada. The data included in the analysis were those pertaining to the years 1963-68 and 1982-88. Infant deaths from hemolytic disease was the outcome variable, while proportion of first births, infant care quality (as measured by the infant survival rate) and the presence/absence of a program of Rh prophylaxis constituted

the independent variables included in the model.

SUB-ANALYSIS BY RACE

The issue of modification of the effect of Rh prophylaxis (and other variables) by race was explored through a reanalysis of the U.S. data after stratifying the population into white and nonwhite categories. The data for this analysis were those pertaining to the years 1964-68 and 1982-88. Data for the year 1963 were excluded, because some of the relevant race-stratified U.S. statistics for this year did not include residents of the state of New Jersey.

EFFECT OF RACE

The effect of race was also directly estimated by regressing the U.S. data for whites and nonwhites combined. Race was represented by a dichotomous indicator: 0 for whites and 1 for nonwhites.

OTHER ANALYSES

The regression analysis was repeated using data for the years 1951-54. As with the similar analysis undertaken for the Canadian population, this required the introduction of a fourth independent variable representing Rh type-specific blood transfusions.

3.1.8 ESTIMATION OF PARAMETERS

ESTIMATION OF RISK RATIO

As mentioned earlier (Section 3.1.2), regression modeling was attempted after transforming the dependent variable with a (natural) log or a logistic link. An attempt was also made to fit the model with an identity link (i.e., outcome rate/risk untransformed), with the error specified as Poisson. However, this latter model was found to be inappropriate (i.e., some of the units returned a fitted mean (risk) less than or equal to zero, not possible under a Poisson error specification) and was abandoned. The beta coefficients from the log-linear model were exponentiated to obtain estimates of the risk ratio. The log-linear model is specified below:

$$\text{Ln } E(c_i) = \ln (n_i) + B_0 + B_1X_1 + B_2X_2 + B_3X_3$$

where $E(c_i)$ = mean value of the Poisson variable, namely, the number of cases with the given outcome in the stratum defined by the subscript i

n_i = the denominator for the i^{th} stratum i.e., the number of births in the i^{th} stratum

$X_1/X_2/X_3$ = independent variables: proportion of first births (X_1), quality of medical care (X_2) and presence/absence of an Rh prophylaxis program (X_3).

B_0 = intercept.

$B_1/B_2/B_3$ = beta coefficients for the variables X_1, X_2 and X_3.

e^{B_1} = risk ratio associated with unit increase in X_1.

The risk ratio for the change in each independent variable seen across the period 1963 to 1988 was estimated by multiplying the beta coefficient for that variable by the total change in the independent variable between 1963 and 1988 and then exponentiating. Thus, the effect of the change in birth order or perinatal care quality between 1963 and 1988 was expressed as

$$\text{Risk ratio} = e^{B_1 * X(1963-1988)}$$

where X(1963-1988) represents the change in the proportion of first births or quality of perinatal care observed between 1963 and 1988. The 95% confidence interval on this risk ratio was estimated by the equation

$$95\%\ \text{CI on } B_1 = e^{((B_1 \pm (1.96 * SE_1)) * (X_1(1963-1988)))}$$

where SE_1 = standard error of the beta coefficient (B_1) of the independent variable X_1.

ESTIMATION OF RISK DIFFERENCE

Although the Poisson regression model with the identity link could not be used (see Section 3.1.8), the results of the log-

linear model were used to calculate risk differences in outcome across the periods under consideration. The reason for estimating risk differences is that this measure of effect is more relevant from the public health standpoint when compared with the risk ratio. The risk difference associated with the change in first-order births between 1963 and 1988 was estimated using the 3-step calculation below

$$P_0 = e^{(B_0 + B_1 X_1(1963) + B_2 X_2(1963) + B_3 X_3(1963))}$$

$$P_1 = e^{(B_0 + B_1 X_1(1988) + B_2 X_2(1963) + B_3 X_3(1963))}$$

$$RD = (P_0 - P_1)$$

where

P_0 = outcome risk predicted by regression model with X_1 assigned the 1963 value and all other independent variables kept at specified background levels (1963/1988).

P_1 = outcome risk predicted by regression model with X_1 assigned the 1988 value and all other independent variables kept at the background levels specified in P_0.

X_1 = proportion of first births

X_2 = quality of perinatal care

X_3 = presence/absence of a Rh prophylaxis program

B_0 = the intercept

$B_1/B_2/B_3$ = the beta coefficients associated with the three independent variables.

The effect modification of the risk difference associated with one factor, by a second factor (exposure=X_1, modifier=X_2) was graphically illustrated. This illustration of effect modification was carried out across different background rates of outcome occurrence, i.e., across different values of X_3. For instance, the effect modification of the risk difference associated with birth order change (X_1) was shown by estimating the magnitude of this risk difference across various levels of perinatal care quality (X_2). These values were separately estimated assuming either the presence or the absence of an Rh prophylaxis program (X_3).

ESTIMATION OF PREVENTIVE FRACTION

The preventive fraction (PF, analogous to etiologic fraction for risk factors) was estimated for each of the preventive determinants using the equations

$PF = (1-RR)$

or

$PF = (I_0 - I_1) / I_0$

where RR = risk ratio associated with the change observed in an independent variable between 1963 and 1988.

I_0 = outcome rate in 1963.

I_1 = outcome rate in 1988.

The preventive fraction associated with any preventive factor was interpreted as the proportion of cases prevented due to the changes observed in that factor between 1963 and 1988. The sum of preventive fractions associated with each of the factors was not expected to sum to 100% since the effect of the various factors is not mutually exclusive. This phenomenon is consistent with contemporary theories of causation [103], and may be explained under the framework of the sufficient cause model. If three components (say A, B and C) of a sufficient cause lead to a disease, the proportion of disease caused by factor A would be 100% since no disease is caused in the absence of A. The same argument holds for the proportion of disease caused by factors B and C. This not to say that all disease is caused by factor A alone; it is understood that these factors act together to produce disease [103].

3.1.9 GOODNESS OF FIT [104]

Measures of goodness of fit for the Poisson regression models are obtained from comparisons of maximum likelihood values - the likelihood of the data given the saturated model is tested against the likelihood of the data given the maximum likelihood estimates of the beta coefficients. The saturated model refers to the unrestricted model invoking one term for each observed outcome value. This is done by estimating the deviance of the model. The quantity

$$D(\beta) = -2 \ln \left(L(y \mid \beta) / L(y \mid \mu) \right)$$

is known as the deviance for the Poisson regression model. It is employed as a goodness-of-fit statistic to assess whether $L(y \mid \beta)$ (i.e., likelihood of the data given the regression estimated beta coefficients) is significantly less than $L(y \mid \mu)$ (i.e., likelihood of the data given the saturated model). In other words, goodness of fit is assessed by checking (through statistical significance testing) whether the regression-estimated beta coefficients of the X variables explain the observed data as well as the saturated model. Deviance can be thought of as a measure of residual variation about the fitted model. $D(\beta)$ behaves like $SSE = \Sigma (y_i - \bar{y})^2$ in standard multiple linear regression analysis (SSE=Sum of Squares due to Error).

The observed and regression-fitted values were also graphed, so as to obtain a visual depiction of the residual variation about the fitted model. This was done because deviance is of limited value in situations where the sample sizes are large [105]. In such situations, a large value of deviance cannot necessarily be considered to be evidence of a poor fit (analogous to the interpretation of a small p value, based on large sample sizes [106]). In the case of the large-sized national data sets, assessment of goodness of fit was therefore based on a visual examination of the extent of deviation of the fitted values from the observed ones.

3.1.10 ASSESSMENT OF COLLINEARITY

Given the correlated nature of the independent variables used in the regression analyses, collinearity problems were expected. The procedure employed to detect collinearity is given below, as are the potential options/solutions considered for interpreting the results of regression given collinearity.

1. Collinearity was considered to be present if aberrantly large standard errors were encountered [107,108]. Since the size of the standard error is sample size dependent, aberrantly large standard errors were identified by comparing the standard error associated with the beta coefficient of a given independent variable before and after the introduction of another potentially collinear variable. For this reason, results of regressions with partial models are also presented to demonstrate changes in standard errors wherever present.
2. If large standard errors were observed, correlations between parameter coefficients were examined to check for the patterns of collinearity, i.e., so as to identify the collinear variables. No meaning was attached to correlation between the beta coefficients in the absence of large standard errors. Given the expectation of an association between determinants and confounders (by definition), independent variables (and therefore beta coefficients of independent variables) were expected to be correlated.
3. If collinearity between two variables (as diagnosed by

large standard errors and correlation of beta coefficients) did not cause imprecision of the parameter estimate for a third variable, then this latter estimate was considered a valid estimate for the effect of the third variable [108].

4. Given collinearity between two variables, the following potential solutions were considered.

   (a) Scaling the data [104]. This involves a change in the unit of measurement for the independent variable. The two specific methods of scaling employed in this study involved the computation of centred and standardized scores. A set of values for an independent variable (X) was centred by subtracting the mean $\bar{x}$ from each individual score.

   $$X_i^* = X_i - \bar{x}$$

   where $\bar{x} = (\Sigma X_i)/n$.

   The computation of standardized scores involved the division of the centred score by the standard deviation of X.

   $$Z_i^* = (X_i - \bar{x})/S$$

   where $S = ((\Sigma(X_i - \bar{x})^2)/(n-1))^{1/2}$

   Centred and standardized scores each have mean 0.

   (b) Increasing the number of observations in the data [108]. This solution would eliminate the problem of

collinearity if the correlation between the offending variables in the new data was not as strong as in the original data or if the direction of the correlation was different. Specifically, when collinearity was encountered in the data set using information for the years 1963-68 and 1982-88, additional data for the years 1951-54 could serve as a possible remedy to the problem. The reasons which governed the choice of the specific years (1951-54) are given elsewhere (Section 3.1.3), although it is pertinent to note that in some cases the correlation pattern of the collinear variables was changed by the inclusion of these years.

(c) Eliminating one of the two collinear variables from the final model. Since collinear variables do not add to the explanatory power of the model, this would not affect the goodness of fit. However, if both collinear variables are known (*a priori*) to have significant effects on disease outcome, then the observed effect of the variable included in the model has to be considered to subsume the effect of the eliminated variable as well.

(d) Summing the beta coefficients of the two collinear variables and estimating a new beta coefficient expressing the combined effect of the two variables. The standard error for this new beta coefficient is estimated from the variances and the covariance of the

two beta coefficients. This option merits consideration, especially as the interpretation of the summed product is meaningful in the context of this particular study. For instance, in a model exhibiting collinearity between proportion of first births and infant survival rate, the new variable combining the effects of these two variables would express the effect of non-program factors in the decline of infant deaths from hemolytic disease. The equations for computing the summed effect (and standard errors) of two collinear variable are given below

$$RR = e^{(B_1X_1 + B_2X_2)}$$

and

$$VAR(B_1X_1+B_2X_2) = (X_1^2*VAR(B_1)) + (X_2^2*VAR(B_2)) + (2*X_1*X_2*COV(B_1,B_2))$$

where B_1 = beta coefficient for BO1

X_1 = change in BO1 between 1963 and 1988

B_2 = beta coefficient for ISR

X_2 = change in ISR between 1963 and 1988

$VAR(B_1)$ = variance of B_1

$COV(B_1,B_2)$ = covariance between the coefficients B_1 and B_2.

3.1.11 VARIANCE ESTIMATION

Although the outcome data in this study are expected to be

Poisson counts, it is generally recommended that the possibility of over/under dispersion in the data be examined [105]. Even though relatively substantial errors in the assumed form of the variance have only a small effect on the conclusions [105], the assumption of Poisson variance was checked by also estimating the variance, based on the following assumption:

$Var(Y_i) = \sigma^2 E(Y_i)$

where $Var(Y_i)$ = the variance of the Poisson outcome Y_i

σ^2 = the dispersion parameter

$E(Y_i)$ = the mean of the Poisson outcome Y_i.

3.1.12 VALIDITY OF REGISTERED DATA

The validity of data from death certification sources has been questioned in studies examining such data from England and Wales [109,110]. The pattern of inaccuracy as assessed by these studies was examined, and the impact of such inaccuracies on regression estimates of the effect of independent variables was explored in the context of potentially similar errors in the Canadian and U.S. mortality data. This was done by first examining rates of overdiagnosis across the pre-prophylaxis and post-prophylaxis years as determined by the British studies. Further, the effect of such data errors on the results of Poisson regression was determined through analyses of data sets corrected for possible overdiagnosis.

3.2 CONDITIONAL PROBABILITY MODELING

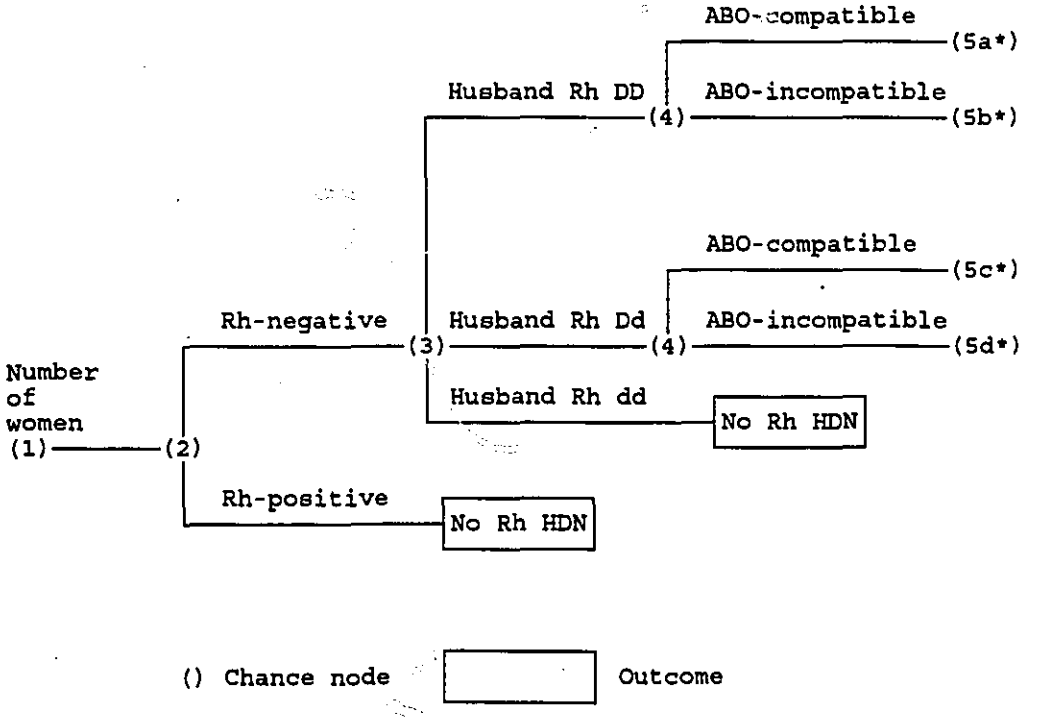
3.2.1 INTRODUCTION

This technique [35,40] was used to estimate the incidence of maternal Rh (D) sensitization and perinatal death from Rh disease in various populations defined on the basis of birth order distribution, racial characteristics and various biological factors. The primary outcomes considered in this analysis were Rh D related, in contrast to the combined Rh D and Rh non-D outcomes previously considered under the Poiss... regression analyses of data from Manitoba. In some situations, however, data limitations led to a focus on both Rh D and Rh non-D related outcomes. Unless otherwise stated Rh sensitization in this section refers to Rh D sensitization.

Variables incorporated in the model included prevalence of the maternal Rh type, prevalence of the paternal Rh genotype, protection afforded by ABO incompatibility against Rh sensitization, probability of maternal Rh sensitization following a Rh-positive delivery, probability of maternal sensitization following abortion and probability of perinatal death given Rh disease. The birth order distribution (i.e., number of births by each birth order, from first-order births up to eighth-order births), stillbirth rate and abortion rate of the specific population-year were also integrated into the model.

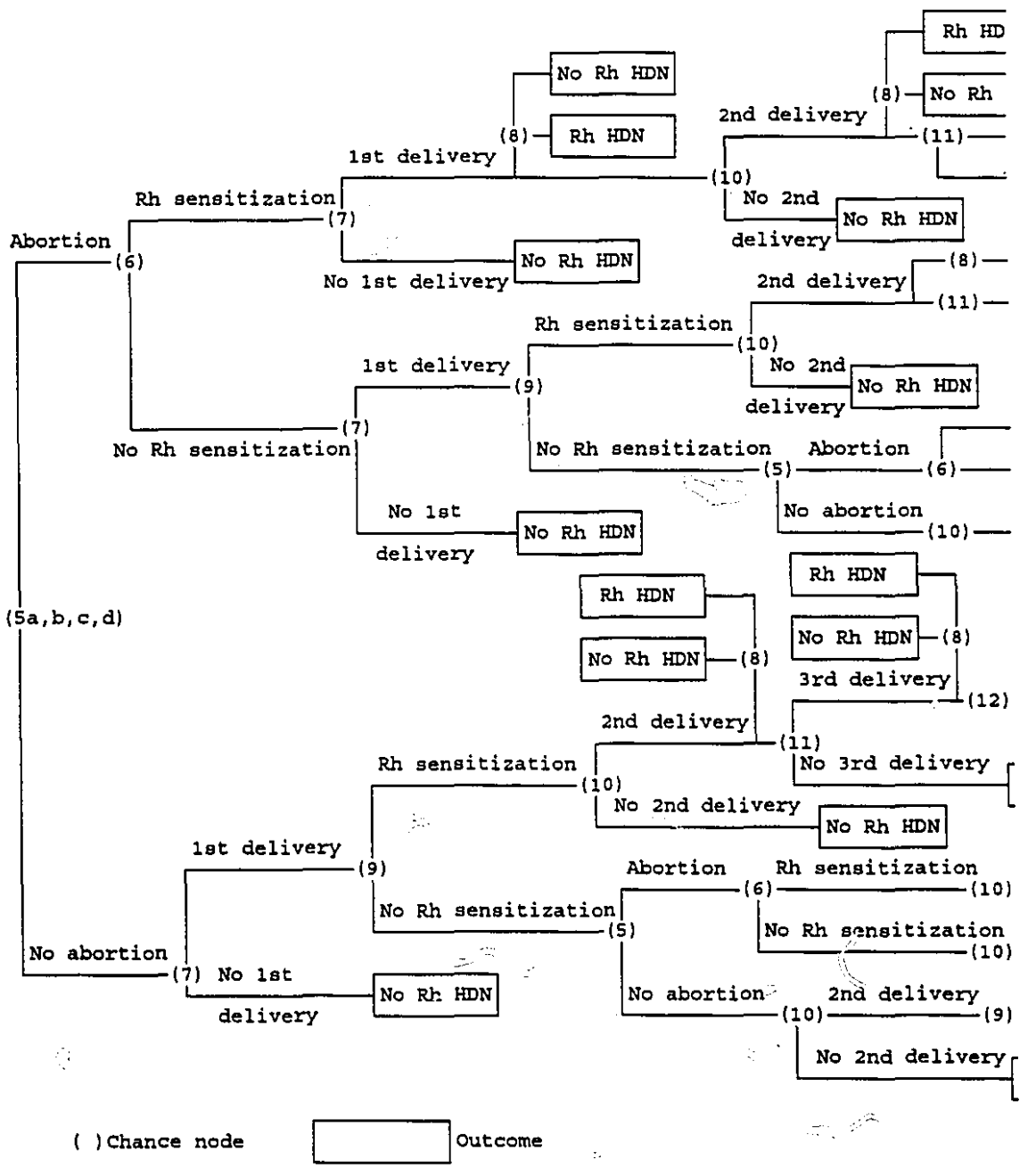
Figures 3 and 4 show the tree used for the conditional probability model. The conditional probabilities

Figure 3: Conditional probability model for estimating the rate of Rh sensitization/hemolytic disease of the newborn (HDN) in a population (continued in Figure 4).



* Subtrees identical in structure though probabilities at some chance nodes vary.

Figure 4: Conditional probability model for estimating the rate of Rh sensitization/hemolytic disease of the newborn in a population (continued from Figure 3). Although the figure shows the tree truncated after the second/third delivery (owing to lack of space), the model extends up to the eighth delivery.



assigned to the various chance nodes were based on published data; for example, the rate of maternal Rh sensitization was based on the peer-reviewed scientific literature, while vital statistics publications provided data for characterizing the birth order distribution, stillbirth rate and abortion rate for any given population-year. The rate of Rh sensitization was calculated for different populations (and for the same population at different times) by repeating the modeling procedure after incorporating the relevant conditional probabilities into the model. The conditional probabilities used for the various chance nodes and the sources (references) on which they are based are detailed below.

3.2.2 MODEL ASSUMPTIONS

Number of Women (chance node 1).

The number of women to be entered into the model was based on the observed number of women giving birth in the population-year under consideration. For instance, model estimation of the rate of Rh sensitization for Manitoba in 1963 was carried out by entering 23,020 women into the model. This number was obtained from vital statistics publications for Manitoba, 1963 [88]. The observed distribution of birth order [88] was then used to specify how many of these women were delivering their first child (chance node 7), second child (chance node 10), etc. Although Figure 4 shows the tree truncated after the second/third delivery (owing to lack of space), the model

extends up to the eighth delivery.

Probability of the Rh-negative type among women (chance node 2).

A probability of 0.17 was assigned to white women in Manitoba [111,112], while a probability of 0.01 was assigned to Native Indian women from Manitoba [53,54,113] based on observed prevalence rates. The probability of the Rh-negative phenotype among Asian Indian women was taken to be 0.05 [114-115].

Probability of the paternal Rh genotype (chance node 3).

Fathers were classified according to the Rh (D) antigen into those homozygous for the Rh-positive trait (DD), heterozygous for the Rh-positive trait (Dd) and those homozygous for the Rh-negative trait (dd). With the frequency of the genotype Rh dd already specified under chance node 2, the frequencies of the other genotypes DD and Dd were estimated using the Hardy-Weinberg law [116] to estimate gene frequencies. For example, in the case of whites from Manitoba, the frequency of the genotype Rh dd was taken to be 0.17, while the frequencies of the genotypes Rh DD and Rh Dd were estimated as follows:

Frequency of the Rh genotype dd = 0.17

Frequency of the Rh gene d = $(0.17)^{1/2}$ = 0.41

Frequency of the Rh gene D = (1-0.41) = 0.59

Frequency of the Rh genotype DD = D^2 = $(0.59)^2$ = 0.35

Frequency of the Rh genotype Dd = 2*D*d = 2*0.59*0.41 = 0.48

Similarly, the frequencies of the homozygous and heterozygous Rh-positive genotypes among Native Indians and Asian Indians were estimated to be 0.81 (DD) and 0.18 (Dd) and 0.60 (DD) and 0.35 (Dd), respectively, based on the observed frequencies of the Rh-negative phenotype (dd) [53,54,113-115].

Probability of ABO incompatibility (chance node 4).

A pregnancy was defined as ABO incompatible if the mother possessed antibodies against the fetus's ABO blood group. For instance, a pregnancy involving an A group or O group mother and a B group fetus was deemed ABO incompatible on account of the innate presence of anti-B antibodies in the maternal serum. The prevalence of such an occurrence was estimated from the observed frequency of the various ABO blood groups in specific populations. For instance, the observed frequencies of the ABO blood types among Manitoba whites are: type A 40.8%, type B 12.7%, type O 41.8% and type AB 4.7% [111,112]. The prevalence of ABO incompatibility was estimated from these frequencies by first calculating genotype frequencies (Hardy-Weinberg law) and then estimating the probability of ABO-incompatibility between mother and fetus (assuming random mating between various blood group types). 11% of pregnancies were thus assumed to be A incompatible, 4% B incompatible and 85% ABO compatible. Similar figures for Native Indians, based on observed ABO blood group frequencies [53,54,113] were 11% A-incompatible, 1% B-incompatible and 88% ABO compatible.

Pregnancies among Asian Indian women were assumed to be A-incompatible in 7% of instances, B-incompatible in 10% of instance and ABO compatible 83% of the time. These estimates were based on the observed frequencies of the various ABO blood types among Asian Indians [117].

Magnitude of protection due to ABO incompatibility.

The protection afforded by ABO incompatible pregnancies against Rh sensitization was one of the key observations that prompted research into Rh immunoglobulin prophylaxis [59]. Numerous other studies have subsequently confirmed this finding. However, investigators studying this phenomenon have arrived at varying estimates of the magnitude of the protection conferred. Several issues have been identified as being responsible for the differing results obtained [69,118,119]. First, selective non-inclusion of some affected stillbirths (because of the difficulty of establishing blood group status among those stillborn) biased the results of some studies. Second, some investigators chose to focus on 'first affected pregnancies,' while others studied all cases of Rh hemolytic disease. The rationale for the more limited focus was based on the presumption that while ABO incompatibility protects against Rh sensitization, no protection is afforded once sensitization has occurred. Studies of first affected pregnancies also benefit from the fact that the possibility of missing stillbirths is largely avoided (first affected

pregnancies do not generally end in stillbirth). Another issue of concern involves the definition of ABO incompatibility; some investigators studied ABO incompatibility between parents, while others focused on the more relevant incompatibility between mother and fetus (or corrected for the effect of genotypic heterozygosity in the father's blood group). Other issues responsible for the varying estimates of ABO-mediated protection against Rh sensitization include differences in analysis and sampling variation.

For modeling purposes, we assumed that A incompatibility (i.e., fetus type A, while mother has anti-A) provides 90% protection against Rh sensitization, while B incompatibility (i.e., fetus type B, while mother has anti-B) provides 55% protection. These figures are based on the findings of Murray et al [69]. Identical analysis of other datasets [120] by these authors showed similar estimates for the magnitude of ABO protection [69]. These estimates imply overall Rh sensitization rates consistent with findings of large studies. The above-mentioned rates of ABO-mediated protection were used to appropriately modify the probability of maternal Rh sensitization (chance nodes 9, etc.).

Probabilities of abortion, stillbirth and livebirth (chance nodes 5, 7, 10, 11, etc.).

The probability for each of these events was obtained from vital statistics publications. For the province of Manitoba,

the rate of abortion for 1963 was assumed to be 4.5 per 100 live births based on the published figure for 1971 [121], since accurate estimates for abortion rates in Canada are available only from 1971 onwards, when abortion was legalized. Possible inaccuracies in these abortion rate estimates for the years 1963 to 1970 were not expected to seriously affect the outcomes of interest, given the low frequency of abortion and the low rate of Rh sensitization following abortion (relative to a delivery/stillbirth). Numbers of deliveries by birth order and numbers of stillbirths in Manitoba were obtained from vital statistics publications [88-91]. For the modeling of Rh sensitization rates for India in 1981, the number of births, birth order distribution, stillbirth rate and abortion rate were obtained from the relevant vital statistics publications of that country [35,122,123].

Probability of antepartum sensitization.

This probability was used solely for the purpose of model validation, based on data from Manitoba for the years 1974-75 [37]. The probability was based on estimates made irrespective of the ABO status of the pregnancy. Varying estimates are available in the literature and range from 0.7-0.9%, although estimates of 1.2-1.8% have also been reported [66,70-72]. We used a value of 0.8%, as the larger probabilities are known to have been a consequence of the use of tests more sensitive than the standard tests used by the Rh surveillance program of

Manitoba (see Section 2.1.5.3).

Probability of maternal Rh sensitization following abortion, stillbirth and livebirth (chance nodes 6, 9, etc.).

The probability of Rh sensitization following the abortion of a Rh-positive fetus was assumed to be 4.5% [42]. Widely varying rates of maternal Rh sensitization following a Rh-positive delivery have been reported in different studies. These studies can be broadly classified into those in which rates of Rh sensitization were determined 6 months after delivery and those in which Rh sensitization rates were determined during a second Rh-positive pregnancy. The difference between the estimates from these two classes of studies arises because it is believed that only about one-half of Rh sensitized mothers manifest circulating antibody immediately after delivery [58]. The other half of so-called 'sensibilized' [58] mothers demonstrate circulating antibody only upon subsequent challenge with another Rh-positive pregnancy. However, this factor alone does not explain the wide variation in rates noted from the various studies. It further appears that rates estimated through clinical trials (i.e., in controls participating in trials assessing immunoglobulin efficacy) with close follow-up are generally higher than those estimated through surveillance programs (see Tables 1 and 2). The sensitivity of the test used for identifying Rh sensitization is another factor responsible for

Table 1: Rates of maternal Rh sensitization following an Rh-positive pregnancy among women tested for anti-D 6 months after delivery. Unless otherwise indicated, the studies were restricted to ABO compatible pregnancies. (95% CI=95% confidence interval).

Authors [Reference]	Number of subjects	% anti-D positive	95% CI
White et al [6]	153	2.0	0.0-4.2
Zipurski et al [15]*	573	3.7	2.1-5.2
German Collab. Study [125]	2300	3.8	3.0-4.6
Ekland et al [66]	792	4.3	2.9-5.7
De Wit et al [8]**	329	5.2	2.8-7.6
Pollack et al and Ascari et al [12,78]	726	7.0	5.2-8.9
Ascari et al [124]	1042	7.0	5.5-8.6
Stenchever et al [5]	28	7.1	0.0-16.7
Western Canada Trial [13]	500	7.2	4.9-9.5
Woodrow et al [44]	949	7.3	5.6-8.9
Borst-Eilers [67]	337	7.7	4.9-10.5
Jorgensen [68]	106	9.0	3.6-14.4
Bishop et al [11]	92	12.0	5.3-18.6
Robertson et al [10]*,***	112	13.4	7.1-19.7

* ABO criteria not mentioned
** No exclusions by ABO status
*** Testing for anti-D with enzymatic methods

Table 2: Rate of maternal Rh sensitization following two successive Rh-positive pregnancies (95% CI=95% confidence interval).

Authors [Reference]	Number of subjects	% anti-D positive	95% CI
Western Canada Trial [13]	18	0.0	0.0-18.5*
German Collaborative Study [125]	369	7.6	4.9-10.3
Pollack et al and Ascari et al [12,78]	63	11.1	3.4-18.9
White et al [6]	8	12.5	1.0-50.0*
Woodrow et al [44]**	217	13.8	9.2-18.4
Ascari et al [124]	102	16.7	9.4-23.9

* upper bound of confidence interval estimated using exact methods.
** extrapolated by the authors to 17%.

the varying rates.

Thus, two alternative values were entertained with regard to the probability of maternal Rh sensitization following delivery of a Rh-positive, ABO compatible infant. These were based on the studies summarized in Tables 1 and 2. The observations of Ascari et al [124] formed the basis for presuming a rate of 17% for the maternal Rh sensitization rate (given an Rh-positive fetus and an ABO compatible pregnancy), while the results of the German Collaborative Study [125] and the Swedish national surveillance study by Ekland et al [66] formed the basis for assuming a rate of 7%. The decision to attempt modeling with this low rate of 7% was motivated by the desire to make the model suitable for comparison with observed data from the surveillance program of Manitoba.

Probability of perinatal death from Rh disease given maternal Rh sensitization (chance node 8).

The probability of perinatal death given maternal Rh sensitization was obtained for each year from the data of the surveillance program in Manitoba [37,87] and directly integrated into the model. For instance, in Manitoba (1963), 26 perinatal deaths from Rh disease were observed among the 223 Rh sensitized women; the probability of perinatal death given maternal Rh sensitization was therefore assumed to be 11.7%. These probabilities were based on all Rh sensitizations and not on Rh D sensitizations alone because such data are not

available from Manitoba for the pre-prophylaxis years.

Adjustment for changes in racial composition.

Adjustments were made for the observed racial composition of Manitoba to allow for the Native Indian segment of the population. These adjustments were based on the proportion of the population cited as Native Indian in census statistics: 3.2% in 1961, 4.3% in 1971, 5.9% in 1981 and 6.9% in 1991 [102,126-129].

Adjustment for non-responders.

Experimental studies involving the transfusion of large amounts of Rh-positive blood into Rh-negative recipients have shown that about 8-10% of subjects fail to respond to the antigen in spite of repeated exposures [55-57] (see Section 2.1.4). This rate of non-response was built into the conditional probability model. The assumption implies that the probability of maternal Rh sensitization declines sequentially (albeit marginally) from the first exposure to a Rh-positive fetus to subsequent exposures. Thus, if the rate of Rh sensitization following a first Rh-positive, ABO compatible pregnancy was assumed to be 17%, the same rate was assumed to be 16.6% for the second pregnancy, 16.2% for the third pregnancy and so on.

3.2.3 MODEL VALIDATION

Model validation was attempted by comparing (graphically) the concordance between model predictions and observed data. Three sets of available data on rates of maternal Rh sensitization were used:

1. Data from Manitoba on the number of maternal antepartum Rh sensitizations during the years 1974 and 1975 [37].
2. Data on the rate of all maternal Rh sensitization as determined by the Rh surveillance program of Manitoba [87]. Data for the years 1963 to 1968 were used for model validation. Data for subsequent years were not used, as precise Rh immunoglobulin coverage rates by year were not available and because of the complexities involved in modeling the latent period between Rh immunoglobulin use and Rh sensitization rates in the population.
3. Data from various studies on the proportion of Rh disease 'first-affected' infants by order of pregnancy [58,130,131]. Crude comparisons were made between the observed distribution of first-affected pregnancies by birth order in these studies and the distribution predicted by the model for Manitoba in 1963. Since these direct comparisons were not standardized for birth order distribution, the model was also used to predict the expected distributions of first-affected pregnancies after controlling for birth order. This was done for the two studies for which information on the birth order

distribution of the source population was available [58,130].

The validity of the model was judged by comparing the graphed observed and predicted values visually.

3.2.4 EFFECT OF CHANGES IN BIRTH ORDER

The effect of changing birth order distribution on Rh sensitization rates in Manitoba between 1963 and 1988 was estimated by first estimating the incidence of Rh sensitization in Manitoba in 1963. This was done by applying the 1963 birth order distribution of Manitoba to the model. The incidence of Rh sensitization in Manitoba in 1988 in the absence of an Rh prophylaxis program was estimated similarly by incorporating the birth order probabilities relevant to 1988. Effects of birth order changes were then estimated based on these two rates. For the purpose of comparing the results obtained from this analysis with the results obtained from the Poisson regression model, the changing rates of abortion were also included in the decision analytic model (Note: since the abortion rate was not included as a determinant in the Poisson regression model, the effects of changes in the abortion rate would have been subsumed under birth order effects for the most part.) The individual effects of birth order changes and changes in abortion rates were also studied, however.

The effect of changing birth order distribution on perinatal deaths from Rh disease was estimated similarly. The

two estimated incidence rates of perinatal deaths from Rh disease allowed the estimation of the unmodified risk ratio. Since modification of the risk difference (between birth order and perinatal deaths from Rh disease) by perinatal care quality was anticipated, the risk difference was estimated at different levels of perinatal care quality, namely, that observed in 1963 and that observed in 1988. These estimates were made assuming the absence of an Rh prophylaxis program.

3.2.5 EFFECT OF CHANGES IN PERINATAL CARE QUALITY

The effect of the quality of medical care (specifically, the quality of perinatal care) was estimated from the rates of perinatal deaths from Rh disease predicted by the model in Manitoba in 1963 and 1988, assuming constancy of other determinants of outcome occurrence. These rates were obtained by applying the perinatal death rates among Rh-sensitized pregnancies observed in Manitoba to the rates of maternal Rh sensitization predicted by the model. These iterations allowed the estimation of the unmodified risk ratio. Given the anticipated modification of the risk difference by the birth order distribution, two risk difference estimates were obtained assuming the 1963 and the 1988 birth order distributions for Manitoba. Since categorization of Rh-sensitized subjects into Rh D and Rh non-D types was not possible (for the pre-prophylaxis years), quality of perinatal care was estimated using perinatal survival given Rh

sensitization, whether Rh D or Rh non-D.

3.2.6 EFFECT OF NON-PROGRAM FACTORS

The effect of all non-program factors was estimated by using the 1963 birth order distribution, abortion rate, racial composition and level of perinatal care quality for the first iteration and the 1988 values of the same variables for the second iteration.

3.2.7 EFFECT OF Rh PROPHYLAXIS

The effects of Rh prophylaxis on the rates of Rh sensitization were estimated indirectly. This was done by first estimating the rate of Rh sensitization in Manitoba with the 1988 birth order distribution, abortion rate and racial composition integrated into the model. This model-predicted rate (which assumed an absence of Rh prophylaxis) was compared with the rate of Rh sensitization observed in Manitoba in 1988 and the difference was attributed to Rh prophylaxis. This assumes that with birth order, abortion rate and racial factors accounted for in the model, the difference between the model-predicted rate of Rh sensitization (i.e., assuming the absence of an Rh prophylaxis program) and the observed rate (given Rh prophylaxis) would be secondary to Rh prophylaxis. Two rates of efficacy were estimated, the first using the observed rate of Rh D sensitization and the second based on all observed Rh sensitizations, whether Rh D or non-D.

3.2.8 EFFECT OF CHANGES IN ABORTION RATES

The rate of Rh sensitization was first estimated assuming the 1963 birth order distribution, racial composition and abortion rate of Manitoba. This rate was contrasted with the rate obtained assuming the 1963 birth order distribution, and racial composition of Manitoba, along with the abortion rate observed in Manitoba in 1988. The estimate of abortion effect was also made with 1988 as the reference year (i.e., first iteration using the 1988 birth order distribution, racial composition and abortion rate of Manitoba and the second iteration with the same specifications except for abortion rate, which was kept at the 1963 level).

3.2.9 EFFECT OF CHANGES IN RACIAL COMPOSITION

Estimation of the effect of changes in racial composition was attempted primarily to support the Poisson regression model, which assumed that the observed change in the racial composition of Manitoba between 1963 and 1988 did not significantly bias estimates of birth order, quality of perinatal care and Rh prophylaxis program effects. The analysis was done by integrating the 1988 birth order distribution and abortion rate of Manitoba into the model along with the 1963 racial composition of Manitoba. The rates of maternal Rh sensitization thus obtained were then compared with those from the model integrating all the characteristics pertinent to Manitoba in 1988 (including racial composition).

The difference in the two rates so obtained was taken to be the effect of changes in racial composition. The same estimate was also made using 1963 as the reference year instead of 1988 (i.e., first iteration using the 1963 birth order distribution, abortion rate, and racial composition of Manitoba and the second iteration using the same assumptions except for the racial composition, which was changed to that observed in Manitoba in 1988).

3.2.10 EFFECT OF RACE

The estimation of the effect of race on Rh sensitization was attempted with the model constructed using variable values specific to Manitoba in 1963 (i.e., birth order distribution and abortion rate). The rates of Rh-negative prevalence (and therefore the rates of Rh DD and Rh Dd) and the rate of ABO incompatibility were changed to those observed among Asian Indians. The model predicted rates of Rh sensitization were then compared with those obtained for whites and Native Indians from Manitoba.

3.2.11 COST-EFFECTIVENESS OF Rh PROPHYLAXIS

Rh prophylaxis was introduced as a variable into the model for this estimation assuming a conservative efficacy of 80 percent for postpartum and post-abortion Rh prophylaxis. Antenatal prophylaxis with Rh immunoglobulin was not included in the model for two reasons. First, since the aim of this exercise

was to optimise Rh prophylaxis strategies for use in developing countries, antenatal prophylaxis was disregarded as an option, given its known lack of cost-effectiveness (antenatal prophylaxis is administered without knowledge of the fetus's Rh type). Second, the number of cases of maternal Rh sensitization prevented by antenatal prophylaxis is small; only 26 cases occurred in Manitoba in the two years 1974 and 1975 [37].

Cost was estimated in terms of the number of doses of Rh immunoglobulin required, and cost-effectiveness was measured by the number of doses of Rh immunoglobulin required to prevent one case of maternal Rh sensitization. The primary outcome chosen for these analyses was maternal Rh sensitization rather than perinatal death from Rh disease; the former outcome is more relevant and comprehensive from the vantage of costs to the health care system. Costs to the health care system arise not only in cases of maternal Rh sensitization where perinatal death results, but in all cases, owing to laboratory tests, altered patient management, etc. For instance, costs secondary to amniocentesis, in utero/exchange transfusions, early delivery and use of neonatal intensive care service accrue in a significant proportion of Rh disease cases, even when perinatal death is avoided. Costs to society are also clearly apparent when kernicterus leads to choreoathetosis and other major disabilities.

The effect of changing birth order distribution on the cost-effectiveness of Rh prophylaxis was investigated by comparing cost-effectiveness using the birth order distributions of Manitoba in 1963 and 1988. Similarly, the effect of race on the cost-effectiveness of Rh prophylaxis was estimated by incorporating the Rh-negative and ABO-incompatibility prevalence rates of different races into the model for Manitoba.

The cost-effectiveness of four different Rh prophylaxis options was evaluated using a decision analytic model. The options considered included post-delivery prophylaxis, post-delivery plus post-abortion prophylaxis (as against isolated post-delivery prophylaxis), post-delivery prophylaxis restricted to ABO compatible pregnancies and, finally, post-delivery prophylaxis restricted to first births. The Rh prophylaxis options were evaluated using the Manitoba populations of 1963 and 1988. Potential modification of these cost-effectiveness estimates by race was also studied. Finally, these options were compared using the 1981 birth order distribution (latest available), abortion and stillbirth rates of India [35,122,123].

3.2.12 SENSITIVITY ANALYSIS

Sensitivity analyses were performed by varying the probabilities at the chance nodes to determine how estimates of relevant indices would change under alternate assumptions.

As mentioned previously, a one-way sensitivity analysis was carried out by varying the probability of maternal Rh sensitization following an Rh-positive, ABO compatible delivery (Section 3.2.2). Multi-way sensitivity analyses were also carried out using the Monte Carlo method [132,133]. Briefly, a range of possible values (and a specific distribution) was considered for the probability at each chance node. For instance, for the prevalence of the Rh-negative type among Manitoba whites (point estimate of 17% obtained from a study of 3100 subjects [111]), the range considered extended from 15 to 19%. Similarly, the uncertainty in the estimated rate of abortion in Manitoba in 1963 (assumed to be 4.5/100 livebirths) was incorporated into the sensitivity analysis. The possible range considered for the above mentioned abortion rate extended from 2/100 livebirths to 7/100 livebirths. The range of values considered for each chance node are shown in Table 4A.

Ten thousand values for each probability were then randomly generated from within the specified ranges. The generation of the random values was carried out with the rule that the values came from a normal distribution and had a 99% probability of falling within the specified range. The various indices of interest were then estimated by carrying out each calculation ten thousand times and obtaining the fiftieth centile (median value) from the computations. Centiles 2.5 and 97.5 values (analogous to the upper and lower bounds of a 95%

confidence interval) were used to assess the uncertainty around the estimates.

4. RESULTS

4.1 EPIDEMIOLOGIC ANALYSIS

The univariate and adjusted estimates of the various measures of effect obtained from each set of data are discussed separately. For data sets where multiple outcome variables were available, the results of the various regression analyses are considered sequentially.

4.1.1 MANITOBA

4.1.1.1 CRUDE CHANGES BETWEEN 1963 AND 1988

Table 3 gives the numbers and rates of the three Rh disease-related outcomes for the years 1963 and 1988. Drastic reductions occurred in the rates of Rh sensitization, Rh disease and perinatal deaths from Rh disease across this period. With the 1963 and 1988 populations considered as the unexposed and exposed groups, respectively, crude measures of effect were calculated for each of the Rh disease-related outcomes (shown in Table 4). Each of the three measures yields similar results for Rh sensitization and Rh disease. The changes in perinatal deaths from Rh disease across this period appear significantly greater, however. The preventive fraction shows that a reduction of approximately 70% occurred in Rh sensitization and Rh disease between the two periods, while perinatal deaths from Rh disease showed a 95% decline.

Table 5 shows that the period in question also witnessed significant changes with regard to proportion of

Table 3: Numbers and rates (per 1000 total births) of three Rh disease outcomes observed in Manitoba in 1963 and 1988.

Year	Rh sensitization		Rh hemolytic disease		Perinatal deaths from Rh disease	
	Number	Rate	Number	Rate	Number	Rate
1963	223	9.61	188	8.10	26	1.12
1988	45	2.64	38	2.23	1	0.06

Table 4: Changes in the frequency of Rh disease outcomes between 1963 and 1988 as estimated using three different measures of effect (RD=risk difference per 1000 total births, RR=risk ratio and PF=preventive fraction).

Year	Rh sensitization	Rh hemolytic disease	Perinatal deaths from Rh disease
RD	6.97	5.87	1.06
RR	0.27	0.28	0.05
PF	72.54	72.50	94.77

Table 5: Changes in the three factors affecting Rh disease occurrence in Manitoba between 1963 and 1988 (Rh HDN=Rh hemolytic disease of the newborn).

Year	First births (percent)	Perinatal survival given Rh HDN	Rh prophylaxis program
1963	25.0	86.2	0
1988	40.2	97.4	1

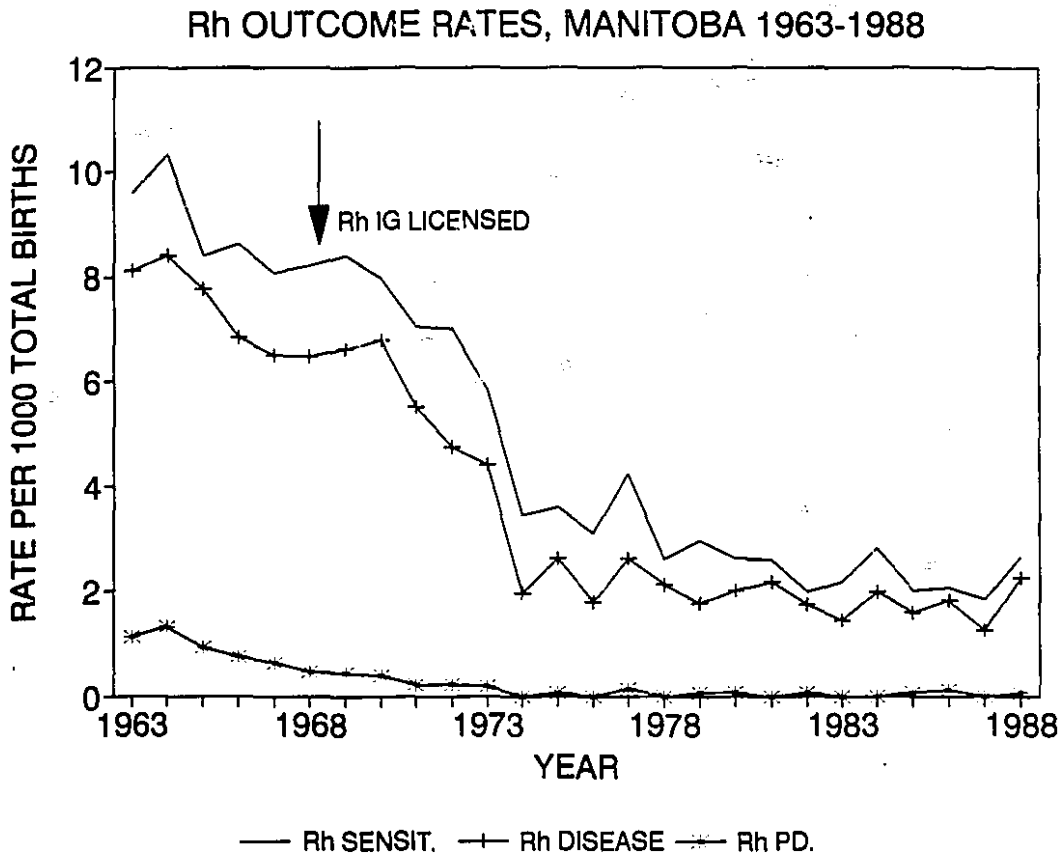
first births and the quality of perinatal care. Some understanding of the effects of these factors may be obtained from an examination of the graphed outcome data (Figure 5). Changes in the outcome rates preceded the introduction of Rh prophylaxis. The changes in the independent and dependent variables across the years are shown in Table 5A (Appendix).

4.1.1.2 POISSON REGRESSION

Rh SENSITIZATION

The unadjusted and adjusted estimates of the risk ratios, risk differences and preventive fractions associated with first birth order and the program of Rh prophylaxis are shown in Tables 6-8. The difference between the crude and adjusted risk ratio estimates for the effect of first births shows strong confounding by the presence/absence of Rh prophylaxis. The magnitude of the change between the crude and adjusted risk ratios for program effect is less striking. The adjusted risk ratio associated with Rh prophylaxis is 0.31 while that for change in first birth order (between 1963 and 1988) is estimated to be 0.76. Both estimates are seen to be significant, i.e., their 95% confidence intervals do not span the null value. Figure 6 shows the observed rates of Rh sensitization in Manitoba along with the predicted rates of Rh sensitization in the absence of an Rh prophylaxis program. The predicted rates show the effect of birth order changes on Rh sensitization rates, while the difference between the two

Figure 5. Data from Manitoba showing rates of Rh sensitization, Rh hemolytic disease and perinatal deaths from Rh disease per 1000 total births between 1963 and 1988.



lines represents the effect of Rh prophylaxis.

The risk differences associated with these variables are tabulated in Table 7. The magnitude of the risk difference is seen to be modified by the background rate of the disease. In the absence of Rh prophylaxis, the adjusted risk difference associated with a change in the proportion of first births (i.e., the change observed in BO1 between 1963 and 1988) is 2.31 per 1000 total births while the same estimate made assuming a program of Rh prophylaxis is 0.71 per 1000 total births. Similarly, the proportion of first births modifies the risk difference associated with Rh prophylaxis: 6.68 per 1000 total births at 1963 levels of BO1 and 5.08 per 1000 total births at the 1988 levels of BO1. This phenomenon of effect modification of the risk difference is depicted in Figures 7 and 8.

Table 8 shows the preventive fraction associated with each independent variable. The change in the proportion of first births between 1963 and 1988 is seen to have prevented 24% of cases of Rh sensitization (95% confidence interval=1 to 41%), while the Rh prophylaxis program prevented 69% of cases of Rh sensitization (95% confidence interval= 61 to 76%).

GOODNESS OF FIT: The statistical assessment of goodness of fit was made through an estimation of the scaled deviance of the fitted regression model (Table 6). The saturated model

Table 6: Result of Poisson regression using data from Manitoba for the years 1963-68 and 1982-88, with rate of Rh sensitization as the outcome and effects expressed in terms of risk ratios. BETA=beta coefficient for unit change in the independent variable, SE=standard error of the beta coefficient estimate, RR=risk ratio (for the observed change in the independent variable between 1963 and 1988) and 95% CI=95% confidence interval on the risk ratio. Note: the initial lines in the table show the results of two different single-variable models, while subsequent lines give the results of the two-variable model.

OUTCOME=Rh SENSITIZATION

VARIABLE (MODEL)	BETA	SE	RR	95% CI
BO1	-0.0908	0.0045	0.25	0.22-0.29
DEVIANCE=95.5, df=11, p<0.001				
PRG	-1.3930	0.0690	0.25	0.22-0.28
DEVIANCE=15.0, df=11, p>0.1				
BO1	-0.0180	0.0088	0.76	0.59-0.99
PRG	-1.1830	0.1241	0.31	0.24-0.39
DEVIANCE=10.74, df=10, p>0.3				

Note: Equivalence of risk ratio and 95% confidence interval estimates for BO1 and PRG effect in the single-variable models is coincidental. The risk ratio for BO1 represents the effect of the observed change in BO1 between 1963 and 1988, while the beta coefficient refers to the effect per unit change in BO1 (i.e., a one percent increase). The risk ratio and beta coefficient for PRG, on the other hand, represent the effect per unit change in PRG. Note that this unit change in PRG (from 0 to 1) also represents the total observed change between 1963 and 1988.

$$RR(BO1) = e^{(Beta*(40.2-25.0))} = 0.2515$$

where Beta = -0.0908
BO1 for 1963 = 40.2%
BO1 for 1988 = 25.0%

$$RR(PRG) = e^{(Beta*(1-0))} = 0.2483$$

where Beta = -1.393
PRG for 1963 = 0
PRG for 1988 = 1

See Section 3.1.8 for calculation of 95% confidence intervals.

Table 7: Result of Poisson regression using data from Manitoba for the years 1963-68 and 1982-88, with rate of Rh sensitization as the outcome and effects expressed in terms of risk differences. B_0=intercept, P_0=outcome rate assuming 1963 value for concerned independent variable, P_1=outcome rate assuming 1988 value for concerned independent variable and RD=risk difference, i.e., $(P_0 - P_1)$. All rates (P_0, P_1 and RD) are expressed per 1000 total births.
OUTCOME=Rh SENSITIZATION

VARIABLE (MODEL)	BETA	B_0 INTERCEPT	P_0	P_1	RD
Background 1963*					
BO1	-0.0180	-4.192	9.63	7.32	2.31
PRG	-1.1830		9.63	2.95	6.68
Background 1988*					
BO1	-0.0180	-4.192	2.95	2.24	0.71
PRG	-1.1830		7.32	2.24	5.08

* Background 1963 (computational details)

(1) Effect of BO1:

$P_0 = e^{(B_0 + B_1*BO1(1963) + B_2*PRG(1963))}$
i.e., BO1=25%, PRG=0

$P_1 = e^{(B_0 + B_1*BO1(1988) + B_2*PRG(1963))}$
i.e., BO1=40%, PRG=0

(2) Effect of PRG:

$P_0 = e^{(B_0 + B_1*BO1(1963) + B_2*PRG(1963))}$
i.e., BO1=25%, PRG=0

$P_1 = e^{(B_0 + B_1*BO1(1963) + B_2*PRG(1988))}$
i.e., BO1=25%, PRG=1

* Background 1988 (computational details)

(1) Effect of BO1:

$P_0 = e^{(B_0 + B_1*BO1(1963) + B_2*PRG(1988))}$
i.e., BO1=25%, PRG=1

$P_1 = e^{(B_0 + B_1*BO1(1988) + B_2*PRG(1988))}$
i.e., BO1=40%, PRG=1

(2) Effect of PRG:

$P_0 = e^{(B_0 + B_1*BO1(1988) + B_2*PRG(1963))}$
i.e., BO1=40%, PRG=0

$P_1 = e^{(B_0 + B_1*BO1(1988) + B_2*PRG(1988))}$
i.e., BO1=40%, PRG=1

Table 8: Result of Poisson regression using data from Manitoba for the years 1963-68 and 1982-88, with rate of Rh sensitization as the outcome and effects expressed in terms of preventive fractions. BETA=beta coefficient for unit change in the independent variable, SE=standard error of the beta coefficient estimate, PF=preventive fraction for the observed change in the independent variable between 1963 and 1988 and 95% CI=95% confidence interval on the preventive fraction.

OUTCOME=Rh SENSITIZATION

VARIABLE (MODEL)	BETA	SE	PF	95% CI
BO1	-0.0908	0.0045	74.8	71.2-78.0
DEVIANCE=95.5, df=11, p<0.001				
PRG	-1.3930	0.0690	75.2	71.6-78.3
DEVIANCE=15.0, df=11, p>0.1				
BO1	-0.0180	0.0088	24.0	1.2-41.5
PRG	-1.1830	0.1241	69.4	60.9-76.0
DEVIANCE=10.74, df=10, p>0.3				

Figure 6. Poisson regression of data from Manitoba showing the observed rate of Rh sensitization and the rate predicted by the regression model assuming no program of Rh prophylaxis (i.e., PRG=0).

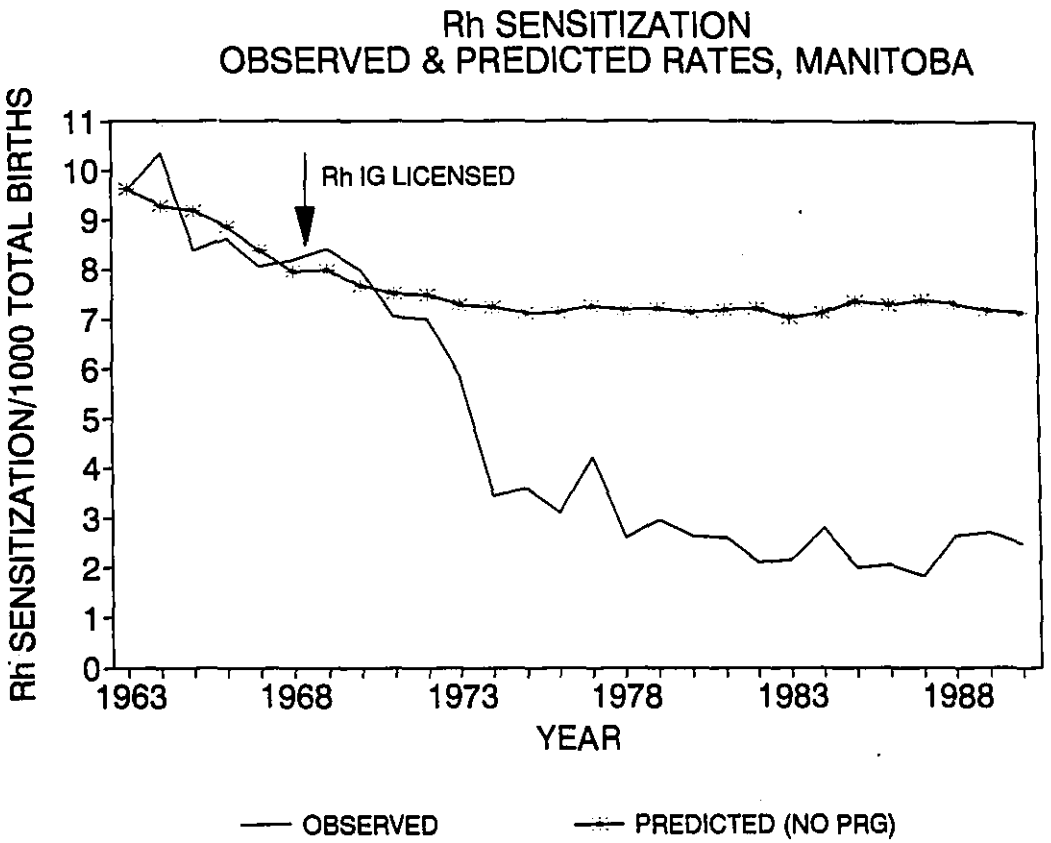


Figure 7. Poisson regression of Manitoba data: graphical depiction of the model predicted effect of a program of Rh prophylaxis on the rate of Rh sensitization (per 1000 total births), with effect modification of the risk difference by the proportion of first births in the population.

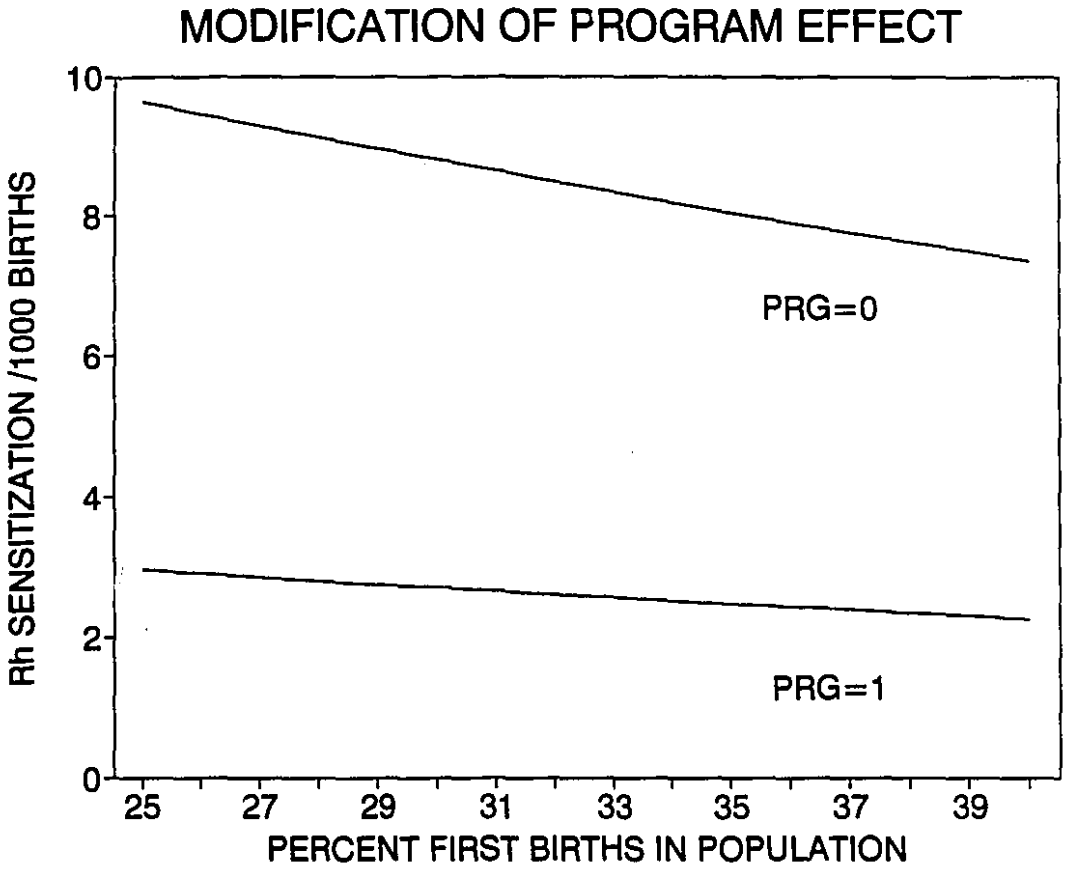


Figure 8. Poisson regression of Manitoba data: graphical depiction of the effect of birth order changes on the rate of Rh sensitization (per 1000 total births), with effect modification of the risk difference by the presence or absence of a program of Rh prophylaxis.

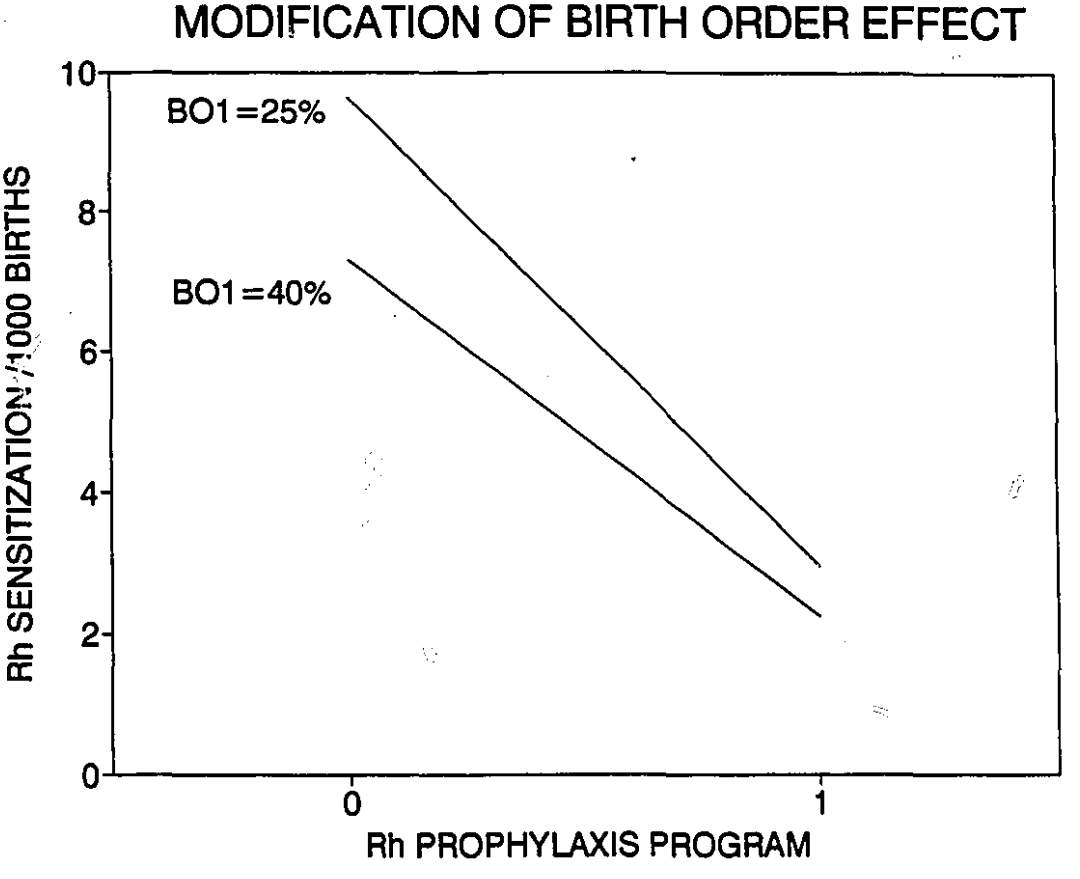
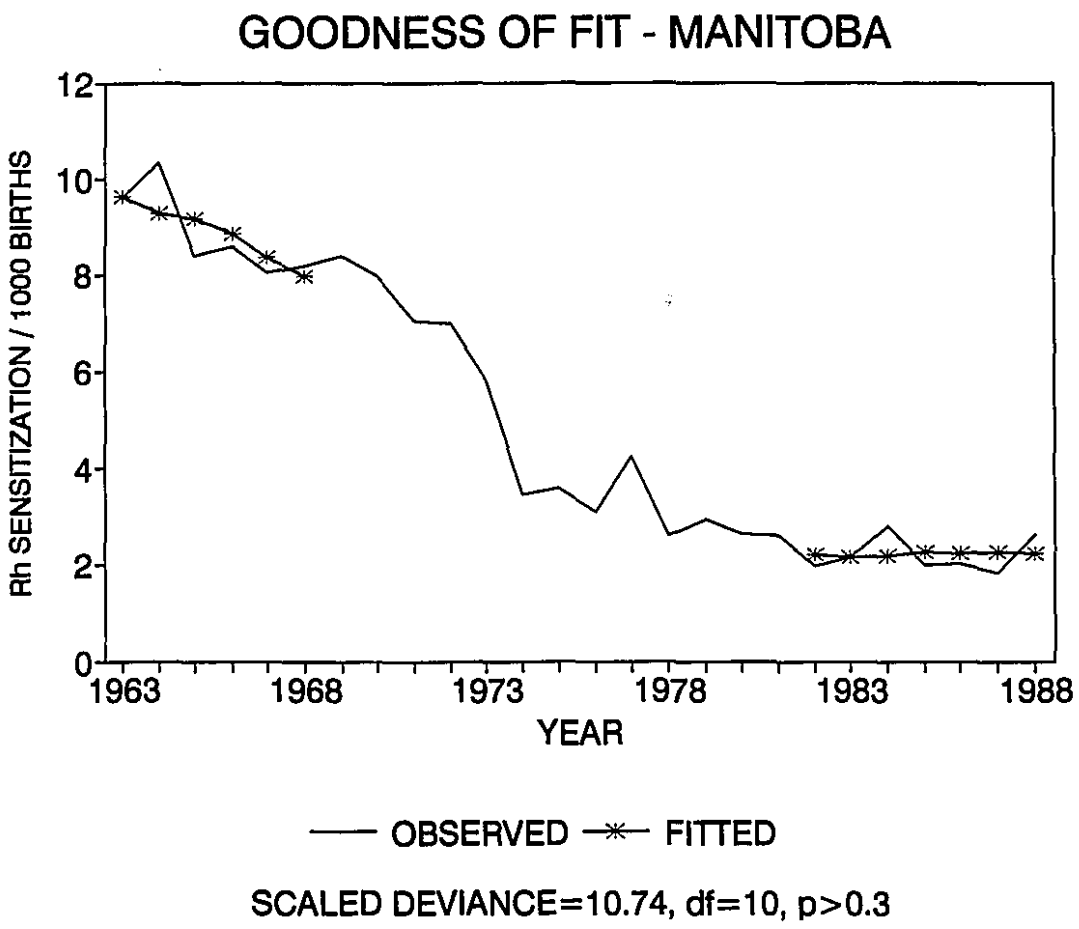


Figure 9. Poisson regression of Manitoba data: graphical depiction of the goodness of fit of the model, with Rh sensitization per 1000 total births as the outcome variable and proportion of first births and presence/absence of the Rh prophylaxis program as independent variables.



(observed data) did not differ significantly from the model including the two independent variables (fitted model). The deviance was 10.74 with 10 degrees of freedom, which translates to a p value of >0.3 when referred to chi-square tables. This shows that there is no lack of fit for the two-variable model. Figure 9 depicts the goodness of fit graphically and shows that the observed and the fitted regression lines are similar.

Deviance statistics also show that the two-variable model provides a significantly better fit than the one-variable model with PRG as the sole explanatory variable (difference in the two deviance values = (15.01-10.74) = 4.27, degrees of freedom = (11-10)= 1, $p < 0.05$).

ASSESSMENT OF COLLINEARITY: Since the standard errors of the beta coefficients for the two independent variables were precise enough to produce significant risk ratios, collinearity was not considered an issue in this model. The correlations among the parameter estimates are given in Table 15, along with the model using perinatal deaths from Rh disease as the outcome.

Rh HEMOLYTIC DISEASE OF THE NEWBORN

Tables 9-11 show the crude and adjusted risk ratios, risk differences and preventive fractions associated with the birth order variable and the Rh prophylaxis program. The adjusted

risk ratio for the change in the proportion of first births (between 1963 and 1988) is 0.67, while the risk ratio for the Rh prophylaxis program is 0.31 (Table 9). These values are only marginally different from the estimates obtained from the model using Rh sensitization as the dependent variable. Change in first birth order is seen to be slightly more protective, while the prophylaxis program is seen to have the same effect. The 95% confidence intervals around the two relative risks do not include the null value, i.e., the point estimates are significant at the 5% level. Figure 10 shows the observed rate of Rh hemolytic disease in Manitoba, along with the predicted rate of Rh disease given no program of Rh prophylaxis. The predicted rates show the effect of birth order changes on Rh disease rates, while the difference between the two lines represents the effect of Rh prophylaxis.

The estimates of effect in terms of risk differences (Table 10) show that the change in the proportion of first births (observed across the years 1963 and 1988) would have led to an adjusted risk difference of 2.73 per 1000 total births in the absence of Rh prophylaxis. This risk difference falls to 0.86 per 1000 total births in the presence of Rh prophylaxis. Similarly, the effect of Rh prophylaxis would be far greater given the BO1 rate of 25% observed in 1963 (adjusted risk difference = 5.67 per 1000 total births) in comparison with the BO1 rate of 40% observed in 1988 (adjusted risk difference = 3.80 per 1000 total births). This phenomenon

Table 9: Result of Poisson regression using data from Manitoba for the years 1963-68 and 1982-88, with rate of Rh hemolytic disease as the outcome and effects expressed in terms of risk ratios.
OUTCOME=Rh HEMOLYTIC DISEASE

VARIABLE (MODEL)	BETA	SE	RR	95% CI
BO1	-0.0968	0.0051	0.23	0.20-0.27
DEVIANCE=73.5, df=11, p<0.001				
PRG	-1.4670	0.0780	0.23	0.20-0.27
DEVIANCE=16.1, df=11, p>0.1				
BO1	-0.0264	0.0097	0.67	0.50-0.90
PRG	-1.1580	0.1392	0.31	0.24-0.41
DEVIANCE=8.58, df=10, p>0.5				

Note: Equivalence of risk ratio and 95% confidence interval estimates for BO1 and PRG effect in the single-variable models is coincidental. The risk ratio for BO1 represents the effect of the observed change in BO1 between 1963 and 1988, while the beta coefficient refers to the effect per unit change in BO1 (i.e. a one percent increase). The risk ratio and beta coefficient for PRG, on the other hand, represent the effect per unit change in PRG. Note that this unit change in PRG (from 0 to 1) also represents the total observed change between 1963 and 1988.

$$RR(BO1) = e^{(Beta*(40.2-25.0))} = 0.2299$$

where Beta = -0.0968
BO1 for 1963 = 40.2%
BO1 for 1988 = 25.0%

$$RR(PRG) = e^{(Beta*(1-0))} = 0.2306$$

where Beta = -1.4670.
PRG for 1963 = 0
PRG for 1988 = 1

See Section 3.1.8 for details regarding calculation of 95% confidence intervals.

Table 10: Result of Poisson regression using data from Manitoba for the years 1963-68 and 1982-88 with rate of Rh hemolytic disease of the newborn as the outcome and effects expressed in terms of risk differences. B_0=intercept, P_0=outcome rate assuming 1963 value for concerned independent variable, P_1=outcome rate assuming 1988 value for concerned independent variable and RD=risk difference i.e., (P_0 - P_1). All rates (P_0, P_1 and RD) are expressed per 1000 total births.
OUTCOME=Rh HEMOLYTIC DISEASE

VARIABLE (MODEL)	BETA	B_0 INTERCEPT	P_0	P_1	RD
Background 1963*					
BO1	-0.0264	-4.136	8.27	5.54	2.73
PRG	-1.1580		8.27	2.59	5.67
Background 1988*					
BO1	-0.0264	-4.136	2.60	1.74	0.86
PRG	-1.1580		5.54	1.74	3.80

* See footnote in table 5 for computational details.

Table 11: Result of Poisson regression using data from Manitoba for the years 1963-68 and 1982-88, with rate of Rh hemolytic disease of the newborn as the outcome and effects expressed in terms of preventive fractions (PF).

OUTCOME=Rh HEMOLYTIC DISEASE

VARIABLE (MODEL)	BETA	SE	PF	95% CI
BO1	-0.0968	0.0051	77.0	73.3-80.2
DEVIANCE=73.5, df=11, p<0.001				
PRG	-1.4670	0.0780	76.9	73.1-80.2
DEVIANCE=16.1, df=11, p>0.1				
BO1	-0.0264	0.0097	33.0	10.5-49.9
PRG	-1.1580	0.1392	68.6	58.7-76.1
DEVIANCE=8.58, df=10, p>0.5				

Note: Equivalence of preventive fraction estimates for BO1 and PRG in the single-variable models is coincidental. The preventive fraction for BO1 represents the effect of the observed change in BO1 between 1963 and 1988, while the beta coefficient refers to the effect per unit change in BO1 (see footnote to Table 9 for details).

Figure 10. Poisson regression of data from Manitoba showing the observed rate of Rh hemolytic disease of the newborn and the rate predicted by the regression model assuming no program of Rh prophylaxis (i.e., PRG=0).

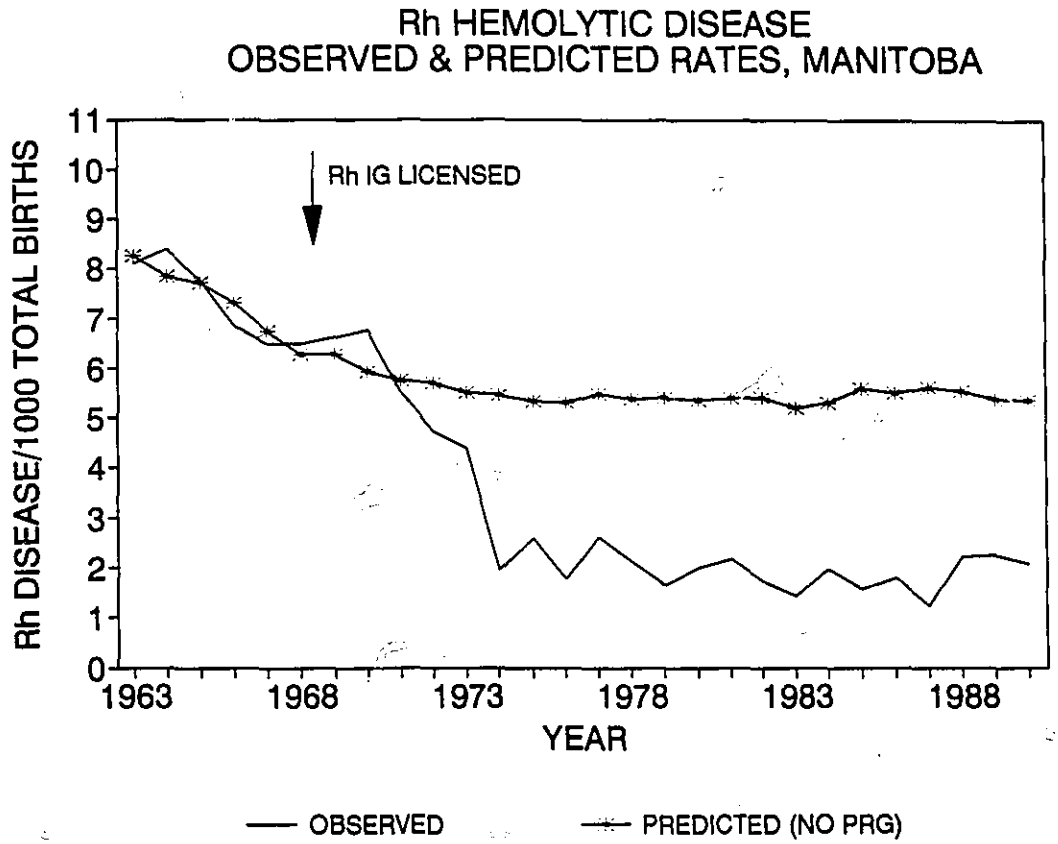


Figure 11. Poisson regression of Manitoba data: graphical depiction of the model predicted effect of a program of Rh prophylaxis on the rate of Rh disease (per 1000 total births), with effect modification of the risk difference by the proportion of first births in the population.

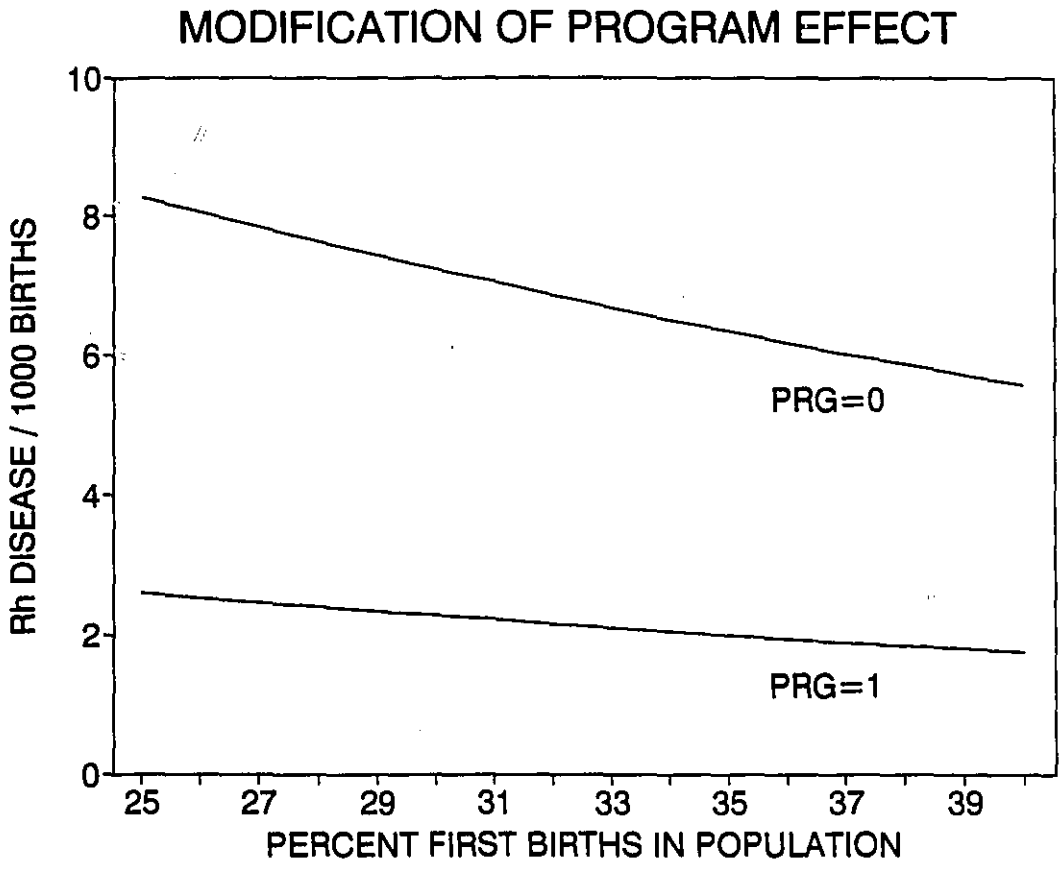


Figure 12. Poisson regression of Manitoba data: graphical depiction of the model predicted effect of birth order changes on the rate of Rh disease (per 1000 total births), with effect modification of the risk difference by the presence or absence of a program of Rh prophylaxis.

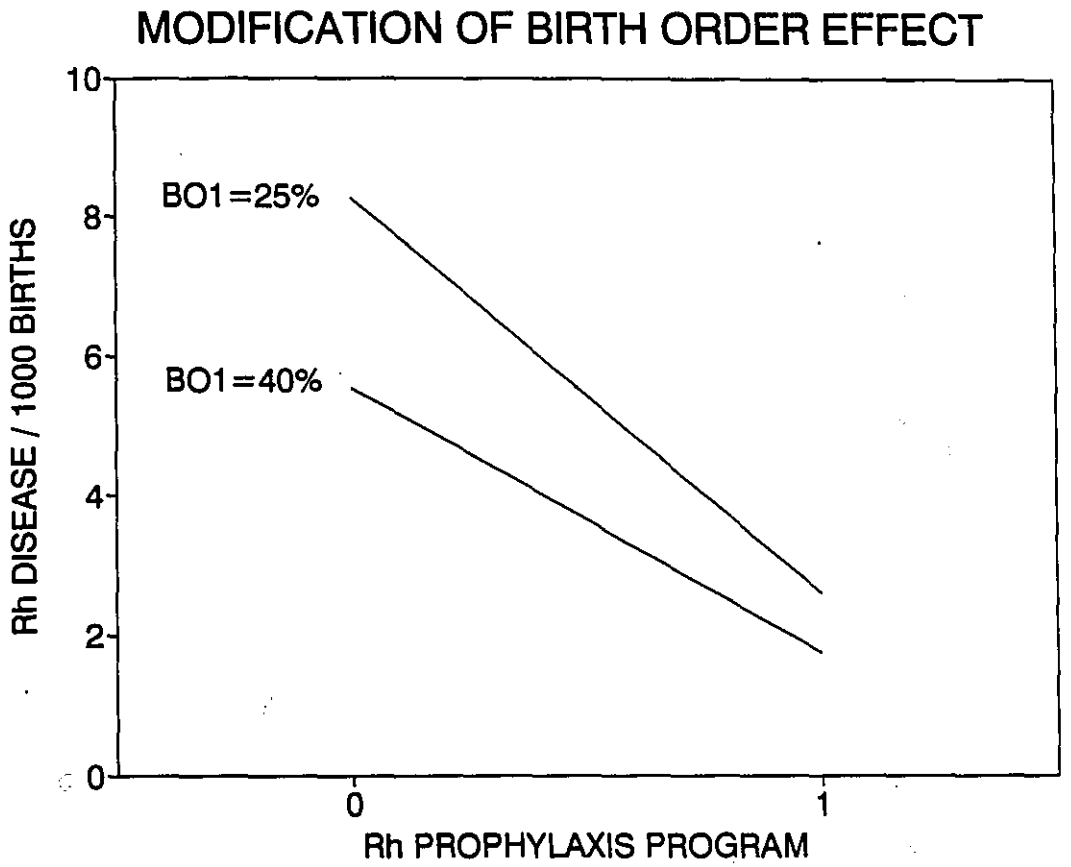
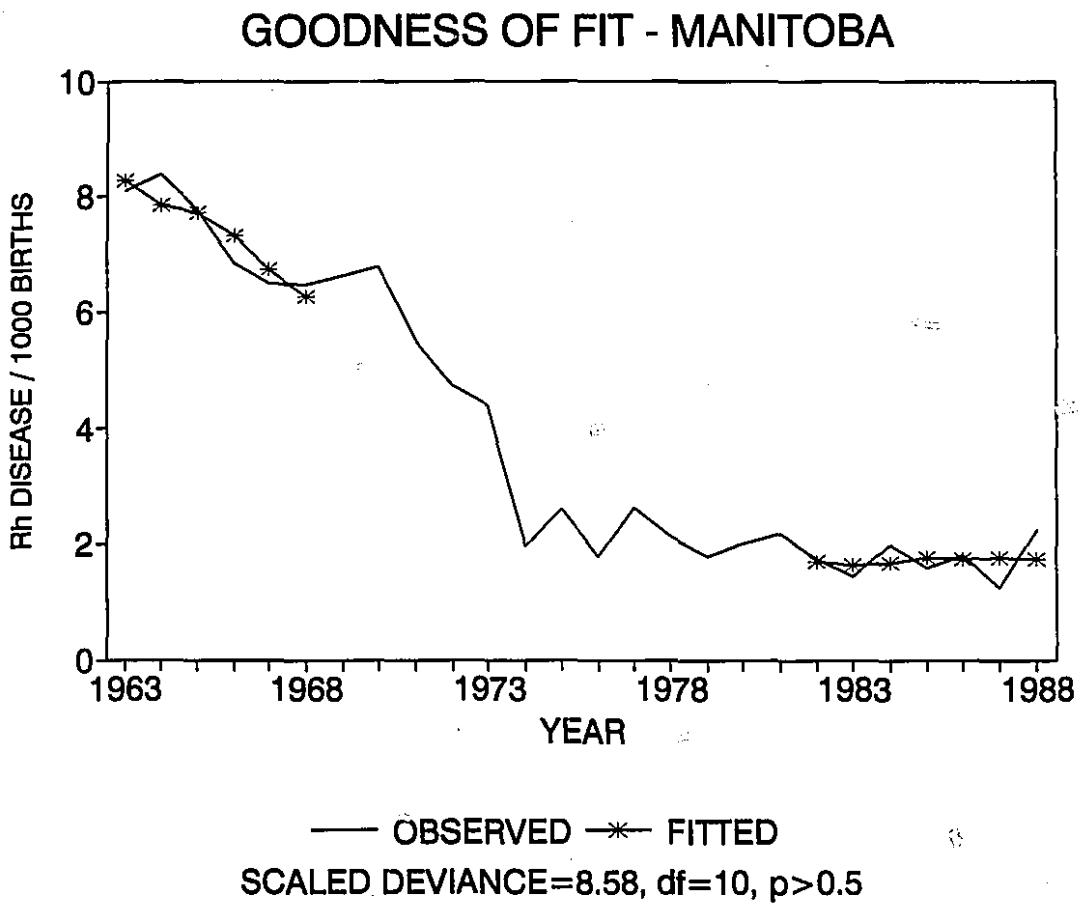


Figure 13. Poisson regression of Manitoba data: graphical depiction of the goodness of fit of the model, with Rh hemolytic disease of the newborn per 1000 total births as the outcome variable and proportion of first births and presence/absence of the Rh prophylaxis program as independent variables.



of effect modification of the risk difference is depicted in Figures 11 and 12.

The estimates of the preventive fractions are provided in Table 11 and show the adjusted reduction in the disease which occurred secondary to each factor. The reduction in Rh disease brought about by the Rh prophylaxis program is seen to be more than twice that which occurred as a consequence of changes in first birth order. With 33% of cases prevented by BO1 and 69% of cases prevented by Rh prophylaxis, this picture resembles that obtained with Rh sensitization as the outcome. As mentioned earlier (Section 3.1.8), the fact that the sum of the two preventive fractions exceeds 100% indicates that the effects of the two factors overlap.

GOODNESS OF FIT: Goodness of fit of the model, as assessed through deviance statistics, was acceptable (Table 9). The deviance was 8.58 with 10 degrees of freedom, which yields a p value of >0.5 when referred to chi-square tables. The graphical depiction of the goodness of fit shows a close similarity between the observed and fitted regression lines (Figure 13). Also, the addition of the BO1 term to the single-variable model containing PRG significantly improves the goodness of fit (difference in the two deviance values =(16.05-8.58) = 7.47, df= (11-10) = 1, $p<0.01$).

PERINATAL DEATHS FROM Rh DISEASE

Tables 12-14 show the crude and adjusted risk ratios, risk differences and preventive fractions associated with first birth order, quality of perinatal care and Rh prophylaxis. The crude and adjusted risk ratio estimates for the effect of the first order births show strong confounding by Rh prophylaxis. Similarly, the quality of perinatal care and the Rh prophylaxis program mutually confound one another.

In the two-variable model with BO1 and PRG as independent variables, the birth order variable appears to have a strong protective effect against perinatal deaths from Rh disease. In the three-variable model, however, the beta coefficient for this variable is significantly reduced, and the standard error increases drastically in relation to the size of the beta coefficient. The 95% confidence interval on the risk ratio of first order births thus extends from 0.18 to 5.07. A similar phenomenon is witnessed with regard to the beta coefficient for perinatal care quality. The beta coefficient for PCQ in the three-variable model increases marginally to a less protective value, and the variance inflation leads to a much wider 95% confidence interval (0.06 to 0.96 compared with 0.10 to 0.51 in the two-variable model). Only the beta coefficient and the standard error estimate for Rh prophylaxis remain unchanged between the two- and three-variable models.

The change in the beta coefficient of BO1 after adjustment for PCQ reveals confounding of the BO1-outcome relation by PCQ. However, the inflation of the standard error of the BO1 beta coefficient suggests collinearity between BO1 and PCQ. The reverse phenomenon is also seen. Collinearity between BO1 and PCQ degrades the precision of the PCQ beta coefficient.

In comparison with the magnitude of the effects seen with Rh sensitization and Rh disease, perinatal deaths from Rh disease appear to show a greater response to the Rh prophylaxis program. Figure 14 shows the observed rate of perinatal death from Rh disease in Manitoba, along with the predicted rate of perinatal death from Rh disease in the absence of an Rh prophylaxis program. The predicted rates show the effect of changes in birth order and perinatal care on perinatal deaths from Rh disease, while the difference between the two lines represents the effect of Rh prophylaxis.

Table 13 shows the risk difference estimates for perinatal deaths from Rh disease. The effect of Rh prophylaxis is seen to depend on the background levels of the other two variables. Given 1963 levels for BO1 (i.e., 25%) and PCQ (i.e., 86%), the prophylaxis program is seen to lead to an adjusted risk difference of 91.1 per 100,000 total births, while with BO1 and PCQ at 1988 levels (i.e., 40% and 97%, respectively) the risk difference for Rh prophylaxis changes to 20.4 per 100,000 total births (see footnote to Table 13 for

calculations). Similarly, PCQ is associated with an adjusted risk difference of 84.2 given a 1963 background (ie. BO1=25% and PRG=0) and 13.8 given a 1988 background (ie. BO1=40% and PRG=1). The adjusted differences associated with first birth order are 4.2 per 100,000 total births given a 1963 background and 0.2 per 100,000 births given a 1988 background. This phenomenon of effect modification of the risk difference is illustrated in Figures 15-17 (Figures 1A-9A, Appendix, illustrate other effect modification scenarios).

Table 14 shows the preventive fractions associated with each of the three independent variables. Both first birth order and perinatal care quality have strong protective effects in the two-variable models, but the addition of a third variable leads to a reduction in the effect of BO1 and to reduced precision.

GOODNESS OF FIT: The goodness of fit of the two-variable models (BO1 + PRG and PCQ + PRG) and the three-variable model, as assessed by the deviance statistic, shows acceptable levels of fit (Table 12). The deviance for the BO1-PRG model was 7.80 with 10 degrees of freedom. This translates to a p value of >0.6. Similarly, the deviances for the PCQ-PRG and BO1-PCQ-PRG models were 3.93 (df=10) and 3.93 (df=9), respectively, both yielding p values of >0.9. The closeness of the fit is also demonstrated by the graphical depiction of the observed and fitted lines in Figure 18. The addition of the BO1 variable to

Table 12: Result of Poisson regression using data from Manitoba for the years 1963-68 and 1982-88, with rate of perinatal deaths from Rh hemolytic disease of the newborn as the outcome and effects expressed as risk ratios. Note: the initial lines in the table represent single-variable models while subsequent lines give the results of two- or three-variable models.

OUTCOME=PERINATAL DEATHS FROM Rh HEMOLYTIC DISEASE

VARIABLE (MODEL)	BETA	SE	RR	95% CI
BO1	-0.1784	0.0203	0.07	0.04-0.12
DEVIANCE=19.1, df=11, p>0.05				
PCQ	-0.2240	0.0249	0.08	0.05-0.14
DEVIANCE=14.8, df=11, p>0.1				
PRG	-3.0520	0.4574	0.05	0.02-0.12
DEVIANCE=17.6, df=11, p>0.05				
BO1	-0.0927	0.0310	0.24	0.10-0.62
PRG	-1.9360	0.5991	0.14	0.04-0.47
DEVIANCE=7.80, df=10, p>0.6				
PCQ	-0.1325	0.0368	0.23	0.10-0.51
PRG	-1.7790	0.5805	0.17	0.05-0.53
DEVIANCE=3.93, df=10, p>0.95				
BO1	-0.0026	0.0559	0.96	0.18-5.07
PCQ	-0.1301	0.0647	0.23	0.06-0.96
PRG	-1.7710	0.6084	0.17	0.05-0.56
DEVIANCE=3.93, df=9, p>0.9				

Table 13: Result of Poisson regression using data from Manitoba for the years 1963-68 and 1982-88, with rate of perinatal deaths from Rh hemolytic disease of the newborn (per 100,000 total births) as the outcome and effects expressed as risk differences.

OUTCOME=PERINATAL DEATHS FROM Rh HEMOLYTIC DISEASE

VARIABLE (MODEL)	BETA	B_0 INTERCEPT	P_0	P_1	RD
Background 1963					
PCQ	-0.1325	4.607	109.8	24.9	84.9
PRG	-1.7790		109.8	18.5	91.2
Background 1988					
PCQ	-0.1325	4.607	18.5	4.2	14.3
PRG	-1.7790		24.9	4.2	20.7
Background 1963*					
BO1	-0.0026	4.465	109.8	105.6	4.2
PCQ	-0.1301		109.8	25.6	84.2
PRG	-1.7710		109.8	18.7	91.1
Background 1988					
BO1	-0.0026	4.465	4.4	4.2	0.2
PCQ	-0.1301		18.0	4.2	13.8
PRG	-1.7710		24.6	4.2	20.4

.* Background 1963 (Three-variable model)

Effect of BO1:

$P_0 = e^{(B_0 + B_1*BO1(1963) + B_2*PCQ(1963) + B_3*PRG(1963))}$
i.e., BO1=25%, PCQ=86% and PRG=0

$P_1 = e^{(B_0 + B_1*BO1(1988) + B_2*PCQ(1963) + B_3*PRG(1963))}$
i.e., BO1=40%, PCQ=86% and PRG=0

Effect of PCQ:

$P_0 = e^{(B_0 + B_1*BO1(1963) + B_2*PCQ(1963) + B_3*PRG(1963))}$
i.e., BO1=25%, PCQ=86% and PRG=0

$P_1 = e^{(B_0 + B_1*BO1(1963) + B_2*PCQ(1988) + B_3*PRG(1963))}$
i.e., BO1=25%, PCQ=97% and PRG=0

Effect of PRG:

$P_0 = e^{(B_0 + B_1*BO1(1963) + B_2*PCQ(1963) + B_3*PRG(1963))}$
i.e., BO1=25%, PCQ=86% and PRG=0

$P_1 = e^{(B_0 + B_1*BO1(1963) + B_2*PCQ(1963) + B_3*PRG(1988))}$
i.e., BO1=25%, PCQ=86% and PRG=1

Table 14: Result of Poisson regression using data from Manitoba for the years 1963-68 and 1982-88, with rate of perinatal death from Rh hemolytic disease of the newborn as the outcome and effects expressed in terms of preventive fractions.

OUTCOME=PERINATAL DEATHS FROM Rh HEMOLYTIC DISEASE

VARIABLE (MODEL)	BETA	SE	PF	95% CI
BO1	-0.1784	0.0203	93.4	87.8-96.4
DEVIANCE=19.1, df=11, p>0.05				
PCQ	-0.2240	0.0249	91.9	86.0-95.3
DEVIANCE=14.8, df=11, p>0.1				
PRG	-3.0520	0.4574	95.3	88.4-98.1
DEVIANCE=17.6, df=11, p>0.05				
BO1	-0.0927	0.0310	75.6	38.5-90.3
PRG	-1.9360	0.5991	85.6	53.3-95.5
DEVIANCE=7.80, df=10, p>0.6				
PCQ	-0.1325	0.0368	77.3	49.1-89.9
PRG	-1.7790	0.5805	83.1	47.3-94.6
DEVIANCE=3.93, df=10, p>0.95				
BO1	-0.0026	0.0559	3.9	-80.3-81.8
PCQ	-0.1301	0.0647	76.7	3.8-94.4
PRG	-1.7710	0.6084	83.0	43.9-94.8
DEVIANCE=3.93, df=9, p>0.9				

Figure 14. Poisson regression of data from Manitoba showing the observed rate of perinatal death from Rh disease and the rate predicted by the regression model assuming no program of Rh prophylaxis (i.e., PRG=0).

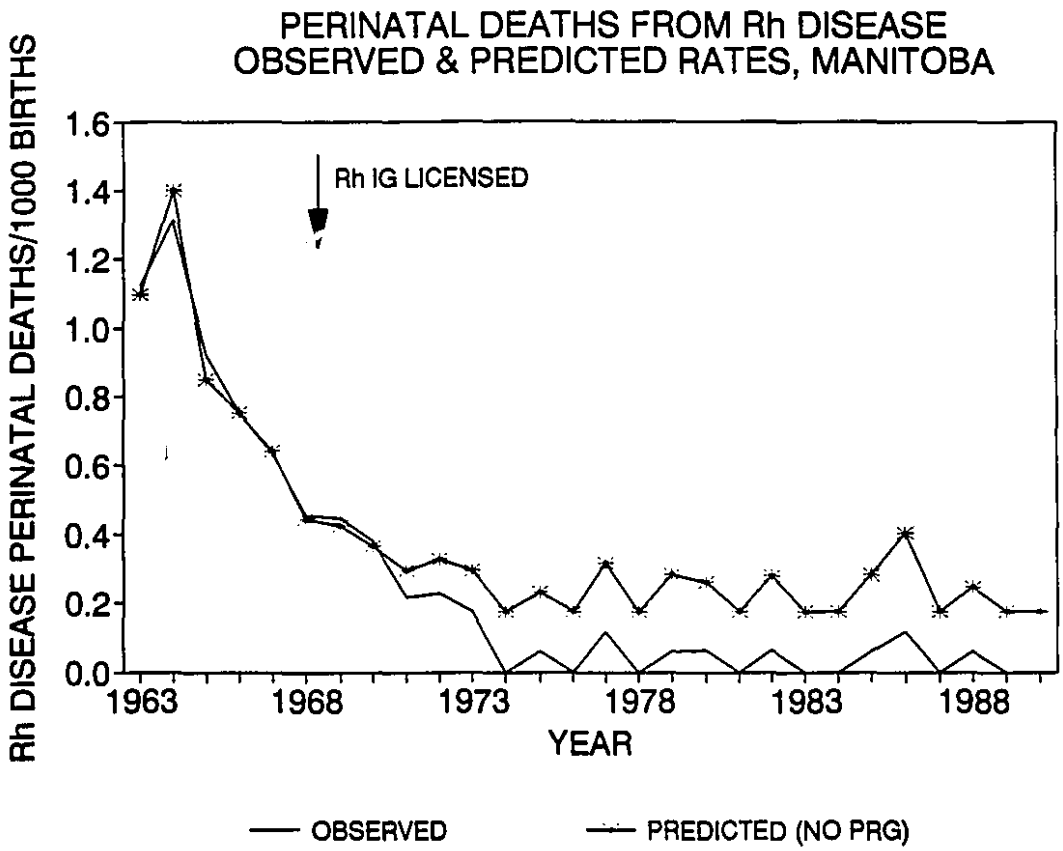


Figure 15. Poisson regression of Manitoba data: graphical depiction of the model predicted effect of birth order changes on the rate of perinatal deaths from Rh disease (per 100,000 total births), with effect modification of the risk difference by the quality of perinatal care (Rh prophylaxis program absent).

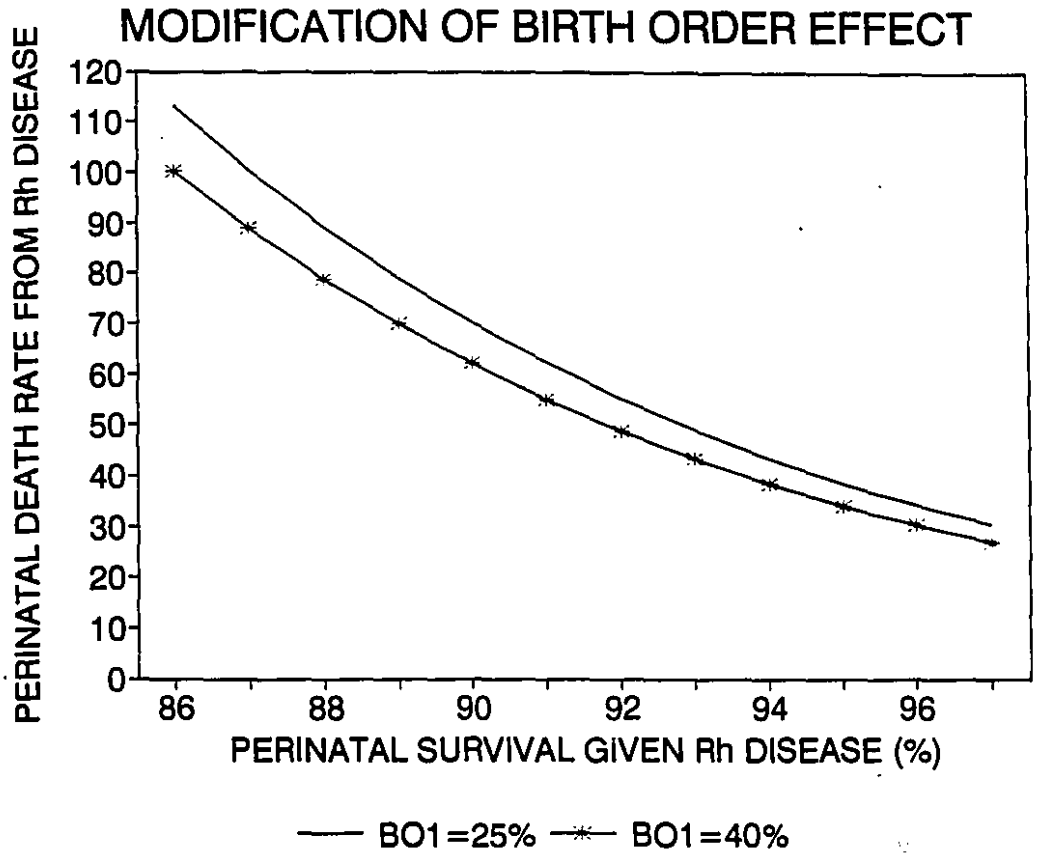


Figure 16. Poisson regression of Manitoba data: graphical depiction of the model predicted effect of a program of Rh prophylaxis on the rate of perinatal deaths from Rh disease (per 100,000 total births), with effect modification of the risk difference by the quality of perinatal care (proportion of first births kept constant at the 1963 level).

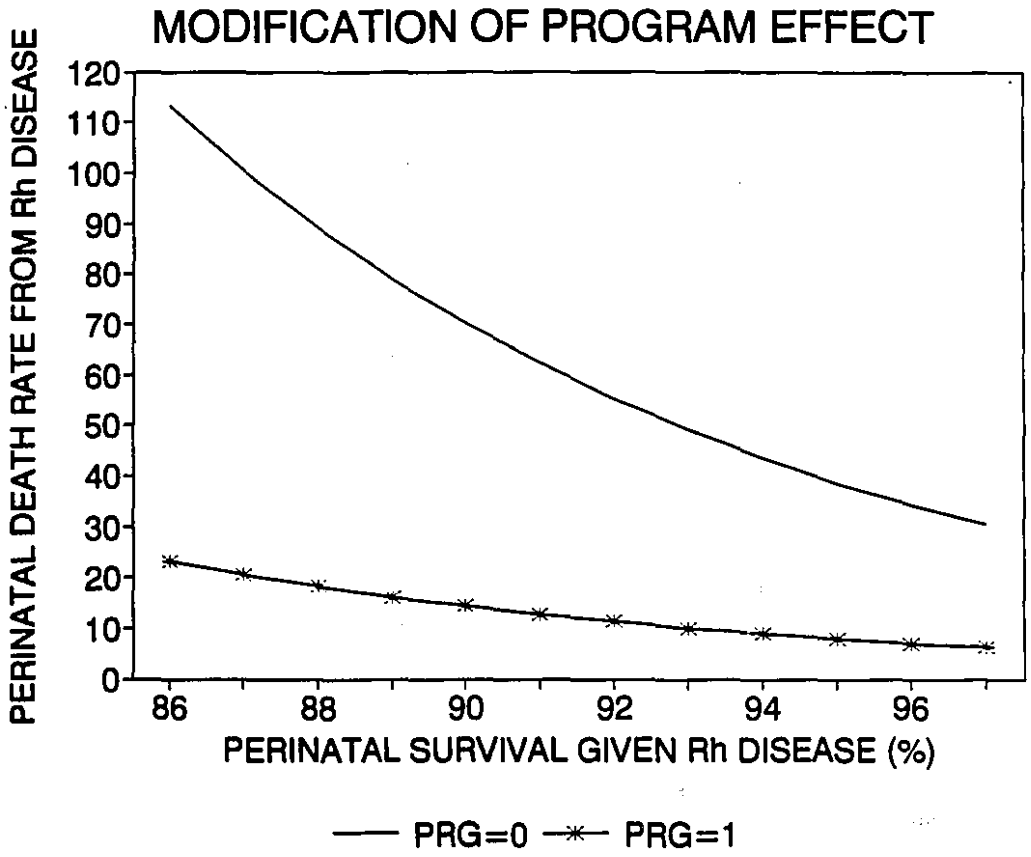


Figure 17. Poisson regression of Manitoba data: graphical depiction of the model predicted effect of the quality of perinatal care on the rate of perinatal deaths from Rh disease (per 100,000 total births), with effect modification of the risk difference by the presence or absence of a program of Rh prophylaxis (proportion of first births kept constant at the 1963 level).

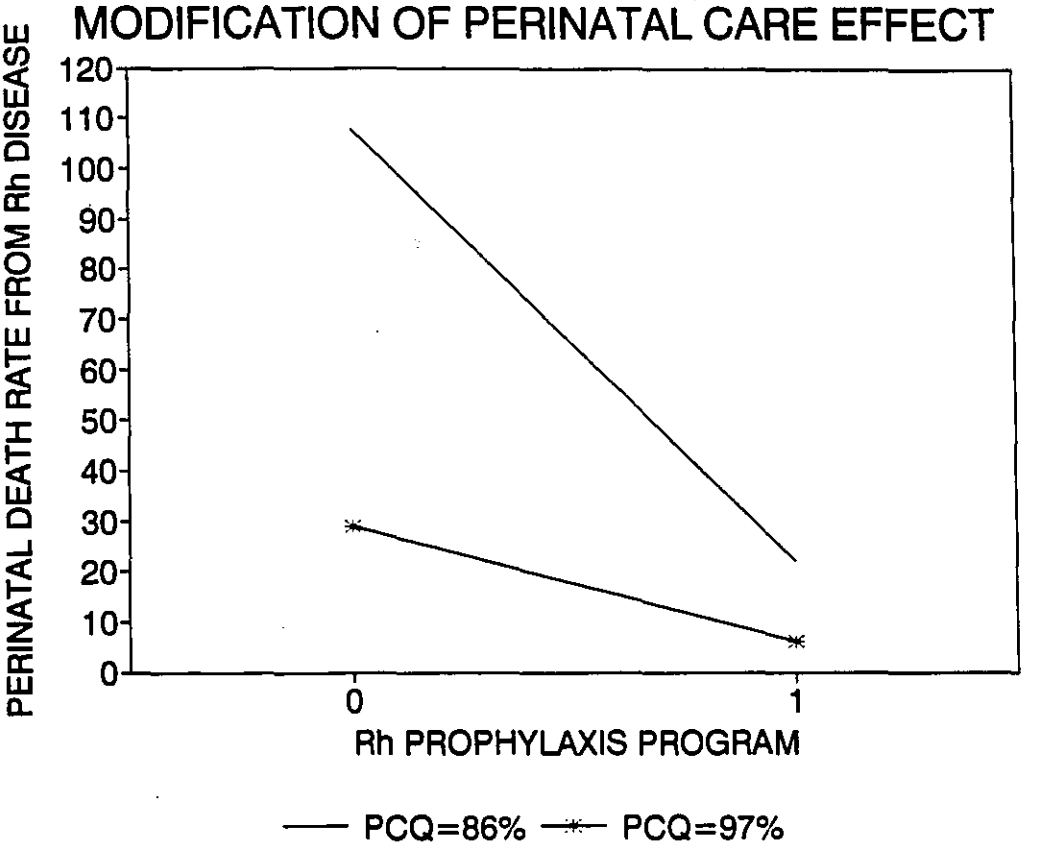


Figure 18. Poisson regression of Manitoba data: graphical depiction of the goodness of fit of the model, with perinatal deaths from Rh disease per 1000 total births as the outcome variable and proportion of first births, perinatal care quality and presence/absence of the Rh prophylaxis program as independent variables.

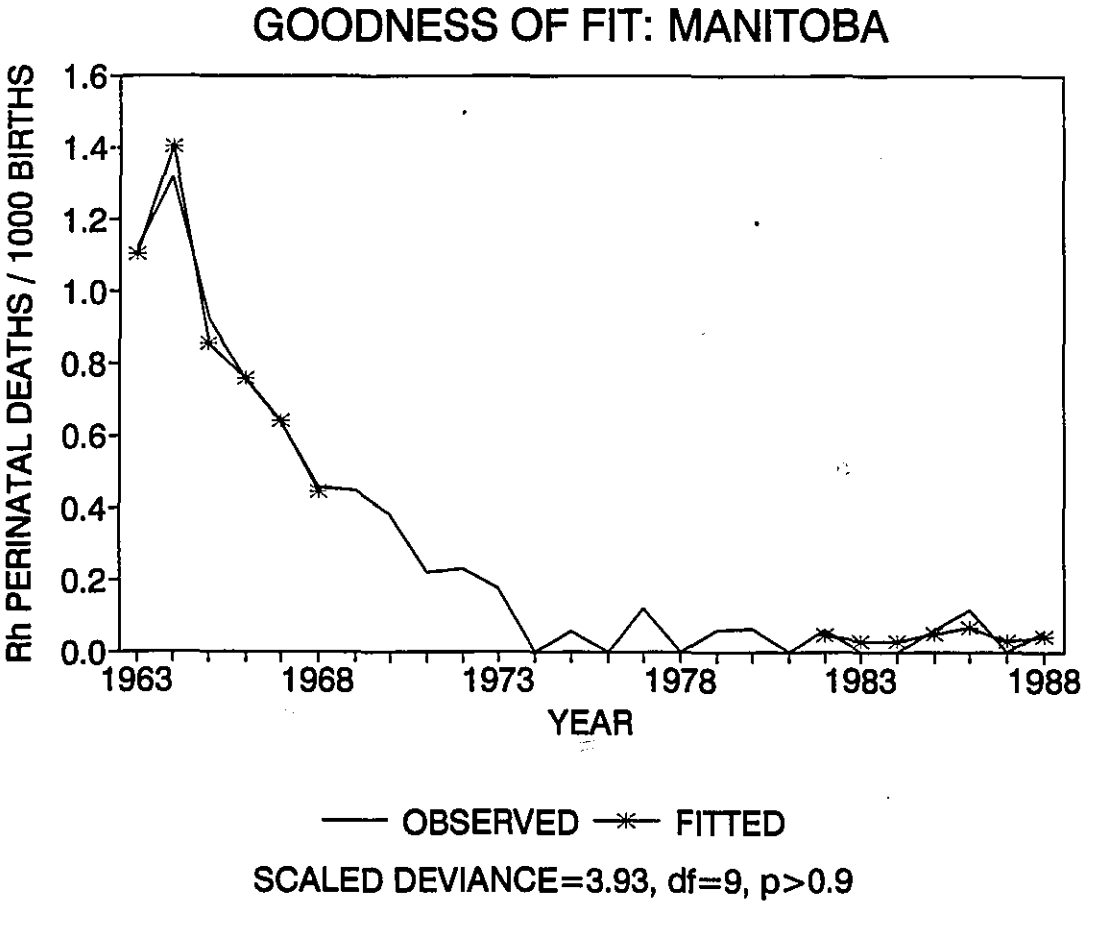


Table 15: Poisson regression using data from Manitoba for the years 1963-68 and 1982-88: correlations among parameter estimates.

OUTCOME=Rh SENSITIZATION		
		PRG
BO1		-0.832
OUTCOME=Rh HEMOLYTIC DISEASE		
		PRG
BO1		-0.829
OUTCOME=PERINATAL DEATHS FROM Rh DISEASE		
		PRG
BO1		-0.646
		PRG
PCQ		-0.615
		PCQ
BO1		-0.904
	PCQ	PRG
BO1	-0.821	-0.296
PCQ		-0.093

Table 16: Results of Poisson regression using data from Manitoba for the years 1963-68 and 1982-88, with rate of perinatal deaths from Rh hemolytic disease of the newborn as the outcome. The variables BO1 and PCQ were centred in an attempt to overcome the problem of collinearity (centred variables termed BO1* and PCQ*) . The correlations between the parameter estimates are shown in the lower of half the table.

OUTCOME=PERINATAL DEATHS FROM Rh HEMOLYTIC DISEASE

VARIABLE (MODEL)	BETA	SE	RR	PF	95% CI on PF
BO1*	-0.0154	0.3552	0.96	3.6	-80.4-81.7
PCQ*	-0.7133	0.3542	0.23	76.8	4.0-94.4
PRG	-1.7660	0.6079	0.17	82.9	43.7-94.8

DEVIANCE=3.90, df=9, p>0.9

CORRELATION OF PARAMETER ESTIMATES

	PCQ*	PRG
BO1*	-0.822	-0.290
PCQ*		-0.099

Table 17: Result of Poisson regression using data from Manitoba for the years 1963-68 and 1982-88, with rate of perinatal deaths from Rh hemolytic disease of the newborn as the outcome. The collinear variables BO1 and PCQ have been combined into one variable (NON-PRG), which expresses the effect of the total change in non-program factors. The beta shown against NON-PRG represents the sum of the two beta coefficients for the total change between 1963 and 1988, estimated by the equation

Beta = $(B_1 * (X_{1(1963)} - X_{1(1988)})) + (B_2 * (X_{2(1963)} - X_{2(1988)}))$

See Section 3.1.10 for details

OUTCOME=PERINATAL DEATHS FROM Rh HEMOLYTIC DISEASE

VARIABLE (MODEL)	BETA	SE	RR	PF	95% CI on PF
NON-PRG	-1.4960	0.4845	0.22	77.6	42.3-91.4
PRG	-1.7710	0.6084	0.17	83.0	43.9-94.8

the model containing PCQ and PRG did not significantly improve the goodness of fit.

COLLINEARITY ASSESSMENT: The variance inflation seen in the three-variable model suggests a collinearity problem in that model. Obviously, the proportion of first births provides information which is very similar to that in perinatal care quality. This is reflected in the lack of improvement in the goodness of fit statistic between the two-variable and three-variable models with and without BO1. Table 15 shows the correlations among the parameter estimates. BO1 and PCQ show collinearity (correlation between parameter estimates = -0.82 in the three variable model) and this is responsible for the inflation of the standard errors, which is reflected in wide confidence intervals.

Three options were explored as potential solutions to this problem of collinearity. The first option considered was scaling/centring the data. The results of regression with centred values for BO1 and PCQ are presented in Table 16. They show no alleviation of the collinearity and suggest that the collinearity problem does not arise from a scaling issue. Second, since the addition of the BO1 variable did not add any information to the model containing PCQ and PRG, this two-variable model was taken to be the full (final) model. The effect of PCQ as observed in this model was assumed to subsume the effect of the first births variable. Finally, BO1 and PCQ

were combined into a single variable whose effect was to be viewed as the effect of non-program factors. Such an approach eliminates the loss of precision induced by collinearity, although it does not help isolate the separate effects of BO1 and PCQ. The results of this approach are shown in Table 17. The preventive fractions obtained from the two-variable model containing PCQ and PRG (second approach, see Table 14) are seen to be very similar to those obtained through this third approach. Non-program factors were responsible for a 76-77% decline in perinatal deaths from Rh disease, while 83% of the reduction occurred secondary to the Rh prophylaxis program.

OTHER ANALYSES

DATA FOR 1989 AND 1990: Since data from Manitoba were available for the years 1989 and 1990, regression analysis was also carried out on a data set which included these years, i.e., with data for the years 1963-68 and 1982-90. The crude and adjusted estimates are provided in Tables 6A-11A (Appendix). The results are similar to those obtained when the recent data is limited to 1982-88.

ALTERNATIVE ANALYSIS USING LOGISTIC REGRESSION

Although the data from Manitoba do not provide information on individuals, it is possible to use a logistic link for the regression analysis with a binomial error specification. The results of such logistic regression analysis are presented in

Tables 12A-14A in the Appendix. The results are almost identical to those obtained using Poisson regression. The choice of Poisson regression over this alternative logistic regression method was dictated by the fact that the beta coefficients obtained through Poisson regression can be transformed to obtain risk ratios, while those obtained using the logistic link yield odds ratios on transformation. The virtual identity of the beta coefficients and their standard errors shows that the odds ratios from logistic regression approximate the risk ratios from Poisson regression, since the assumption of rare disease is met.

ALTERNATE ANALYSIS FOR THE EFFECT OF BIRTH ORDER

The birth order distribution for any given year was represented in previous models by the proportion of first births for that year. The choice of this variable for characterizing the birth order distribution of the population was based on the belief that this birth order (as against subsequent birth orders) has the greatest effect on Rh sensitization rates. The most common birth order in any given year is the first birth order. For example, 25% of Manitoba births in 1963 were first births and this proportion rose to 40% by 1988. In contrast, births orders 4, 5, 6, 7, 8 and greater represented less than 35% of births in 1963 and less than 10% of births by 1988.

However, the question arises as to whether birth

order distribution is better represented by a birth order proportion other than the proportion of first births – for example, proportion of second births or proportion of third births. This issue could be especially relevant in the context of perinatal deaths from Rh disease, since severe cases of Rh disease generally tend to occur in late order births as opposed to first births. Second births constituted 23% of births in 1963 and 33% of all births in 1988, while the same figures for proportion of third births were 18% and 17%, respectively. This hypothesis (regarding appropriate characterization of birth order distribution) was explored using the model with perinatal deaths from Rh disease as the outcome. The results (Table 15A, Appendix) show that the representation of birth order distribution using proportion of second or third births does not appear to offer any significant advantage. The three-variable model with BO2 as the birth order variable showed multicollinearity (variance inflation affected the PRG estimate as well) while the model with BO3 as the birth order variable yielded results virtually identical to those obtained with BO1. Goodness of fit was identical across the different models.

The inclusion of more than one birth order in the model led to standard error inflation due to collinearity among the birth order variables. Goodness of fit was not significantly improved by such multiple representation of birth order. In fact, the loss of degrees of freedom incurred

secondary to the addition of more independent variables into the model led to a decrease in the statistical goodness of fit.

4.1.2 COMBINED MANITOBA-NOVA SCOTIA

As mentioned in Chapter 3 (Section 3.1.5), this analysis was undertaken with the purpose of duplicating published analyses from a multivariate, rather than a univariate, viewpoint. For this analysis, the outcome rates and values of the independent variables for the early years (1963-68) were those observed in Manitoba while those for later years (1982-88) represent events observed in Nova Scotia.

4.1.2.1 CRUDE CHANGES BETWEEN 1963 AND 1988

Tables 16A-18A (Appendix) provide outcome rates, values of independent variables and estimates of the crude measures of effect across the period 1963-1988 (see also Figure 10A). The rate of Rh sensitization in Nova Scotia in 1988 is seen to be higher than the same rate in Manitoba (Table 3). On the other hand, the rate of Rh disease is lower and there were no perinatal deaths from Rh disease in Nova Scotia in 1988. The magnitude of the change, as reflected in the crude measures of effect, reflect these differences in the underlying outcome rates. Some of the differences observed between the results from the Manitoba data set and those from Manitoba-Nova Scotia may be explained on the basis of random error and differences

in racial composition; Manitoba has a small proportion of Native Indians who are known to experience lower rates of Rh outcomes. The opposite direction of the differences between Rh sensitization and disease rates, however, represents a curious feature. Note also that the proportion of first births in Nova Scotia in 1988 (44%) is higher than that seen in Manitoba in 1988 (40%). Similarly, perinatal survival given Rh disease is also marginally higher. Both these difference can be expected to detract from the effect of the Rh prophylaxis program in the multivariate analysis.

4.1.2.2 POISSON REGRESSION

Rh SENSITIZATION, Rh DISEASE AND PERINATAL DEATHS

The data set used for Poisson regression (combined Manitoba-Nova Scotia) is shown in Table 19A (Appendix). With Rh sensitization as the outcome variable, the adjusted risk ratio for birth order was similar to that obtained from the Manitoba data (beta coefficients = -0.0163 and -0.0180, respectively), although the estimate for the Rh prophylaxis program was significantly lower (risk ratio=0.53 compared to 0.31 from the Manitoba data set, see Appendix, Table 20A). For Rh disease, the adjusted effects of birth order and Rh prophylaxis were more consistent with the results from Manitoba. The beta coefficient for first births was -0.0256 in the combined Manitoba-Nova Scotia data as compared to -0.0264 obtained from the data from Manitoba alone. The Rh prophylaxis program

effect was similar, with a risk ratio of 0.26 for the combined Manitoba-Nova Scotia data and 0.31 for Manitoba (Appendix, Table 21A).

The model with perinatal deaths from Rh disease also showed results similar to those obtained from the same model using only the Manitoba data (Appendix, Table 22A). Marginally greater protective effects are seen for PCQ and PRG, while a lesser protective effect was obtained for BO1 in the three-variable model. The two-variable models also showed similar results. Figures 11A-16A (Appendix) show modification of the effects of the various determinants. The patterns are consistent with those seen in the analysis of the Manitoba data.

Goodness of fit as assessed by deviance statistics was acceptable for most of the multivariable models (for the model with Rh sensitization as the outcome, the p value was just under 0.05). Figure 16A (Appendix) graphically depicts the goodness of fit for the three models. Collinearity (as assessed by variance inflation) was seen in the models using Rh sensitization and perinatal deaths from Rh disease as the outcome. However, in the latter model this collinearity between BO1 and PCQ did not render the beta coefficient for perinatal care quality statistically nonsignificant. The matrix for the correlation between parameter estimates from these models is shown in the Appendix (Table 23A).

4.1.3 CANADA

The outcome variable for this analysis was infant deaths from hemolytic disease of the newborn. As mentioned earlier (Methods, Section 3.1.3), this outcome differs from perinatal deaths from Rh disease in that:

1. Affected stillbirths are included in perinatal deaths but not in infant deaths.
2. Infant deaths include deaths occurring through the first year of life, while perinatal deaths are restricted to those that occur in the first week of life.
3. The outcome, infant deaths from hemolytic disease of the newborn, encompasses all fatal cases of hemolytic disease of the newborn among infants irrespective of etiology, whether Rh or non-Rh.

4.1.3.1 CRUDE CHANGES BETWEEN 1951, 1963 AND 1988

Tables 18-19 provide outcome rates, values of independent variables and estimates of the crude measures of effect across the periods 1951-63, 1963-88 and 1951-88 (see also Figure 19). No comparisons can be made with the data previously presented from Manitoba given the disparate nature of the outcomes. The crude measures of effect clearly show that significant reductions in mortality occurred between 1951 and 1963 even in the absence of Rh prophylaxis. However, the reduction in mortality that occurred between 1963 and 1988 is substantially greater – mainly as consequence of the introduction of Rh

prophylaxis in late 1968 but also due to changes in birth order distribution and quality of medical care.

4.1.3.2 POISSON REGRESSION

Besides the different outcome considered (in comparison to the data from Manitoba), the analysis for the Canadian data also differed in that the infant survival rate (ISR) was used to express the quality of infant care quantitatively. Table 20 shows the results of Poisson regression with data for the years 1963-68 and 1982-88. Effects are expressed as risk ratios, preventive fractions (Table 20) and risk differences (Appendix, Table 24A). The model with 'Rh prophylaxis program' as the sole explanatory variable is much improved in terms of goodness of fit by the addition of the other independent variables (see deviance statistics, Table 20). The two-variable models with PRG and BO1/ISR as independent variables show significant effects for both these variables. However, the collinearity between the two variables BO1 and ISR leads to a loss of precision in the three-variable model. Neither BO1 nor ISR show significant effects, as the variance inflation leads to wide confidence intervals. The standard error of the risk ratio for the Rh prophylaxis program effect is not similarly affected, however, and the point estimate for the risk ratio (RR=0.10) from the three-variable model has fairly tight confidence bounds (95% confidence interval=0.03 to 0.33). Figure 20 shows the observed rate of infant death

from hemolytic disease of the newborn in Canada, along with the predicted rate of infant death from HDN in the absence of an Rh prophylaxis program. The predicted rates show the effect of changes in birth order and quality of infant care on infant deaths from hemolytic disease, while the difference between the two lines represents the effect of Rh prophylaxis.

Table 24A (Appendix) gives the risk difference estimates based on the beta coefficient estimates from the two-variable model. Modification of the effect of the independent variables is illustrated in Figures 21-22.

GOODNESS OF FIT: The goodness of fit, as assessed by deviance statistics, suggests that the fitted regression model with all three independent variables does not fit the observed data very well (Table 20), since the difference between the observed and fitted lines is statistically significant at the 5% level. However, the graphical depiction of the goodness of fit shows that the observed and fitted lines are in fact very similar (see Figure 23). This discordance between the statistical and graphical approaches to goodness of fit arises because deviance statistics break down when the sample size is very large [105]. An examination of the observed and fitted rates of infant death from hemolytic disease reveals that the values are generally similar.

ASSESSMENT OF COLLINEARITY: The three-variable model shows

collinearity between BO1 and ISR; the variances associated with the betas of these variables are inflated (Table 20), and the correlation between the parameter estimates is high (Table 25A, Appendix). Combining the two variables (Table 20) does not solve the problem, and the only recourse is to consider the results of the two-variable model with ISR and PRG. The effect of ISR from this model can be considered to subsume the effects of changes in BO1. This analysis reveals a 73% preventive fraction associated with non-program factors and a 91% reduction in outcome occurrence secondary to Rh prophylaxis.

4.1.3.3 OTHER ANALYSES

Analyses were also undertaken using data from Canada prior to 1963. The data for the years 1951-54 were included and a fourth independent variable (TRA) was added to the model to signify presence/absence of Rh-specific blood transfusions (see Methods, Section 3.1.6, Other analyses). The results of the analysis are shown in Table 21. The addition of the TRA variable is seen to significantly improve the goodness of fit of the model (deviance change=4.49, df=1, $p<0.05$). Collinearity between ISR and TRA results in an inflation of the variance of ISR (the correlation between parameter estimates is shown in Table 26A, Appendix). The effect of the Rh prophylaxis program (PF=95%) is similar to that obtained from the data set for the years 1963-68 and 1982-88, while the

effect of non-program factors is slightly reduced (66% in this analysis versus 72% in the previous analysis). Goodness of fit for the four-variable model was not acceptable as judged by deviance statistics (p just under 0.05), although graphically the observed and regression fitted values were very similar (Figure 24).

Table 18: Numbers and rates of infant deaths from hemolytic disease (per 100,000 live births) in Canada in 1951, 1963 and 1988 and levels of the factors affecting outcome occurrence. No infant deaths were recorded in 1988; the 1 death shown in the table represents an average of infant deaths observed in 1988 and 1989.

Year	Infant deaths from HDN		First births (%)	Infant survival rate/1000 livebirths	Rh type specific transfusions	Rh prophylaxis program
	No.	Rate				
1951	336	88.2	28.4	961.5	0	0
1963	289	62.1	26.4	973.7	1	0
1988	1	0.3	43.8	992.8	1	1

Table 19: Changes in the frequency of infant death from hemolytic disease between 1963 and 1988, as estimated using three different measures of impact (RD=risk difference per 100,000 livebirths, RR=risk ratio and PF=preventive fraction). No infant deaths from hemolytic disease were observed in 1988; the average of the infant deaths for the years 1988-89 is used in the table below for estimating the risk ratio.

	1951 vs. 1963	1963 vs. 1988	1951 vs. 1988
RD	26.12	61.78	87.90
RR	0.70	0.004	0.003
PF	29.62	99.57	99.70

Figure 19. Data from Canada showing rates of infant death from hemolytic disease of the newborn (per 100,000 live births) between 1950 and 1988.

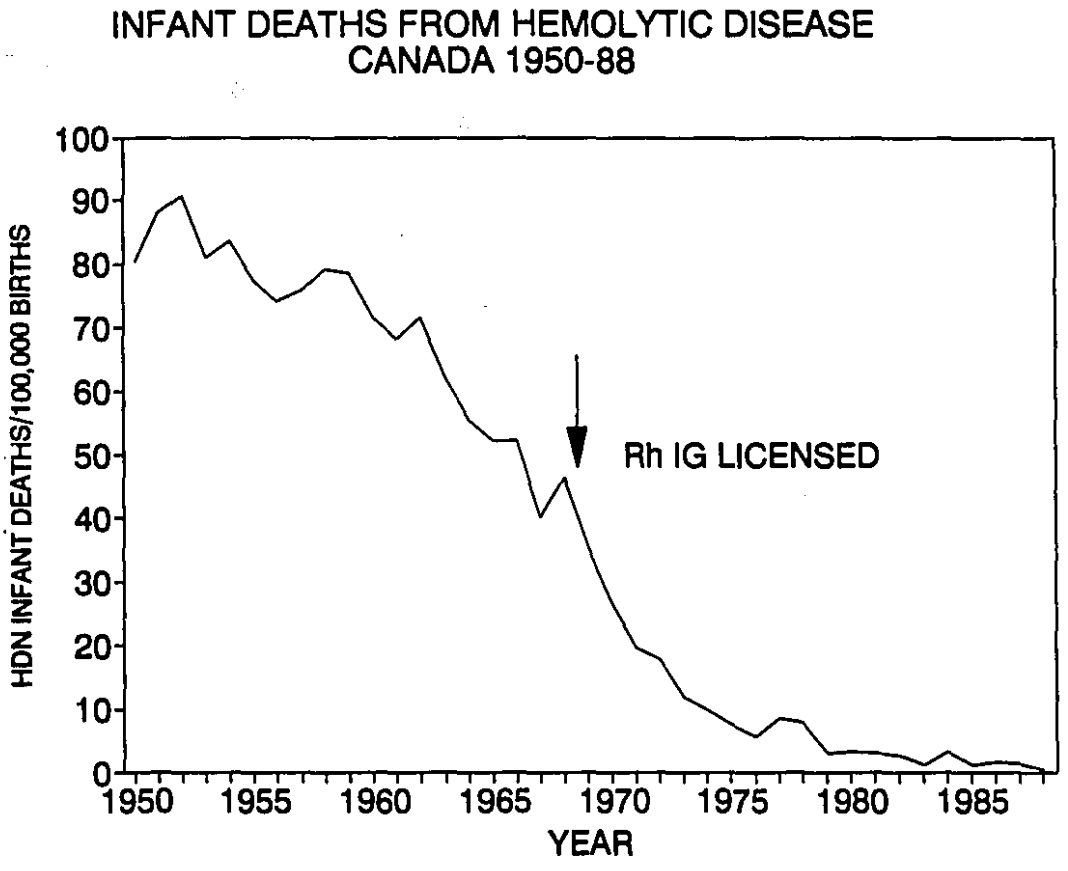


Table 20: Result of Poisson regression using data from Canada for the years 1963-68 and 1982-88, with rate of infant deaths from hemolytic disease of the newborn as the outcome and effects expressed as risk ratios and preventive fractions.

CANADA 1963-68, 1982-88
OUTCOME=INFANT DEATHS FROM HEMOLYTIC DISEASE

VARIABLE (MODEL)	BETA	SE	RR	PF	95% CI on PF
BO1	-0.138	0.005	0.09	91.0	89.5-92.3
DEVIANCE=426.64, df=11, p<0.001					
ISR	-0.185	0.007	0.03	97.1	96.2-97.7
DEVIANCE=88.48, df=11, p<0.001					
PRG	-3.478	0.157	0.03	96.9	95.8-97.7
DEVIANCE=37.58, df=11, p<0.001					
BO1	-0.028	0.007	0.61	39.0	23.0-51.8
PRG	-3.110	0.181	0.04	95.5	93.6-96.9
DEVIANCE=20.17, df=10, p<0.05					
ISR	-0.068	0.016	0.27	72.8	51.2-84.9
PRG	-2.409	0.292	0.09	91.0	84.1-94.9
DEVIANCE=18.53, df=10, p<0.05					
BO1	0.004	0.026	1.01	-6.5	-61.1-55.9
ISR	-0.076	0.059	0.23	76.7	-53.2-97.5
PRG	-2.331	0.629	0.10	90.3	66.7-97.2
DEVIANCE=18.51, df=9, p<0.05					
BO1, ISR	-1.393	0.706	0.25	75.2	-0.96-93.8
PRG	-2.331	0.629	0.10	90.3	66.7-97.2

BO1, ISR represents the combined effects of BO1 and ISR. The beta coefficient was calculated using the formula

$$\text{Beta} = (B_1 * (BO1_{(1963)} - BO1_{(1988)})) + (B_2 * (ISR_{(1963)} - ISR_{(1988)}))$$

The risk ratio thus represents the combined effects of changes observed in BO1 and ISR between 1963 and 1988.

Figure 20. Poisson regression of Canadian data showing the observed rate of infant death from hemolytic disease of the newborn (per 100,000 live births) and the rate predicted by the regression model assuming no program of Rh prophylaxis (i.e., PRG=0).

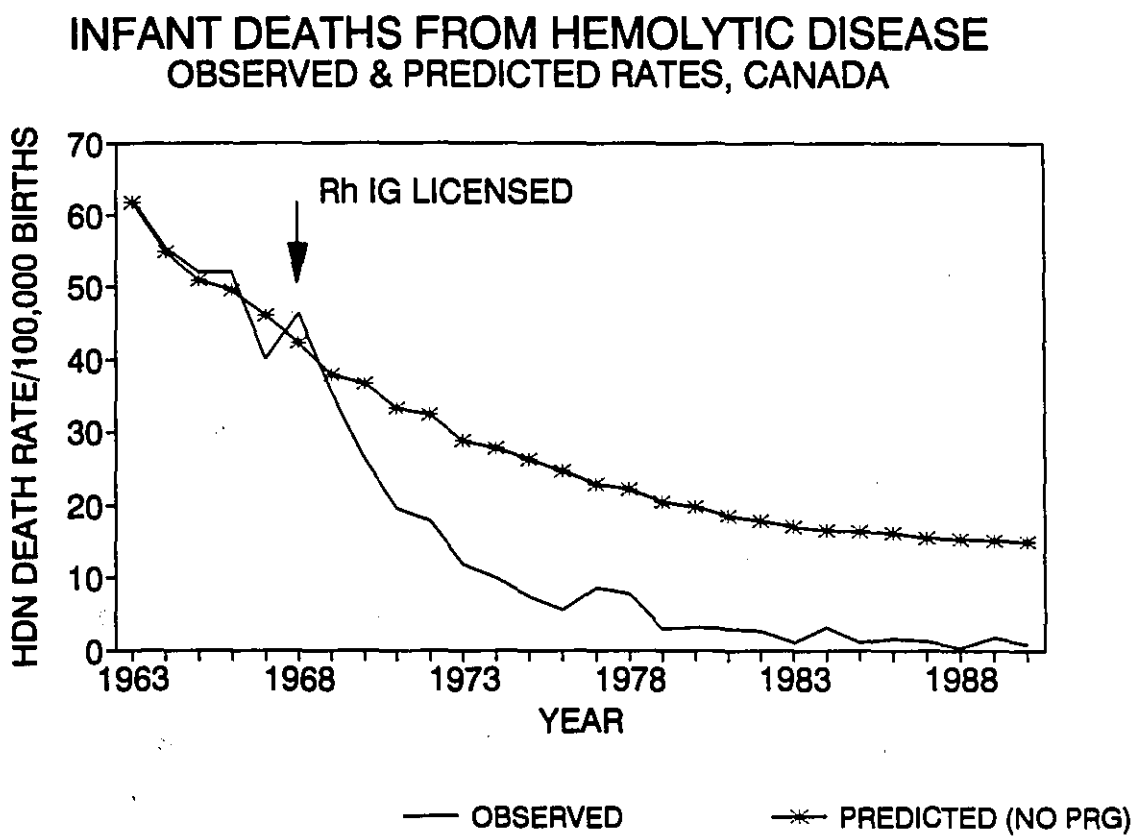


Figure 21. Poisson regression of Canadian data showing the effect of an Rh prophylaxis program on the rate of infant deaths from hemolytic disease (per 100,000 live births), with effect modification of the risk difference by non-program factors (BO1 and ISR).

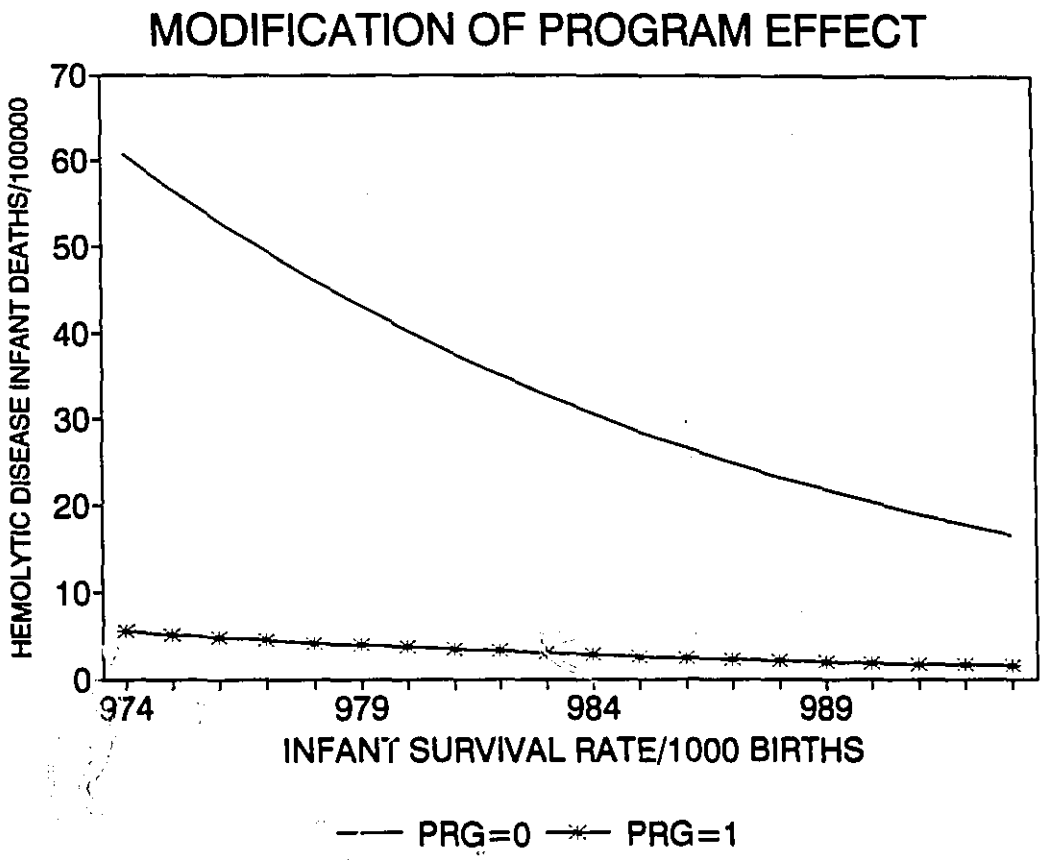


Figure 22. Poisson regression of Canadian data showing the effect of non-program factors (BO1 and ISR) on the rate of infant deaths from hemolytic disease (per 100,000 live births), with effect modification of the risk difference by the presence/absence of an Rh prophylaxis program.

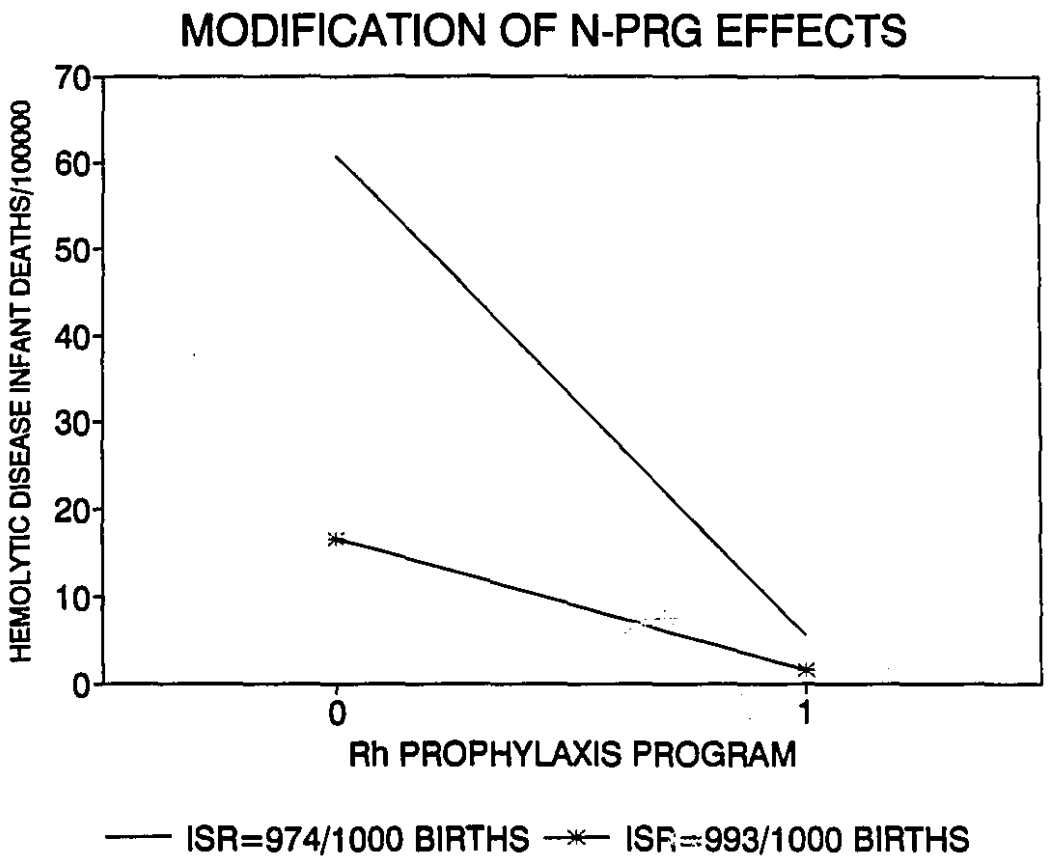


Figure 23. Poisson regression of Canadian data: graphical depiction of the goodness of fit of the model with infant deaths from hemolytic disease of the newborn (per 100,000 live births) as the outcome variable and proportion of first births, infant survival rate and presence/absence of a Rh prophylaxis program as independent variables.

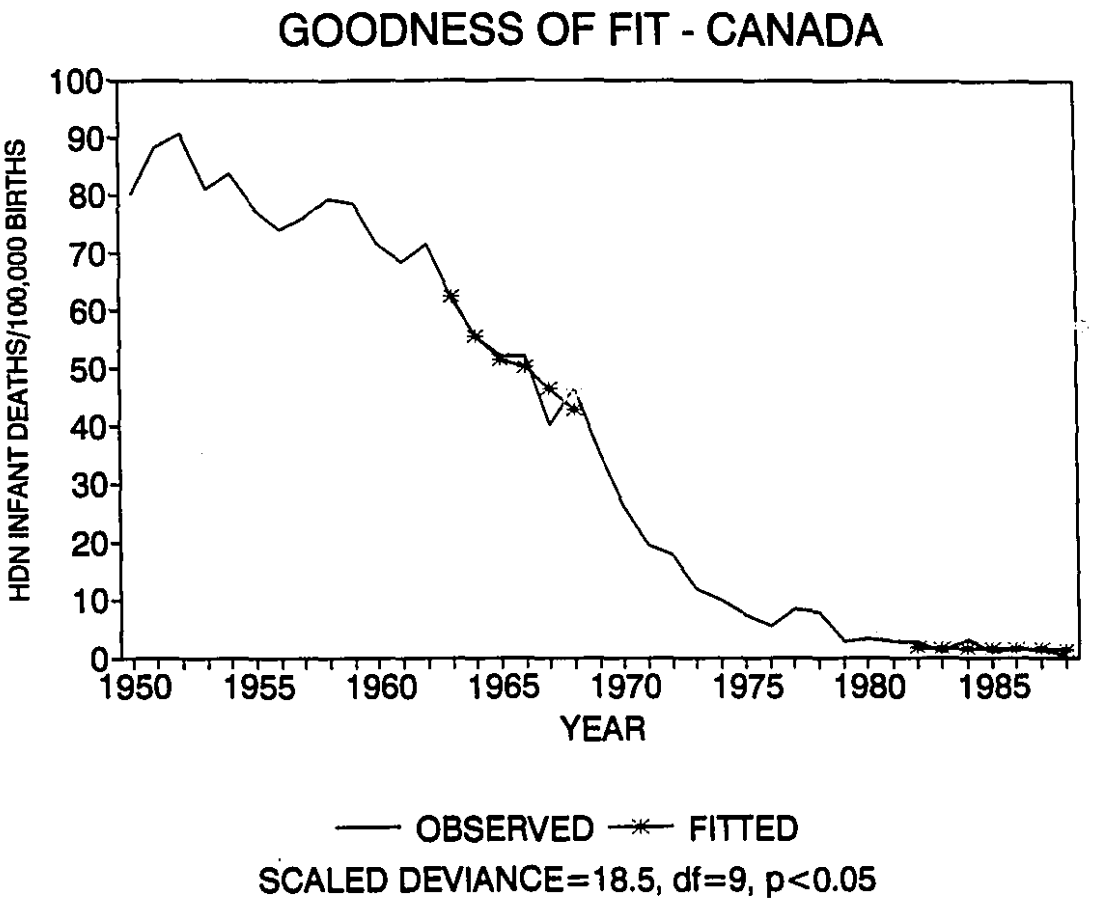


Table 21: Results of Poisson regression using data from Canada for the years 1951-54, 1963-68 and 1982-88, with rate of infant deaths from hemolytic disease of the newborn as the outcome and effects expressed as risk ratios and preventive fractions. TRA=presence/absence of Rh type-specific blood transfusions.

CANADA 1951-54, 1963-68, 1982-88

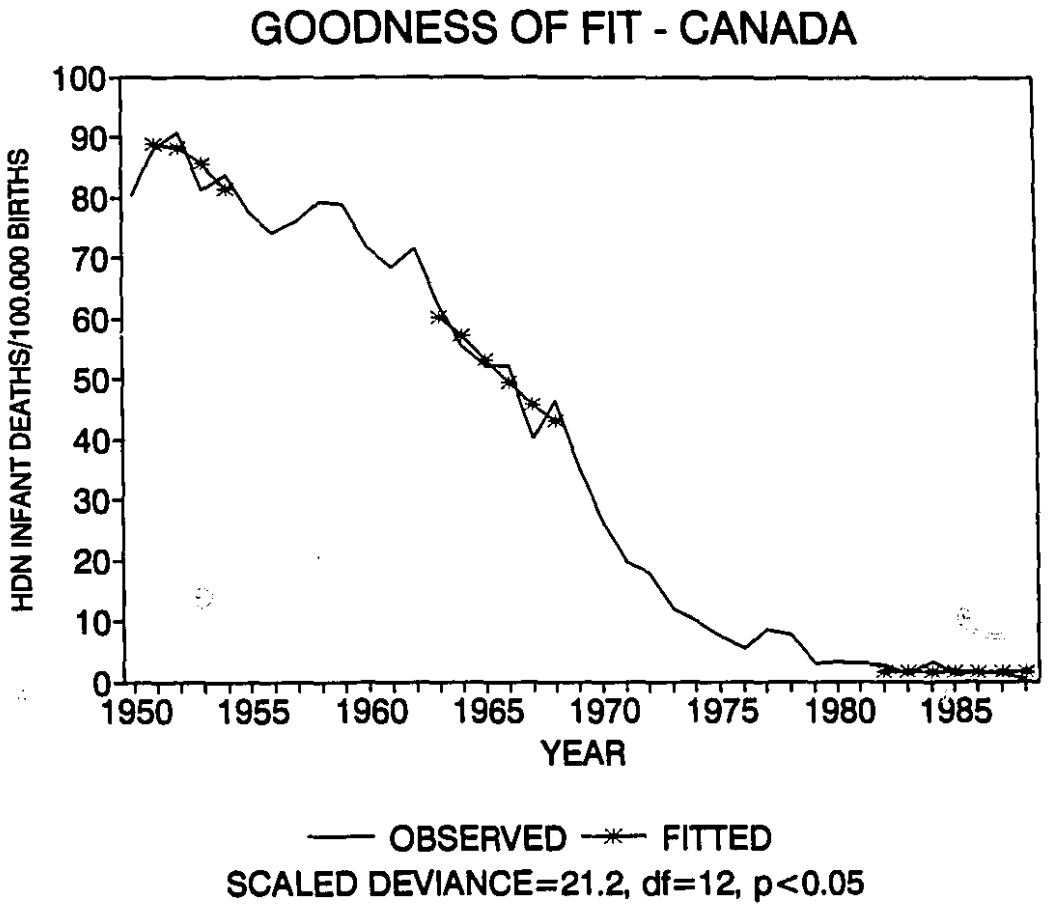
VARIABLE (MODEL)	BETA	SE	RR	PF	95% CI on PF
BO1	-0.150	0.004	0.10	90.0	88.6-91.2
DEVIANCE=497.8, df=15, p<0.001					
ISR	-0.082	0.002	0.08	92.4	91.4-93.3
DEVIANCE=539.6, df=15, p<0.001					
PRG	-3.709	0.155	0.03	97.6	96.7-98.2
DEVIANCE=208.4, df=15, p<0.001					
TRA	-1.194	0.038	0.30	69.7	67.3-71.9
DEVIANCE=1576.5, df=15, p<0.001					
BO1	-0.017	0.007	0.77	23.3	4.3-38.5
ISR	-0.034	0.004	0.34	65.8	57.6-72.5
PRG	-2.730	0.181	0.06	93.5	90.7-95.4
DEVIANCE=25.65, df=13, p<0.05					
TRA	-0.247	0.115	0.78	21.9	2.0-37.7
BO1	-0.022	0.008	0.71	28.6	10.0-43.4
ISR	-0.015	0.010	0.62	38.3	-10.8-65.6
PRG	-2.953	0.209	0.05	94.8	92.1-96.5
DEVIANCE=21.16, df=12, p<0.05					
TRA, BO1, ISR *	-1.066	0.167	0.34	65.6	52.3-75.2
PRG	-2.953	0.209	0.05	94.8	92.1-96.5

* TRA, BO1, ISR represents the combined effects of TRA, ISR AND BO1. The beta coefficient was calculated using the formula

$$\text{Beta} = (B_1 * (\text{TRA}(1951) - \text{TRA}(1988))) + (B_2 * (\text{BO1}(1951) - \text{BO1}(1988))) + (B_3 * (\text{ISR}(1951) - \text{ISR}(1988)))$$

The risk ratio thus represents the combined effects of changes observed in TRA, ISR and BO1 between 1951 and 1988.

Figure 24. Poisson regression of Canadian data: graphical depiction of the goodness of fit of the model with infant deaths from hemolytic disease of the newborn (per 100,000 live births) as the outcome variable and proportion of first births, infant survival rate, presence/absence of Rh-specific blood transfusion and presence/absence of a program of Rh prophylaxis as independent variables.



4.1.4 UNITED STATES - TOTAL POPULATION

This analysis was identical to the one using Canadian data. Infant deaths from hemolytic disease of the newborn constituted the outcome of interest and the independent variables included in the model were the same as those used in the analysis of the Canadian data. The routine categorization of U.S. statistics according to race (white vs nonwhite) provided an opportunity to examine effects by race to see if relationships between determinants and disease were affected by racial characteristics. The analysis below uses data from the entire population; subsequent analyses (Sections 4.1.5 and 4.1.6) examine whites and nonwhites separately.

4.1.4.1 CRUDE CHANGES BETWEEN 1951, 1963 AND 1988

Tables 22-23 provide outcome rates (see also Figure 25), rates of independent variables and crude measures of effect estimated across the three study periods. The rates of infant death from hemolytic disease of the newborn in the United States are different from those observed in the Canadian population for comparable years. Rates from Canada for 1951 and 1963 are significantly higher at 83.2 and 62.1 per 100,000 live births, respectively, although the 1988 Canadian rate is marginally lower at 0.3 per 100,000 live births (corresponding U.S. rates being 68.8, 44.8 and 1.2 per 100,000 live births, respectively). The differences in these rates is responsible for some large differences in the crude measures of effect

between Canada and the United States. Differences are also seen with regard to the proportion of first births and infant survival rate between Canada and the United States.

4.1.4.2 POISSON REGRESSION

Results from the analysis of the U.S. data (total population) are shown in Table 24, with effects expressed in terms of risk ratios and preventive fractions. The results in terms of risk differences are shown in Table 27A (Appendix).

The results of the analysis of this data set show qualitative similarities with the results of the analysis of the Canadian data. The direction of the various coefficients are the same and BO1 and ISR exhibit collinearity problems. However, there are differences in the magnitudes of the beta coefficients. For instance, the BO1 and ISR coefficients have larger values in the US data set, while Canadian Rh prophylaxis program effects marginally exceed those from the United States. The collinearity between BO1 and ISR led to an inflation of the standard errors of the betas of both these variables, although this did not lead to a non-significant estimate for ISR in the U.S. data (attributable to the larger sample size). On combining the effects of BO1 and ISR it is seen that non-program factors were responsible for a 76% decline in infant deaths from hemolytic disease, while Rh prophylaxis was responsible for an 88% decrease. This is

Table 22: Number and rate of infant deaths from hemolytic disease (per 100,000 live births) in the United States (total population) in 1951, 1963 and 1988 and levels of three factors affecting outcome occurrence.

Year	Infant deaths from HDN		First births (%)	Infant survival rate/1000 livebirths	Rh type specific transfusions	Rh pro-phylaxis program
	No.	Rate				
1951	2627	68.8	31.5	971.6	0	0
1963	1835	44.8	27.6	974.8	1	0
1988	45	1.2	41.0	990.0	1	1

Table 23: Changes in the annual rate of infant death from hemolytic disease in the Unites States (total population) between 1951 and 1963, 1963 and 1988 and 1951 and 1988, as estimated using three different measures of effect (RD=risk difference per 100,000 live births, RR=risk ratio, PF=preventive fraction).

	1951 vs 1963	1963 vs 1988	1951 vs 1988
RD	23.99	43.63	67.62
RR	0.65	0.03	0.02
PF	34.88	97.43	98.33

Figure 25. Data from the United States by race, showing rates of infant death from hemolytic disease of the newborn per 100,000 live births between 1950 and 1988.

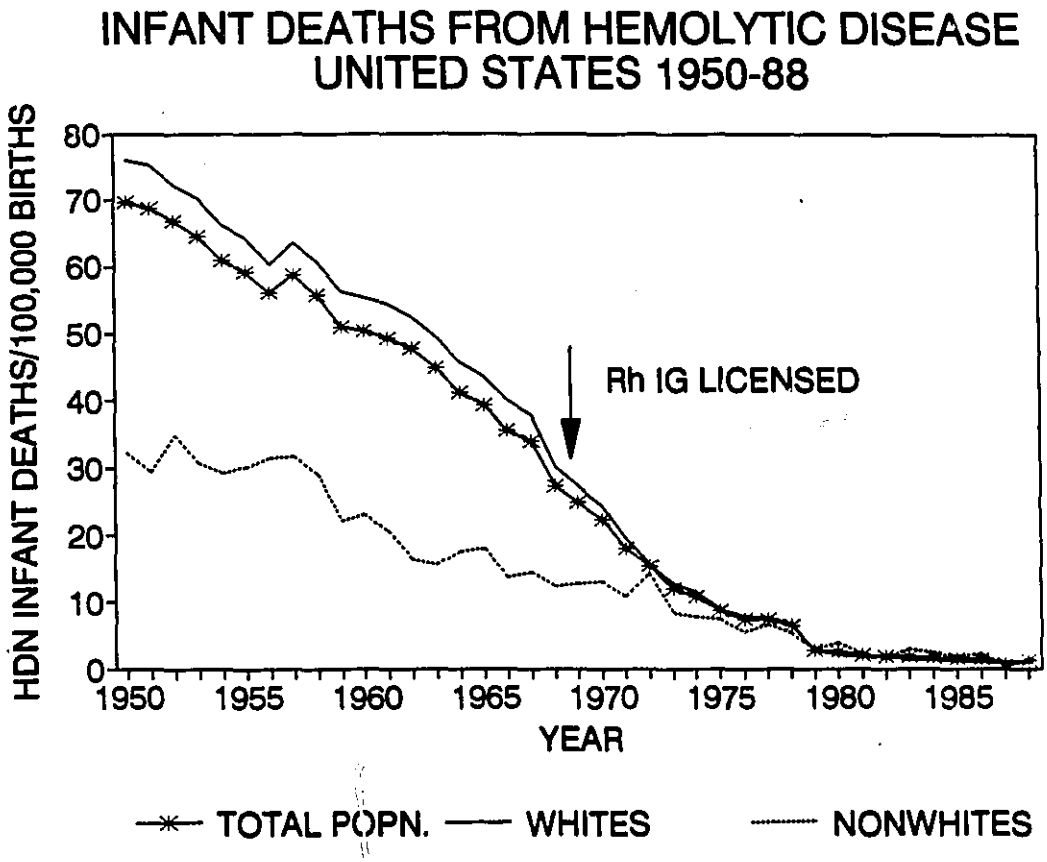


Table 24: Results of Poisson regression using data from the United States (total population) for the years 1963-68 and 1982-88, with rate of infant deaths from hemolytic disease of the newborn as the outcome and effects expressed as risk ratios and preventive fractions.

USA TOTAL POPULATION 1963-68, 1982-88

VARIABLE (MODEL)	BETA	SE	RR	PF	95% CI on PF
BO1	-0.1744	0.0022	0.10	90.4	89.9-91.0
DEVIANCE=2820.0, df=11, p<0.001					
ISR	-0.2308	0.0034	0.03	97.0	96.7-97.3
DEVIANCE=193.7, df=11, P<0.001					
PRG	-3.3250	0.0544	0.04	96.4	96.0-96.8
DEVIANCE=219.5, df=11, p<0.001					
BO1	-0.0427	0.0032	0.56	43.7	38.8-48.2
PRG	-2.9030	0.0632	0.05	94.5	93.8-95.2
DEVIANCE=35.81, df=10, p<0.001					
ISR	-0.1218	0.0090	0.16	84.3	79.5-88.0
PRG	-1.7080	0.1322	0.18	81.9	76.5-86.0
DEVIANCE=30.92, df=10, p<0.01					
BO1	-0.0153	0.0110	0.81	18.5	-8.0-39.0
ISR	-0.0808	0.0308	0.29	70.7	26.6-88.3
PRG	-2.1020	0.3120	0.12	87.8	77.5-93.4
DEVIANCE=28.97, df=9, p<0.01					
BO1 ⌐ ISR ⌙ *	-1.433	0.3303	0.24	76.1	54.4-87.5
PRG	-2.1020	0.3120	0.12	87.8	77.5-93.4

*
BO1⌐
ISR⌙ represents the combined effects of BO1 and ISR. The beta coefficient was calculated using the formula

$$\text{Beta} = (B_1 * (\text{BO1}(1963) - \text{BO1}(1988))) + (B_2 * (\text{ISR}(1963) - \text{ISR}(1988)))$$

The risk ratio thus represents the combined effects of changes observed in BO1 and ISR between 1963 and 1988.

Figure 26. Poisson regression of data from the United States (total population) showing the observed rate of infant death from hemolytic disease of the newborn (per 100,000 live births) and the rate predicted by the regression model assuming no program of Rh prophylaxis.

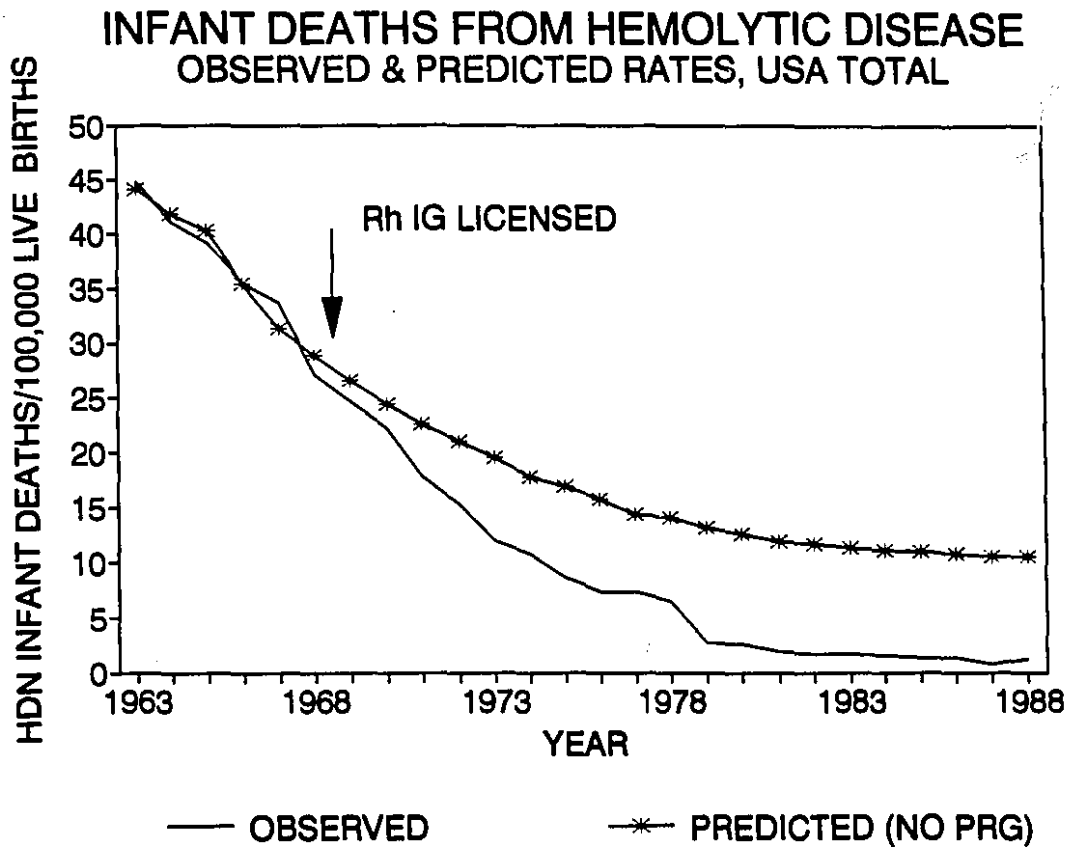
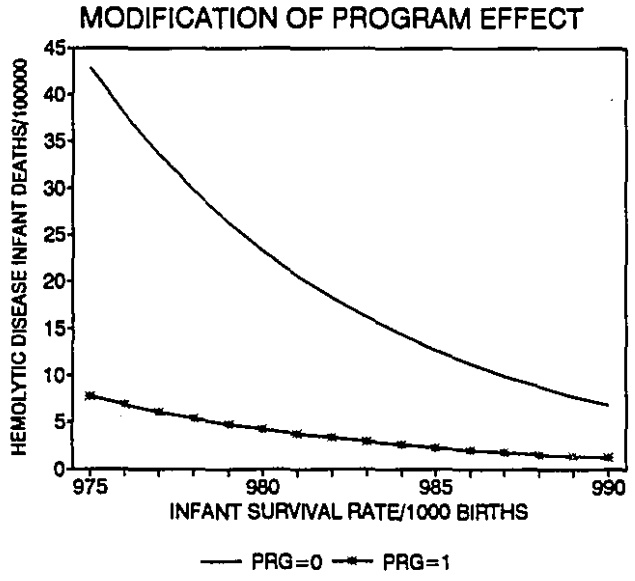


Figure 27. Poisson regression of U.S. data (total population). The upper figure shows the effect of an Rh prophylaxis program on the rate of infant deaths from hemolytic disease (per 100,000 live births) with effect modification of the risk difference by non-program factors (BO1 and ISR). The lower figure depicts modification of the risk difference associated with non-program factors by the presence/absence of an Rh prophylaxis program.



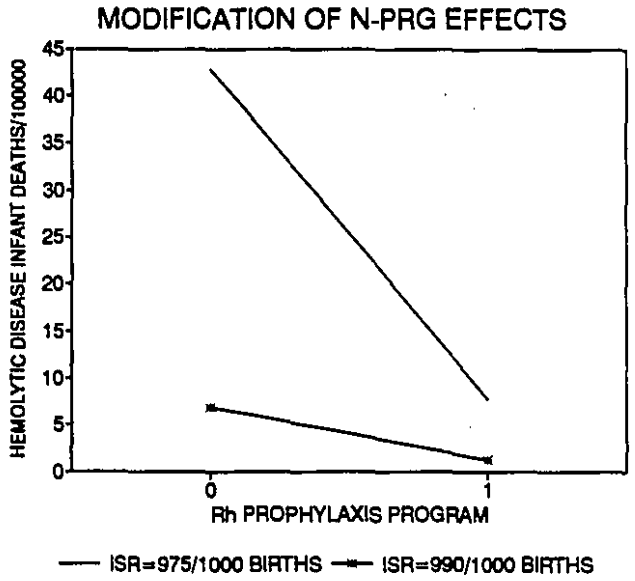
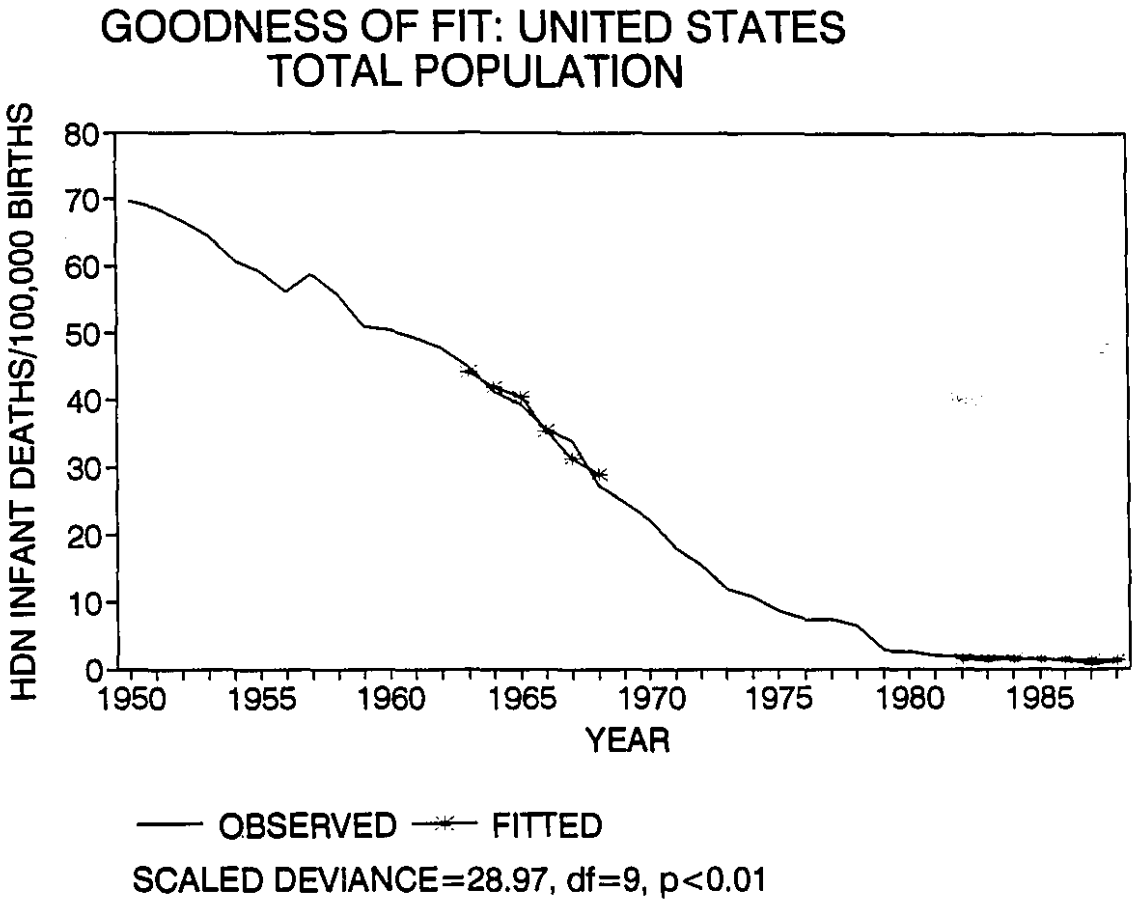


Figure 28. Poisson regression of data from the United States (total population): graphical depiction of the goodness of fit, with infant deaths from hemolytic disease of the newborn (per 100,000 live births) as the outcome variable and proportion of first births, infant survival rate, and presence/absence of an Rh prophylaxis program as independent variables.



similar to the cause-specific attribution for disease reduction seen from the Canadian analysis (75% and 90%, respectively). The Rh prophylaxis program appears to have been slightly less effective in the United States, while non-program factors appear to have had a slightly greater effect. This is especially evident in the results from the two-variable model with ISR and PRG. Figure 26 shows the observed rate of infant deaths from hemolytic disease of the newborn in the United States (total population), along with the predicted rate of infant death from HDN in the absence of an Rh prophylaxis program. The predicted rates show the effect of changes in birth order and quality of infant care on infant deaths from hemolytic disease, while the difference between the two lines represents the effect of Rh prophylaxis. Results of the Poisson regression, with effects expressed as risk differences, are shown in Table 27A (Appendix) and pictorially in Figures 27, 17A-19A (Appendix).

GOODNESS OF FIT: As with the Canadian analysis, the deviance statistics suggest that the goodness of fit of all the two- and three-variable models is poor. The graphical depiction, however, shows a very close fit (Figure 28).

ASSESSMENT OF COLLINEARITY: The imprecision of the estimate of BO1 in the three-variable model suggests its collinear association with one of the other variables. The correlation

of parameter estimates shows close correlation between all the beta coefficients (Table 28A, Appendix). Given this collinearity problem, effects have to be assessed from either the two-variable model (with ISR and PRG) or the last model in Table 24 in which the effects of the non-program variables from the three-variable model are combined.

4.1.4.3 OTHER ANALYSES

United States data for the years 1951-54 were included in the data set for Poisson regression, with a term to indicate the presence/absence of Rh-specific blood transfusions. The results are shown in Table 25; the beta coefficients are very similar to those obtained after regressing the data for the years 1963-68 and 1982-88. Goodness of fit is shown using deviance statistics (Table 25) and graphically (Figure 29). The large sample size results in a "poor" goodness of fit assessment according to the statistical index, although the graphical depiction shows a good fit. No collinearity problems were present in this analysis, with all the beta coefficients being associated with standard errors precise enough to yield significant 95% confidence intervals. Correlation of parameter estimates are given in Table 29A, Appendix. The effects of Rh prophylaxis (preventive fraction=88%) and non-program factors (preventive fraction=84%) are similar to those obtained from regression of the data restricted to the years after 1963.

Table 25: Result of Poisson regression using data from the United States (total population) for the years 1951-54, 1963-68 and 1982-88, with rate of infant deaths from hemolytic disease of the newborn as the outcome and effects expressed as risk ratios and preventive fractions.

USA TOTAL POPULATION 1951-54, 1963-68, 1982-88

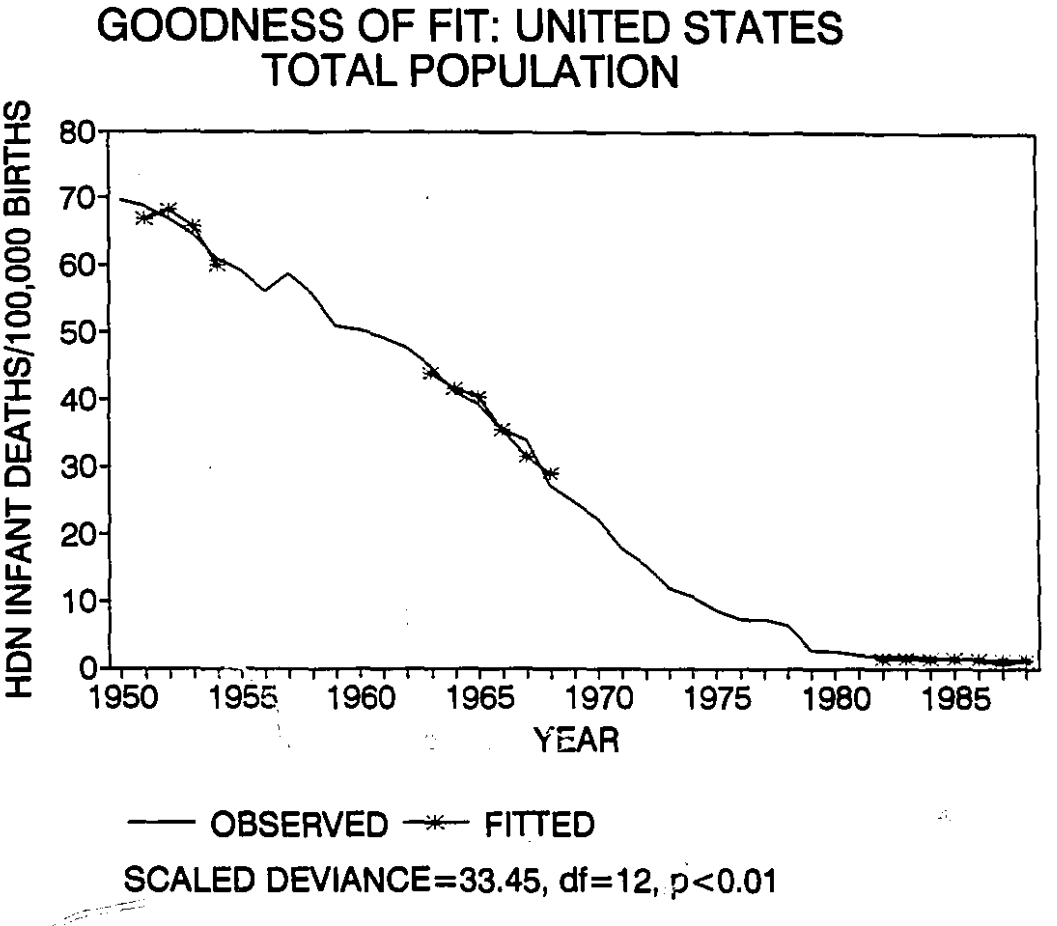
VARIABLE (MODEL)	BETA	SE	RR	PF	95% CI on PF
BO1	-0.1830	0.0019	0.18	82.7	82.1-83.3
DEVIANCE=4229.2, df=15, p<0.001					
ISR	-0.1937	0.0021	0.03	97.2	97.0-97.4
DEVIANCE=523.4, df=15, p<0.001					
PRG	-3.5930	0.0538	0.03	97.3	96.9-97.5
DEVIANCE=1693.1, df=15, p<0.001					
TRA	-1.2900	0.0146	0.27	72.5	71.7-73.3
DEVIANCE=10696, df=15, p<0.001					
BO1	-0.0040	0.0034	0.96	3.8	-2.6-9.79
ISR	-0.1331	0.0041	0.09	91.4	90.0-92.6
PRG	-1.5360	0.0757	0.21	78.5	75.0-81.4
DEVIANCE=69.02, df=13, p<0.01					
TRA	-0.2123	0.0353	0.81	19.1	13.3-24.5
BO1	-0.0138	0.0038	0.88	12.4	5.9-18.4
ISR	-0.0822	0.0094	0.22	78.0	69.0-84.3
PRG	-2.0970	0.1202	0.12	87.7	84.5-90.3
DEVIANCE=33.45, df=12, p<0.01					
TRA, BO1, ISR *	-1.8530	0.1230	0.16	84.3	80.0-87.7
PRG	-2.0970	0.1202	0.12	87.7	84.5-90.3

* TRA, BO1, ISR represents the combined effects of TRA, ISR AND BO1. The beta coefficient was calculated using the formula

$$\text{Beta} = (B_1 * (\text{TRA}(1951) - \text{TRA}(1988))) + (B_2 * (\text{BO1}(1951) - \text{BO1}(1988))) + (B_3 * (\text{ISR}(1951) - \text{ISR}(1988)))$$

The risk ratio thus represents the combined effects of changes observed in TRA, ISR and BO1 between 1951 and 1988.

Figure 29. Poisson regression of data from the United States (total population): graphical depiction of the goodness of fit, with infant deaths from hemolytic disease of the newborn (per 100,000 live births) as the outcome variable and proportion of first births, infant survival rate, presence/absence of Rh-specific blood transfusion and presence/absence of an Rh prophylaxis program as independent variables.



4.1.5 UNITED STATES – WHITES ONLY

4.1.5.1 CRUDE CHANGES BETWEEN 1951, 1964 AND 1988

The rates of infant death from hemolytic disease of the newborn among U.S. whites (Table 26 and Figure 25) are higher than rates from the total U.S. population for the same years. This is an expected finding, since nonwhites have a lower prevalence of the Rh-negative phenotype, which predisposes them to lower rates of morbidity from the disease. The crude Canadian rates of infant death from hemolytic disease for 1951 and 1963 are, however, higher than the rates among U.S. whites for the years 1951 and 1964. On the other hand, the crude rate for 1988 is marginally lower in Canada when compared with the rate for U.S. whites. Three factors need to be considered when addressing these differences. First, the difference in racial composition; the Canadian rate is based on the total population, which includes a small proportion of nonwhites, who experience lower rates of hemolytic disease. This fact, however, should lead to a lower rate for the total Canadian population and does not explain the higher Canadian rates. The other factors which are more likely explanations for the higher rates in 1951 and 1963/64 have to do with birth order distribution and infant survival rates during those years. These indices were more favourable among US whites in 1951 and 1964 and could explain the difference. Since the crude measures of effect (Table 27) are based on these rates, differences seen in these measures can be similarly explained

as a consequence of differences in background rates.

4.1.5.2 POISSON REGRESSION

The results of Poisson regression using the data from U.S. whites for the years 1964-68 and 1982-88 are presented in Table 28. The results are very similar to the results of the analysis done using the total population of the United States. This is to be expected, since whites constitute a majority of the total U.S. population. Marginal differences are seen with regard to the beta coefficients of the independent variables. The data from U.S. whites yields a slightly greater protective effect for ISR while the beta coefficients for BO1 and PRG are slightly reduced. The three-variable model shows the beta for BO1 to be non-significant. Figure 30 shows the observed rate of infant death from hemolytic disease of the newborn in the United States (whites only), along with the predicted rate of infant death from HDN in the absence of an Rh prophylaxis program. Results of Poisson regression with effects expressed as risk differences are shown in Table 30A (Appendix) and pictorially in Figures 20A-23A.

GOODNESS OF FIT: Goodness of fit according to deviance statistics appears unacceptably low, though in fact the fitted regression line is remarkably similar to the observed one (Figure 31).

Table 26: Number and rate of infant deaths from hemolytic disease (per 100,000 live births) in the United States (whites only) in 1951, 1964 and 1988 and levels of three factors affecting outcome occurrence.

Year	Infant deaths from HDN		First births (%)	Infant survival rate/1000 livebirths	Rh type specific transfusions	Rh prophylaxis program
	No.	Rate				
1951	2467	75.3	32.6	974.2	0	0
1964	1544	45.8	29.8	978.4	1	0
1988	34	1.1	41.6	991.5	1	1

Table 27: Changes in the annual rate of infant deaths from hemolytic disease in the Unites States (whites only) between 1951 and 1964, 1964 and 1988 and 1951 and 1988, as estimated using three different measures of effect (RD=risk difference, RR=risk ratio, PF=preventive fraction).

	1951 vs 1964	1964 vs 1988	1951 vs 1988
RD	29.50	44.71	74.21
RR	0.61	0.02	0.01
PF(%)	39.16	97.56	98.52

Table 28: Results of Poisson regression using data from the United States (whites only) for the years 1964-68 and 1982-88, with rate of infant deaths from hemolytic disease of the newborn as the outcome and effects expressed as risk ratios and preventive fractions.

USA WHITES ONLY 1964-68, 1982-88

VARIABLE (MODEL)	BETA	SE	RR	PF	95% CI on PF
BO1	-0.2074	0.0028	0.09	91.2	90.6-91.8
DEVIANCE=2350.2, df=10, p<0.001					
ISR	-0.2832	0.0047	0.02	97.6	97.2-97.8
DEVIANCE=139.1, df=10, p<0.001					
PRG	-3.4730	0.0638	0.03	96.9	96.5-97.3
DEVIANCE=129.31, df=10, p<0.001					
BO1	-0.0437	0.0044	0.60	40.1	33.7-45.8
PRG	-3.0960	0.0745	0.05	95.5	94.8-96.1
DEVIANCE=29.07, df=9, p<0.01					
ISR	-0.1417	0.0136	0.16	84.4	77.8-89.0
PRG	-1.8580	0.1686	0.16	84.4	78.3-88.8
DEVIANCE=19.45, df=9, p<0.05					
BO1	-0.0016	0.0142	0.98	1.9	-26.5-29.2
ISR	-0.1370	0.0441	0.17	83.4	48.5-94.6
PRG	-1.8980	0.3914	0.15	85.0	67.7-93.0
DEVIANCE=19.44, df=8, p<0.05					
BO1 ISR *	-1.8140	0.5117	0.16	83.7	55.5-94.0
PRG	-1.8980	0.3914	0.15	85.0	67.7-93.0

* See table 22 for explanation.

Figure 30. Poisson regression of data from the United States (whites only), showing the observed rate of infant deaths from hemolytic disease of the newborn (per 100,000 live births) and the rate predicted by the regression model assuming no program of Rh prophylaxis.

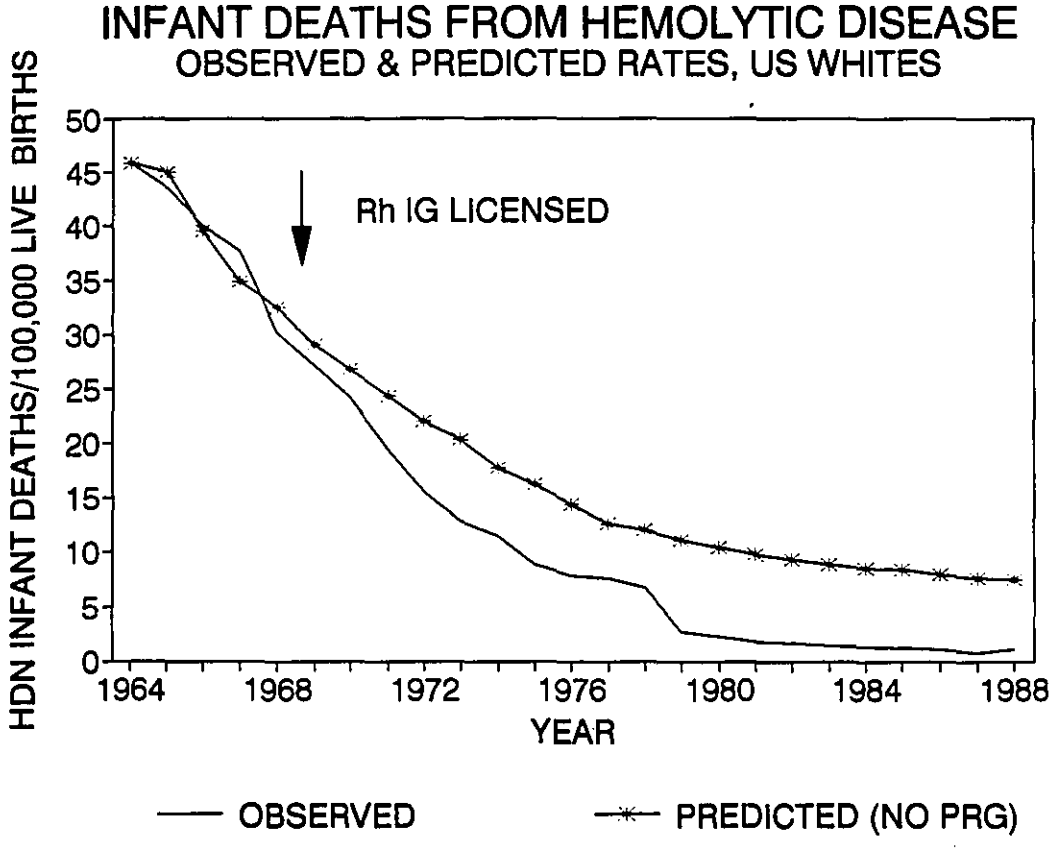
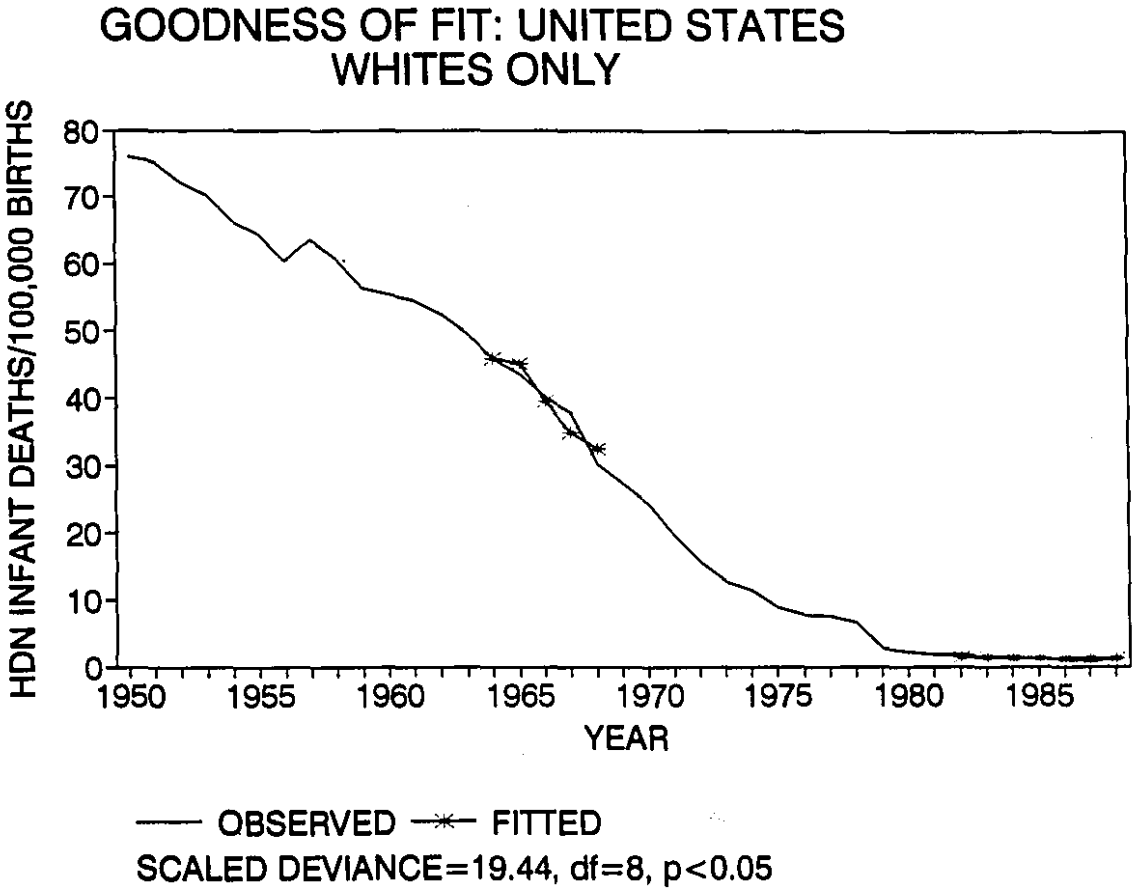


Figure 31. Poisson regression of data from the United States (whites only): graphical depiction of the goodness of fit, with infant deaths from hemolytic disease of the newborn (per 100,000 live births) as the outcome variable and proportion of first births, infant survival rate, and presence/absence of an Rh prophylaxis program as independent variables.



ASSESSMENT OF COLLINEARITY: The precision of the BO1 estimate was affected because of collinearity between this variable and ISR. Although the correlation of parameter estimates (Appendix, Table 31A) shows that all estimates are closely correlated, no standard error inflation is seen in the two-variable models (BO1 and PRG or ISR and PRG). This suggests collinearity between BO1 and ISR. The preventive fraction estimates for program and non-program effects are similar whether these figures are obtained from the two-variable (ISR and PRG) model or from the three-variable model with the BO1 and ISR estimates summed together. Non-program factors were responsible for 84% of the decline, while Rh prophylaxis was responsible for 85% of the reduction in infant deaths from hemolytic disease.

4.1.5.3 OTHER ANALYSES

Results of the Poisson regression analysis using data from 1951-54, 1964-68 and 1982-88 are presented in Table 29. Again the results are very similar to those obtained from the same analysis using data from the total U.S. population. The point estimates of the beta coefficients from this analysis are also similar to those obtained using data from 1964-68 and 1982-88. The four-variable model has an acceptable graphical goodness of fit (Figure 32) and shows no serious variance inflation due to collinearity in spite of correlations between independent variables (see Table 32A, Appendix, for correlations among

parameter estimates). Non-program factors were responsible for 84% of the decline, while the prophylaxis program was responsible for 90% of the mortality reduction.

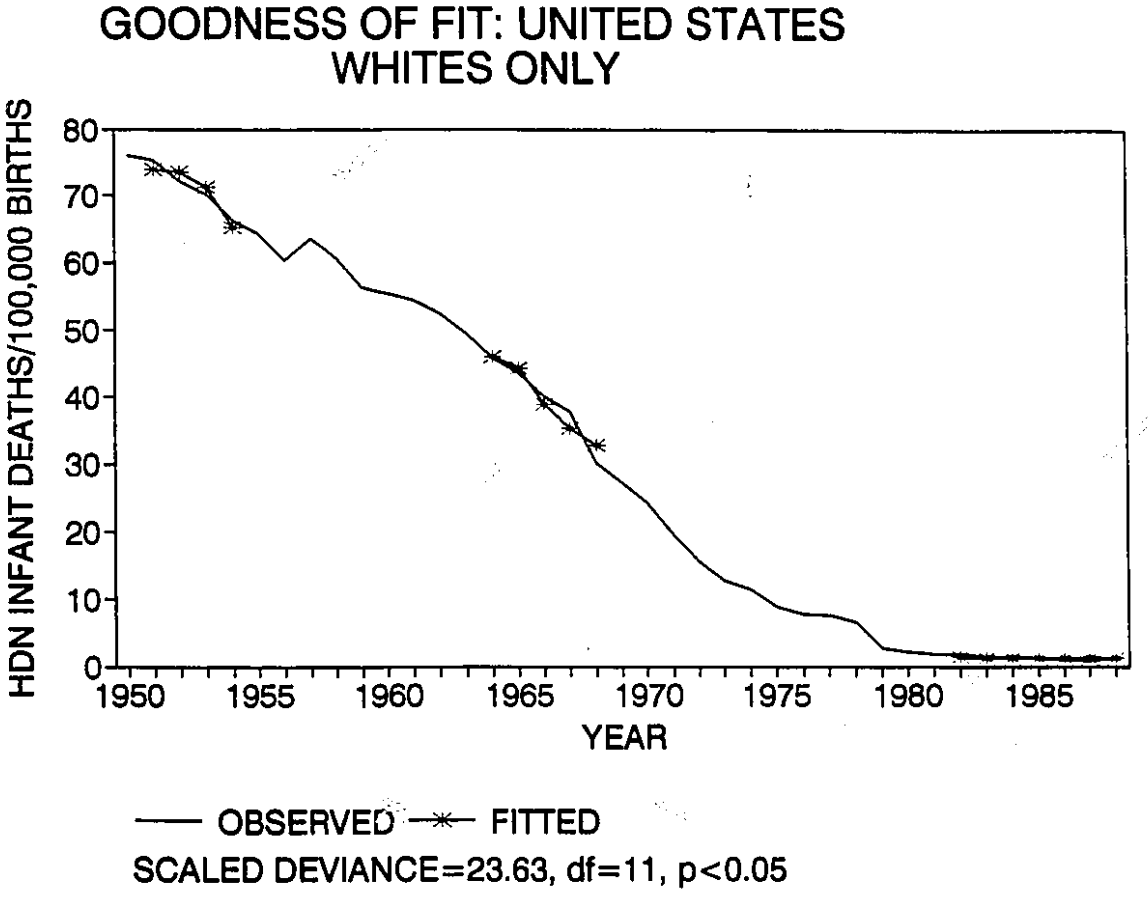
Table 29: Results of Poisson regression using data from the United States (whites only) for the years 1951-54, 1964-68 and 1982-88, with rate of infant deaths from hemolytic disease of the newborn as the outcome and effects expressed as risk ratios and preventive fractions.

USA WHITES ONLY 1951-54, 1964-68, 1982-88

VARIABLE (MODEL)	BETA	SE	RR	PF	95% CI on PF
BO1	-0.2066	0.0022	0.16	84.3	83.6-84.9
DEVIANCE=3345, df=14, p<0.001					
ISR	-0.2012	0.0022	0.03	96.9	96.7-97.1
DEVIANCE=817.91, df=14, p<0.001					
PRG	-3.7870	0.0630	0.02	97.7	97.4-98.0
DEVIANCE=1439, df=14, p<0.001					
TRA	-1.3960	0.0162	0.25	75.2	74.4-76.0
DEVIANCE=8722, df=14, p<0.001					
BO1	-0.0137	0.0041	0.88	11.5	4.9-17.7
ISR	-0.1187	0.0043	0.13	87.2	85.1-88.9
PRG	-2.0100	0.0804	0.13	86.6	84.3-88.6
DEVIANCE=31.68, df=12, p<0.01					
TRA	-0.1320	0.0465	0.88	12.4	4.0-20.0
BO1	-0.0149	0.0041	0.87	12.5	5.9-18.6
ISR	-0.0916	0.0105	0.20	79.5	70.7-85.6
PRG	-2.3000	0.1299	0.10	90.0	87.1-92.2
DEVIANCE=23.63, df=11, p<0.05					
TRA, BO1, ISR *	-1.849	0.1298	0.16	84.3	79.7-87.8
PRG	-2.3000	0.1299	0.10	90.0	87.1-92.2

* See table 23 for explanation.

Figure 32. Poisson regression of data from the United States (whites only): graphical depiction of the goodness of fit, with infant deaths from hemolytic disease of the newborn (per 100,000 live births) as the outcome variable and proportion of first births, infant survival rate, presence/absence of Rh-specific blood transfusion and presence/absence of an Rh prophylaxis program as independent variables.



4.1.6 UNITED STATES – NONWHITES ONLY

4.1.6.1 CRUDE CHANGES BETWEEN 1951, 1964 AND 1968

The crude rates of hemolytic disease among nonwhites across the different years show some unique features (Table 30 and Figure 25). The outcome rates for 1951 and 1964 are much lower when compared to similar figures for Canada or whites from the United States. This is in spite of lower rates of infant survival and first order birth proportion and is due to differences in racial characteristics, i.e., lower prevalence of the Rh-negative phenotype. However, the infant death rate from hemolytic disease among nonwhites for 1988 is approximately the same as that for US whites. This is unexpected and is apparently a consequence of changes over the decades (differential access to Rh prophylaxis, is a possibility) that have acted to eliminate the racial advantage enjoyed by nonwhites in the context of hemolytic disease.

These rates affect the magnitude of the risk differences and ratios estimated across the study periods (Table 31). The risk differences are much smaller than those seen in previous analyses, although the risk ratio from 1951 to 1964 is very similar to that seen among whites during the same period. However, the risk ratios between 1964 and 1988 (and also for the entire period 1951 to 1988) are very different from those seen among US whites. This may not be obvious given the nature of the scale on which protective risk ratios are expressed. For instance a risk ratio of 0.02 for

U.S. whites (1964 versus 1988) means that the death rate declined by a factor of 50 while a risk ratio of 0.07 for nonwhites (1964 versus 1988) means that the death rate fell by a factor of 14.

4.1.6.2 POISSON REGRESSION

The Poisson regression analysis for nonwhites yielded results different from those presented so far (Table 32). The model with ISR as the sole explanatory term showed a goodness of fit that was far more acceptable than that seen in any other data set (deviance=23.1, df=10, $p<0.05$ compared to a deviance of 139.1, df=10, $p<0.001$ for whites). These deviance values are not directly comparable, however, given the large difference in sample size. Instead, the goodness of fit for the model containing PRG alone can be compared with the goodness of fit of the model with ISR as the sole independent variable. In the data from nonwhites, ISR achieves a better goodness of fit than PRG (deviance 23.1 and 27.02, respectively), while in the case of whites PRG fits the data better in comparison with ISR (deviance 129.31 and 139.1, respectively).

The three-variable model shows multicollinearity involving all three variables, and all 95% confidence limits are wide. The beta coefficient estimate for BO1 has a non-negative value, suggesting that first-order birth is associated with an increased risk. Given the wide confidence interval around the point estimate of BO1, however, and the

small (negative) value for the beta of this variable in the other data sets, this is not entirely unexpected. The model appears to have assigned all the protection seen (in fact, more) to the ISR term. The two-variable model with ISR and PRG does not suffer from this collinearity problem and yields significant estimates for both beta coefficients. The preventive fraction associated with PRG is 61%, while that associated with ISR is 75%. Figure 33 shows the observed rate of infant death from hemolytic disease of the newborn in U.S. nonwhites, along with the predicted rate of infant death from HDN in the absence of an Rh prophylaxis program. Table 33A (Appendix) shows the results according to risk differences; the value of the risk differences associated with each independent variable is much lower than that seen from the analysis on whites (see also Figure 24A, Appendix). This suggests effect modification of the risk difference measure by racial factors which is expected.

GOODNESS OF FIT: The deviance statistics are presented in Table 32 and suggest a poor goodness of fit. In fact, the observed and fitted regression lines are fairly close, as is seen in Figure 34.

ASSESSMENT OF COLLINEARITY: As mentioned, all three standard error estimates in the three-variable model show the effects of collinearity. Correlations among parameter estimates are

Table 30: Number and rate (per 100,000 total births) of infant deaths from hemolytic disease in U.S. nonwhites in 1951, 1964 and 1988 and levels of three factors affecting outcome occurrence.

Year	Infant deaths from HDN No.	Rate	First births (%)	Infant survival rate/1000 livebirths	Rh type specific transfusions	Rh prophylaxis program
1951	160	29.4	24.4	955.2	0	0
1964	115	17.5	24.6	958.9	1	0
1988	11	1.3	39.3	985.0	1	1

Table 31: Changes in the annual rate of infant death from hemolytic disease in U.S. nonwhites between 1964 and 1988 and 1951 and 1988, as estimated using three different measures of effect (RD=risk difference, RR=risk ratio, PF=preventive fraction).

	1951 vs 1964	1964 vs 1988	1951 vs 1988
RD	11.89	16.19	28.08
RR	0.60	0.07	0.04
PF(%)	40.50	92.71	95.66

Table 32: Results of Poisson regression using data from U.S nonwhites for the years 1964-68 and 1982-88, with rate of infant deaths from hemolytic disease of the newborn as the outcome and effects expressed as risk ratios and preventive fractions.

USA NONWHITES ONLY 1964-68, 1982-88

VARIABLE (MODEL)	BETA	SE	RR	PF	95% CI on PF
BO1	-0.1441	0.0070	0.12	87.9	85.2-90.1
DEVIANCE=124.3, df=10, p<0.001					
ISR	-0.0934	0.0047	0.09	91.3	88.9-93.1
DEVIANCE=23.14, df=10, p<0.05					
PRG	-2.1610	0.1118	0.12	88.5	85.7-90.8
DEVIANCE=27.16, df=10, p<0.01					
BO1	-0.0339	0.0123	0.61	39.2	13.3-57.3
PRG	-1.8130	0.1712	0.16	83.7	77.2-88.3
DEVIANCE=19.51, df=9, p<0.05					
ISR	-0.0541	0.0186	0.25	75.7	37.1-90.6
PRG	-0.9488	0.4330	0.39	61.3	9.5-83.4
DEVIANCE=18.46, df=9, p<0.05					
BO1	0.0232	0.0527	1.02	-28.8	-84.4-69.1
ISR	-0.0879	0.0788	0.10	89.9	-82.4-99.8
PRG	-0.4330	1.2490	0.65	35.1	-86.7-94.4
DEVIANCE=18.27, df=8, p<0.05					

Figure 33. Poisson regression of data from the United States (nonwhites only), showing the observed rate of infant deaths from hemolytic disease of the newborn (per 100,000 live births) and the rate predicted by the regression model assuming no program of Rh prophylaxis.

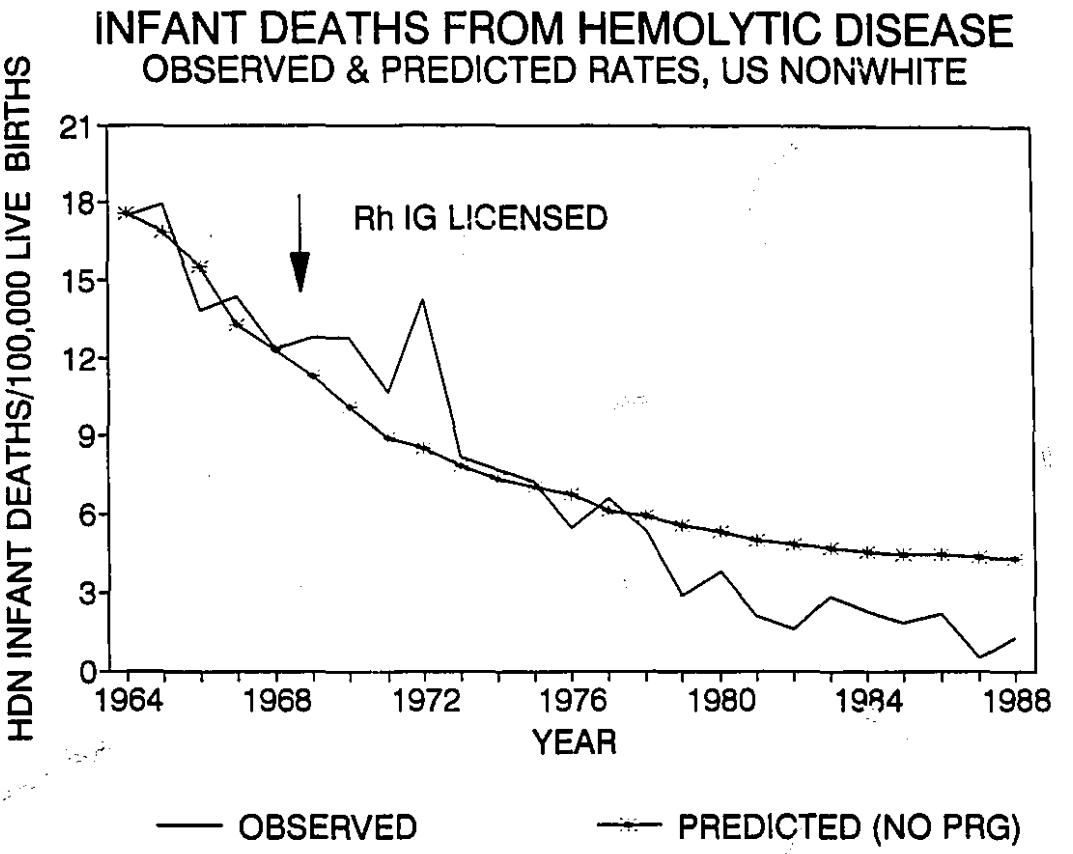
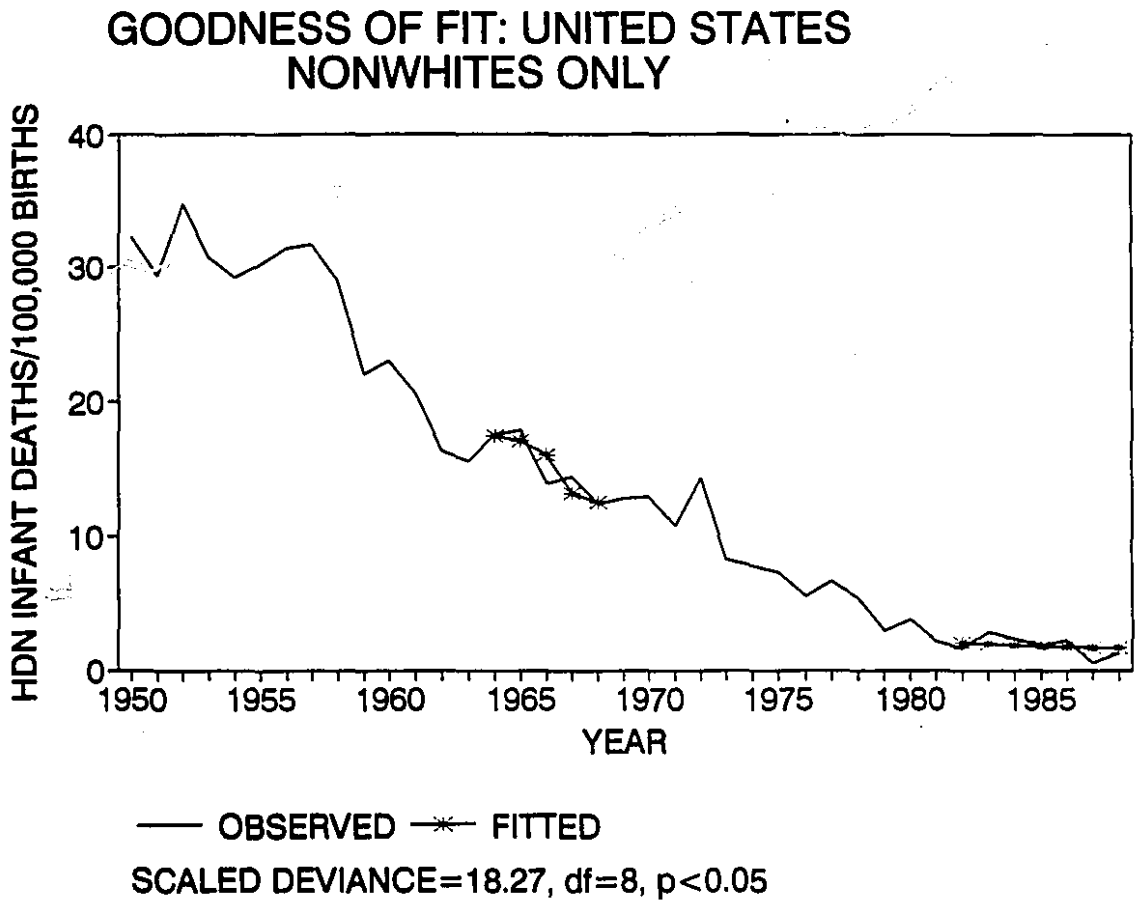


Figure 34. Poisson regression of data from the United States (nonwhites only): graphical depiction of the goodness of fit, with infant deaths from hemolytic disease of the newborn (per 100,000 live births) as the outcome variable and proportion of first births, infant survival rate, and presence/absence of an Rh prophylaxis program as independent variables.



shown in Table 34A (Appendix). The previously used procedure of combining the beta coefficients of collinear variables cannot be used in this situation because the collinearity extends to involve the PRG variable also. The best available estimates for program and non-program effects may be obtained from the two-variable (ISR and PRG) model.

4.1.6.3 OTHER ANALYSES

Poisson regression was repeated on the data after including information for the years 1951-54. The results, which are presented in Table 33, are similar to those obtained with the for the two-variable model, with the data set limited to the more recent years. The prophylaxis program was associated with a preventive fraction of 67%, while non-program factors appear to have reduced the disease by 84% since 1951. The goodness of fit of the model was acceptable according to deviance statistics, and the graphical depiction (Figure 35) also shows close concordance between observed and fitted lines. Collinearity is seen to affect the precision of the estimates of BO1 and ISR (see Table 35A, Appendix, for correlation among the parameter estimates).

DIFFERENCES BETWEEN RACES

The results from the regression analysis of the data from whites and nonwhites, show differences in the effects associated with the Rh prophylaxis program and the quality of

infant care. While disparities in the risk differences can be disregarded on account of racial variation in the baseline risk of disease, the same cannot be said for the differences in the risk ratios. The protective effect of Rh immunoglobulin prophylaxis, for instance, is believed to be the same irrespective of race. However, the data show that the Rh prophylaxis program was responsible for a 61-67% decrease in infant deaths from hemolytic disease of the newborn among nonwhites, while the same figure among whites was 85-90%. Similarly, the effects of improvements in the quality of infant care are seen to be greater among whites than among nonwhites (80-84% versus 74-76%). Both the Rh prophylaxis program and improvements in the quality of medical services contributed approximately equally to the mortality decline from HDN observed in whites. The reduction in infant deaths from hemolytic disease among nonwhites, on the other hand, occurred more because of improvements in the quality of medical care than secondary to the Rh prophylaxis program. This phenomenon may be graphically visualized by considering the time trends in infant mortality rates and infant deaths rates from hemolytic disease among whites and nonwhites (Figure 36). The decline in the infant death rate from hemolytic disease among nonwhites paralleled the decline in infant mortality rates with no dramatic change in the hemolytic disease mortality rates following the introduction of Rh prophylaxis. In the case of whites, however, the steep

Table 33: Results of Poisson regression using data from U.S. nonwhites for the years 1951-54, 1964-68 and 1982-88, with rate of infant deaths from hemolytic disease of the newborn as the outcome and effects expressed as risk ratios and preventive fractions.

USA NONWHITES ONLY 1951-54, 1964-68, 1982-88

VARIABLE (MODEL)	BETA	SE	RR	PF	95% CI on PF
BO1	-0.1519	0.0053	0.10	89.6	87.9-91.1
DEVIANCE=130.7, df=14, p<0.001					
ISR	-0.0972	0.0036	0.05	94.5	93.2-95.5
DEVIANCE=30.89, df=14, p<0.01					
PRG	-2.5220	0.1060	0.08	92.0	90.1-93.5
DEVIANCE=175.6, df=14, p<0.001					
TRA	-1.5380	0.0563	0.21	78.5	76.0-80.8
DEVIANCE=561.6, df=14, p<0.001					
BO1	0.0055	0.0196	1.09	-7.9	-48.1-38.8
ISR	-0.0985	0.0185	0.05	94.7	84.4-98.2
PRG	-0.0641	0.2906	0.94	6.2	-39.7-46.9
DEVIANCE=30.59, df=12, p>0.01					
TRA	-0.3837	0.1135	0.68	31.9	14.9-45.5
BO1	-0.0055	0.0198	0.92	7.9	-39.2-48.4
ISR	-0.0452	0.0242	0.26	74.0	-6.5-93.7
PRG	-1.0920	0.4186	0.33	66.5	23.8-85.2
DEVIANCE=19.13, df=11, p>0.05					
TRA, BO1, ISR *	-1.8130	0.4391	0.16	83.7	61.4-93.1
PRG	-1.0920	0.4186	0.33	66.5	23.8-85.2

* See table 23 for explanation.

Figure 35. Poisson regression of data from the United States (nonwhites only): graphical depiction of the goodness of fit, with infant deaths from hemolytic disease of the newborn (per 100,000 live births) as the outcome variable and proportion of first births, infant survival rate, presence/absence of Rh-specific blood transfusion and presence/absence of an Rh prophylaxis program as independent variables.

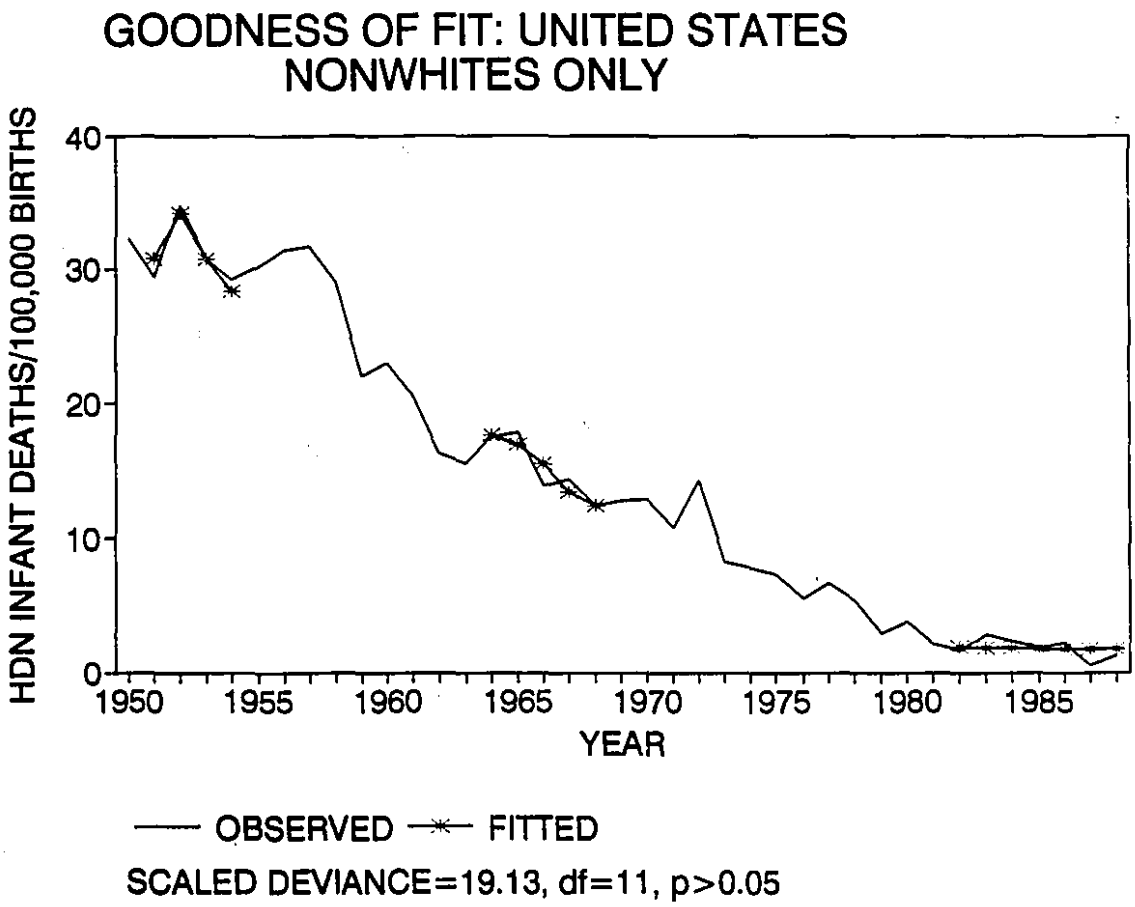
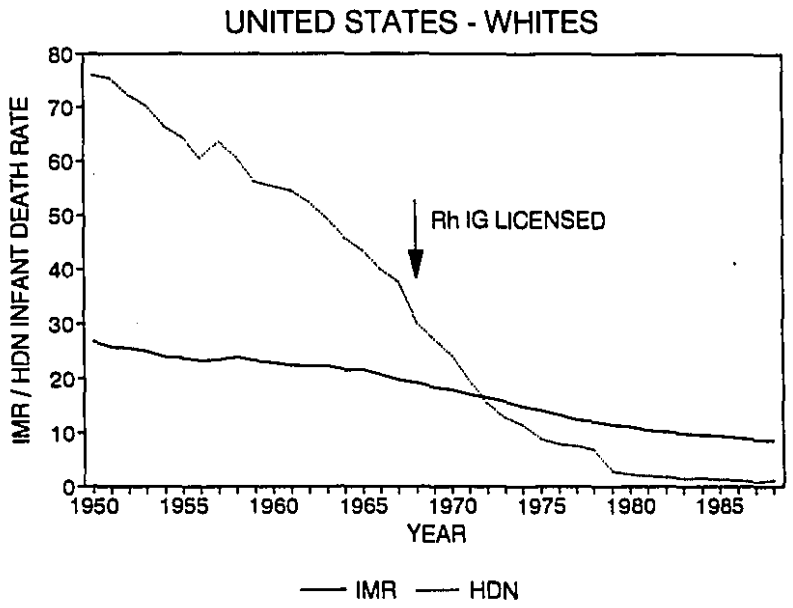
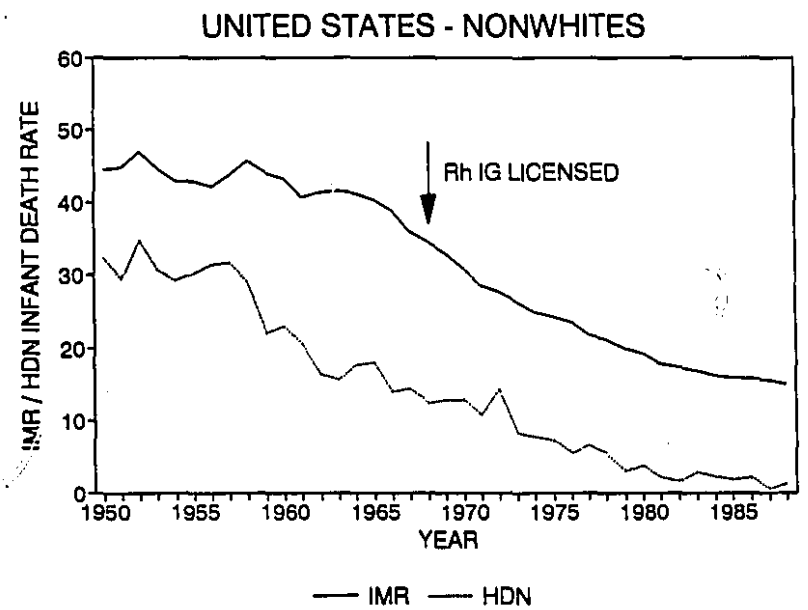


Figure 36. Data from the United States showing time trends in infant mortality rates (per 1000 live births) and infant deaths from hemolytic disease of the newborn (per 100,000 live births) between 1950 and 1988 by race.





decline in infant deaths from hemolytic disease shows a further dip (increase in the slope) following the introduction of Rh prophylaxis.

EFFECT OF RACE

The effect of race on the occurrence of infant death from hemolytic disease was estimated by regressing the combined U.S. data from whites and nonwhites after stratifying by race. Race was represented by a dichotomous indicator — 0 for whites and 1 for nonwhites. Since the results of the previous analyses by race showed modification of the effect of the independent variables by race, product terms involving the race variable were introduced into the model. Both the two-variable model (without BO1) and the three-variable model (with BO1) were estimated. The estimates of the beta coefficients for PRG, ISR and BO1 were similar to those obtained from whites, because whites were coded 0 for the race variable. The interaction terms do not apply to whites because of the manner in which the race variable was constructed (race = 0 for whites, 1 for nonwhites).

The results of regression with the two-variable model plus the interaction terms are shown in Table 34. No meaningful interpretation can be given to the beta coefficient of the race variable alone, because race is also involved in two interaction terms. The effect of race (in terms of the risk ratio) is modified by the presence/absence of an Rh

Table 34. Poisson regression of data from the United States, 1964-68 and 1982-88. The data are stratified by race using a dichotomous indicator (0 for whites and 1 for nonwhites), with interaction terms involving race introduced into the model.

VARIABLE (MODEL)	BETA	SE
INTERCEPT	131.0000	13.3600
RACE	-87.6900	22.2800
ISR	-0.1417	0.0136
PRG	-1.8580	0.1686
RACE*ISR	0.0876	0.0230
RACE*PRG	0.9089	0.4647
DEVIANCE=37.9, df=18, p<0.01		

Table 35. Poisson regression of data from the United States, 1964-68 and 1982-88. The regression equation (Table 34) was used to predict rates of infant death from hemolytic disease of the newborn among whites and nonwhites. Risk ratios expressing the relationship between race and HDN infant deaths (adjusted for ISR and PRG) were estimated from these predicted values.

YEAR	ISR	PRG	HDN INFANT DEATHS/100,000 WHITES	NONWHITES	RISK RATIO
1964	978.4	0	48.1	6.5	7.4
1965	978.5	0	47.4	6.5	7.3
1966	979.4	0	41.8	6.2	6.8
1967	980.3	0	36.8	5.9	6.3
1968	980.8	0	34.3	5.7	6.0
1982	989.9	1	1.5	0.5	2.7
1983	990.3	1	1.4	0.5	2.6
1984	990.6	1	1.3	0.5	2.5
1985	990.7	1	1.3	0.5	2.5
1986	991.1	1	1.3	0.5	2.5
1987	991.4	1	1.2	0.5	2.4
1988	991.5	1	1.2	0.5	2.4

prophylaxis program and the level of infant care. To obtain a meaningful estimate of the effect of race, model-predicted values of the outcome were calculated using the regression equation with specific values of ISR and PRG. The results are shown in Table 35. It is seen that the effect of race was far greater during the pre-prophylaxis years.

4.1.7 ASSESSMENT OF DISPERSION

As mentioned in Section 3.1.11, the validity of the variance estimate obtained under the Poisson assumption was evaluated by estimating a dispersion parameter and the variance without recourse to the Poisson assumption. This alternative estimation procedure was carried out for all data sets. In all the analyses based on the data from Manitoba, the dispersion parameter was small. With Rh sensitization, Rh disease and perinatal deaths from Rh disease as the outcome variables, the dispersion parameters were estimated to be 1.07, 0.86 and 0.44 respectively. This means that the variance estimated not using the Poisson assumption was 1.07, 0.86 and 0.44 times that assumed under the Poisson model for the three data sets, respectively. Table 36A (Appendix) shows the results of this alternative estimation of the variance for data from Manitoba, with perinatal deaths from Rh disease as the outcome. The dispersion parameters were slightly larger in the analysis of the Canadian and U.S datasets (on account of the increased variability), although the results of the analysis remained

essentially unchanged. These findings confirmed the a priori expectation that the data could be modeled by counts following a Poisson distribution.

4.1.8 VALIDITY OF REGISTERED DATA

The number of deaths from hemolytic disease as reported by death certification procedures have been found to be seriously inaccurate. Studies from England and Wales have found such figures to significantly overestimate the deaths due to hemolytic disease [109,110]. For instance, in 1953 of 411 infants certified as having died due to hemolytic disease of the newborn in England and Wales, detailed study of hospital notes showed that only 312 (76%) actually died from hemolytic disease [109]. The remaining deaths occurred mainly due to kernicterus of prematurity. The same study also revealed that only 315 (79%) of 400 infant deaths certified as being due hemolytic disease in 1955 were in fact due to hemolytic disease. Such overdiagnosis of hemolytic disease has also been reported in more recent studies from England and Wales [110]. Of 31 perinatal deaths registered as having occurred due to hemolytic disease of the newborn in 1988, only 24 (77%) were found to have died secondary to hemolytic disease of the newborn. Table 37A (Appendix) summarizes the findings of the two studies on the validity of the death certified information from England and Wales. Note that the overdiagnosis of HDN deaths is approximately constant across the years.

Similar criticisms regarding overdiagnosis of infant deaths from hemolytic disease do not appear to have been made about the Canadian and U.S. death statistics. On the contrary, these data have been presented in papers on the epidemiology of hemolytic disease in the United States [101]. A similar phenomenon of overdiagnosis in Canada and the United States means that estimates of the absolute rate of infant deaths from hemolytic disease are seriously compromised. The effects of such overdiagnosis on the regression estimates obtained in this study, however, are much less important. If the outcome rate for each year overestimates the true rate by any fraction, this will not bias the magnitude of the beta coefficients, as long as the artificial increase in rate is constant across the years. The effects of such a non-differential increase in the outcome rate will only be manifest in the size of the standard error and the goodness of fit as assessed through deviance statistics. Standard errors will tend to be smaller, while statistical goodness of fit will be affected unfavourably.

This phenomenon is illustrated in Tables 38A and 39A. Table 39A shows the results of Poisson regression of data from the total population of the United States (1963-68 and 1982-88) after the outcome rates were reduced by a factor of ten. This was done by introducing a decimal point before the last digit of the number of infant deaths from hemolytic disease observed for each year. Beta coefficients obtained

from the data set with 'decimated' rates are similar to those obtained when the actual rates are employed for regression. Goodness of fit is markedly improved, while standard errors increase because of the smaller number of outcome events. This analysis also illustrates how goodness of fit as estimated through deviance statistics depends of the numbers of outcome events. When these numbers are large, as is the case in a data set covering an entire country, the large sample size leads to significant differences between observed and model predicted values, even when such differences are fairly small.

Although, as mentioned above, such inaccuracy of outcome information does not bias the risk ratios and preventive fractions obtained from Poisson regression, it does affect the magnitude of the estimated risk differences. If the Canadian and U.S. data sets suffer from inaccuracies, then the absolute values of estimated risk differences cannot be relied upon. True risk differences are likely to be smaller in magnitude. If the level of outcome rate overestimation in the Canadian and U.S. data is accepted to be on par with that observed in the data from England and Wales (i.e., true infant death rates from hemolytic disease are approximately 25% less than those quoted), then the risk differences estimated from these data sets will be higher than the true risk differences by about 25%. Effect modification scenarios can be considered to represent the actual trends, however, because of the constant overestimation of outcome rates.

4.2 CONDITIONAL PROBABILITY MODEL

4.2.1 MODEL VALIDATION

4.2.1.1 ANTEPARTUM Rh SENSITIZATION (MATERNAL)

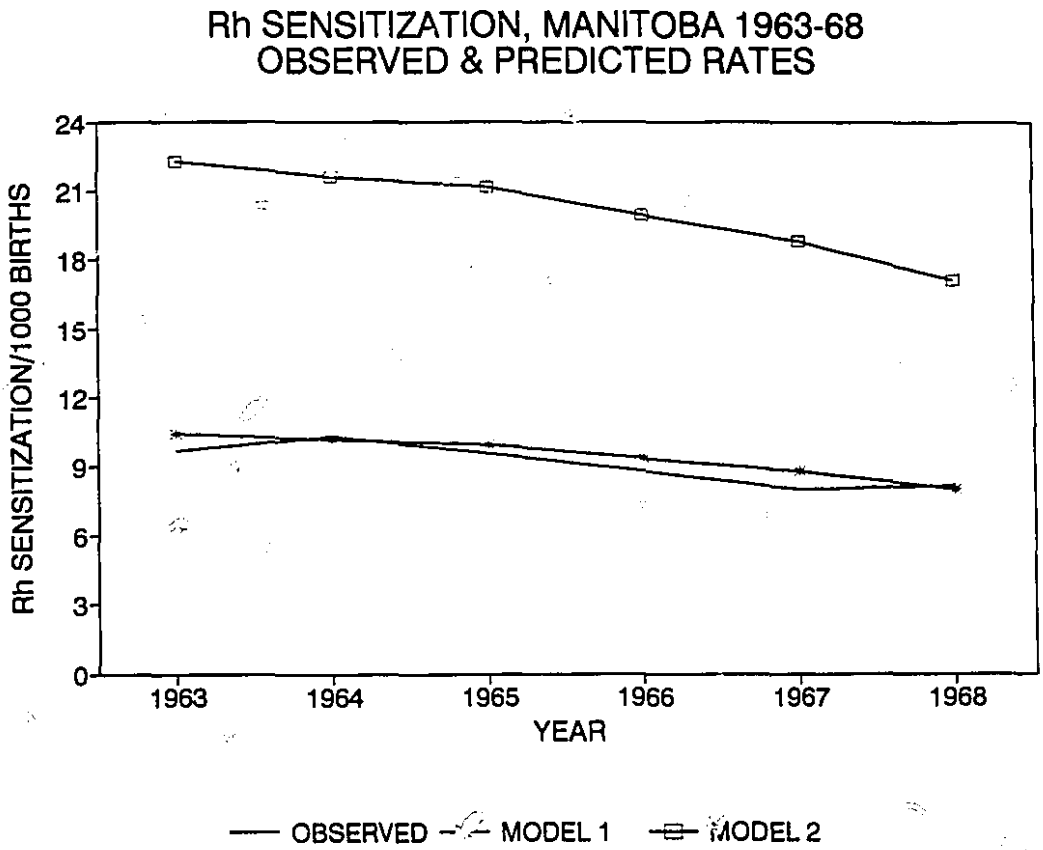
Model validation was first attempted for the rate of maternal antepartum Rh sensitization. Data from Manitoba shows that 26 mothers became Rh sensitized during pregnancy in 1974 and 1975 [37]. A simplified form of the model shown in Figures 3 and 4 was constructed based on the probability of the Rh-negative phenotype among women, probability of the Rh-positive genotype among fathers, probability of maternal antepartum sensitization, birth order distribution and stillbirth rate of Manitoba for 1974-75, with adjustment for the racial composition of the population. The model predicted 26-27 cases of maternal Rh sensitization, in close agreement with the 26 observed cases. Note that the model was based on the 1974-75 birth order distribution observed in Manitoba; probabilities used at the other chance nodes (such as the probability of antepartum Rh sensitization) were not obtained from Manitoba.

4.2.1.2 MATERNAL Rh SENSITIZATION

Data on all maternal Rh sensitization obtained from the surveillance program of Manitoba for the years 1963-68 were used to test model predictions. As mentioned previously, two models were constructed, the first assuming a rate of 7% for the probability of Rh sensitization (following an Rh-positive pregnancy given ABO compatibility) and the second assuming a

rate of 17% for the same parameter. The results are shown in Figure 37 (Table 40A, Appendix, gives the observed and predicted values). Changes in the predicted rates of Rh sensitization according to year (from 10.45 per 1000 total births for 1963 to 7.98 per 1000 total births for 1968 under model 1) are a consequence of integrating the birth order distribution of the specific year into the model. The rates predicted by model 1, which assumed a rate of 7% for Rh sensitization (following an Rh-positive pregnancy given ABO compatibility), are in close agreement with the rates of maternal Rh sensitization observed by the Rh surveillance program of Manitoba. Since model 1 was constructed based on the rates of Rh sensitization documented in national surveillance programs in Sweden [66] and Germany [125] (unlike model 2 which was based on Rh sensitization rates reported from clinical trials), its results were in agreement with the observed data from the population-based surveillance program of Manitoba. The close approximation between observed and predicted rates has to be interpreted with caution, however, since the observed rates include cases on Rh non-D sensitization. The predicted rates are thus overestimates of the true rates of Rh D sensitization. The magnitude of the overestimation is not likely to be large, however. During the period in question (1963 to 1968), most Rh sensitizations were due to the Rh D antigen; this ratio changed subsequently following the introduction of Rh prophylaxis in late 1968.

Figure 37. Validation of the conditional probability model using data for the years 1963 to 1968 from the Rh surveillance program of Manitoba. Results of both models are shown; model 1 assumed a rate of 7% for the probability of maternal Rh sensitization given an Rh-positive, ABO-compatible pregnancy, while model 2 assumed the same rate to be 17%.



For instance, even as late as 1974 (the earliest year for which Rh sensitization data from Manitoba can be categorized into Rh D and Rh non-D groups), about 80% of Rh sensitizations were Rh D sensitizations.

4.2.1.3 FIRST AFFECTED PREGNANCIES

As a general test for model validity, the proportion of first affected infants across the different birth orders was estimated by the model and graphed along with the same frequency distribution observed in various studies [58,130,131]. Figure 38 shows that the model predicted distribution is generally similar to the observed findings reported from the various studies. This comparison is only approximately valid, since no adjustment has been made for differing birth order distributions. Since birth order distributions for two of the quoted studies were available [58, 130], the model was also used to predict the proportion of first affected pregnancies according to birth order, using the birth order distribution from these two studies. The results of model prediction are similar to the observed values (see Figure 39).

4.2.2 Rh SENSITIZATION

4.2.2.1 EFFECT OF CHANGES IN BIRTH ORDER DISTRIBUTION

Table 36 shows the effect of changes in birth order distribution (observed in Manitoba between 1963 and 1988) on

Figure 38. Validation of the conditional probability model: proportion of first affected infants according to order of pregnancy from the studies by Nevanlinna [58], Knox and Walker [130] and Zoutendyk [131] and the conditional probability (C.P.) model based on data from Manitoba, 1963. No correction was made for the differing birth order distributions in each study.

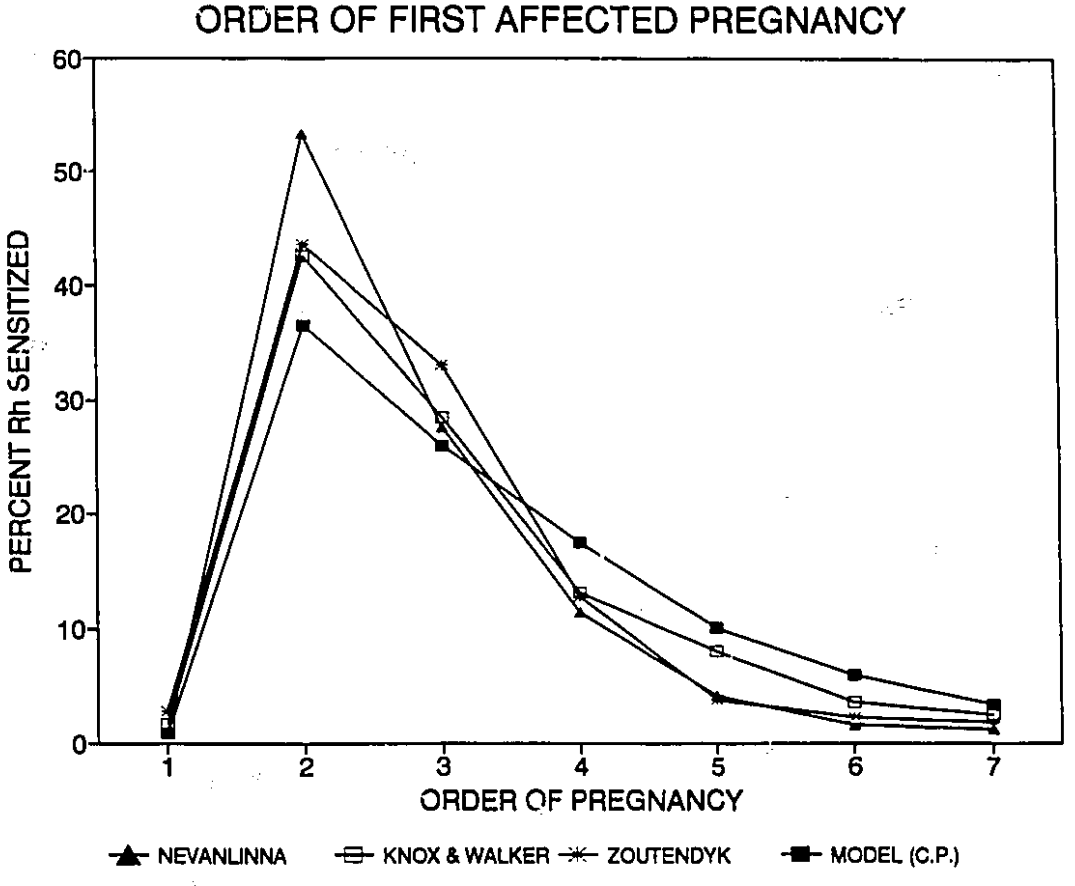
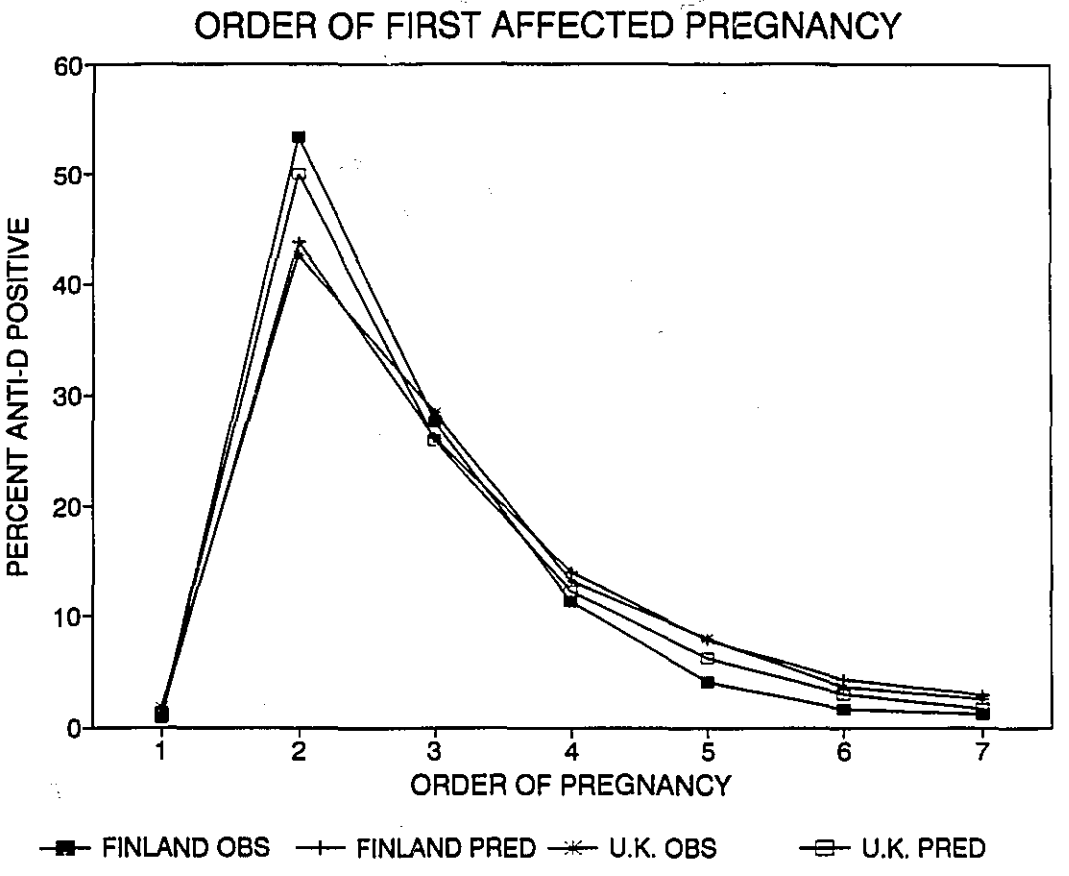


Figure 39. Validation of the conditional probability model: proportion of first affected infants according to order of pregnancy from the studies by Nevanlinna in Finland, 1949 [58], Knox and Walker in England, 1951 [130], and the conditional probability (C.P.) model based on the birth order distributions of the same two study populations (OBS=Observed, PRED=Predicted).



the rate of maternal Rh sensitization per 1000 total births. The effects were estimated for two models. Model 1 assumes the rate of Rh sensitization following a Rh-positive, ABO-compatible pregnancy to be 7%, while model 2 assumes this rate to be 17%. The rate of maternal Rh sensitization predicted by model 1 was 10.45 per 1000 total births in Manitoba in 1963 and this fell to 6.93 per 1000 total births by 1988 as a consequence of changes in birth order distribution and abortion rate alone. It should be noted that these two determinants (birth order distribution and abortion rate) acted in opposite directions and hence the results presented give a net effect. The racial composition of the births was kept constant at the 1963 level for this analysis, so as to exclude effects secondary to changes in racial composition. Thus, between 1963 and 1988, birth order changes prevented 34-36% of Rh sensitizations. Since this estimate was made based on predicted rates assuming the absence of an Rh prophylaxis program, the effect can be compared with the Poisson regression estimate of 24% (95% confidence interval=1.2 to 41.5%, see Table 8). Figure 40 shows the observed rates of Rh sensitization in Manitoba between 1963 and 1990, along with the rate predicted by the model in the absence of an Rh prophylaxis program. Figure 25A (Appendix) compares the conditional probability model predictions for the rate of Rh sensitization with those predicted by the Poisson regression model. The consistently greater effect of changing birth order

distribution seen with the conditional probability model is probably because of the more complete representation of birth order in this model, as compared with the Poisson model, where birth order distribution was represented using proportion of first births alone.

The effect of birth order distribution on maternal Rh sensitization is approximately similar for both models 1 and 2 when effects are expressed in terms of risk ratios or preventive fractions. However, given modification of the risk difference by the background rate of maternal Rh sensitization, the two models yield very different estimates when risk difference is used to express the magnitude of effect.

The isolated effect of changes in birth order distribution were also estimated by keeping the abortion rate constant at the 1963 levels (Table 41A, Appendix). Since the increase in the abortion rate served to increase the rate of Rh sensitization, this estimate of birth order effect was larger in magnitude compared with the previous estimate made using the model integrating the changing abortion rates. However, these estimates assume a constant abortion rate and are therefore not comparable with the estimates of birth order effect obtained from the Poisson regression model, as the Poisson regression estimates did not consider birth order and abortion effects separately.

4.2.2.2 EFFECT OF THE Rh PROPHYLAXIS PROGRAM

The Rh prophylaxis program of Manitoba was found to have been responsible for a 84% reduction in the rate of maternal Rh D sensitization between 1963 and 1988 (Table 37). This estimate of Rh prophylaxis effect is probably somewhat inflated, since the conditional probability model tends to slightly overestimate the rate of Rh D sensitization (see Section 4.2.1.2). The Rh prophylaxis effect was also estimated with regard to all Rh sensitizations, whether Rh D or Rh non-D (Table 42A, Appendix). The Rh prophylaxis program was responsible for a 61-62% reduction in the rate of all maternal Rh sensitization. This compares with an estimate of 69.4% (95% confidence interval = 60.9 to 76.0%) obtained from Poisson regression of data from Manitoba (see Table 8).

4.2.2.3 EFFECT OF CHANGES IN ABORTION RATES

Table 38 shows the effect of changes in the abortion rate as observed in Manitoba. If Manitoba had experienced the 1988 rate of abortion in 1963 (an abortion rate of 16.6 per 100 livebirths, as against the 1963 rate of 4.5 per 100 livebirths), a 12% increase in the rate of Rh sensitization would have been observed. Reducing the abortion rate in 1988 from 16.6 to 4.5 per 100 livebirths would have reduced the Rh sensitization rate by 14%. These estimates were obtained with model 1 assuming the absence of an Rh prophylaxis program. The effect of abortions is halved when model 2 is used to obtain

Table 36: Effect of changes in birth order distribution and abortion rate in Manitoba between 1963 and 1988 (and 1963 and 1990) on the rate of maternal Rh sensitization (per 1000 total births), assuming the absence of a program of Rh prophylaxis. The racial composition of the births was kept constant at the 1963 values. Results from both models are presented and effects are presented in terms of risk ratios (RR), risk differences (RD) and preventive fractions (PF).

Year	Rate of Rh sensitization/1000 total births	RR	RD	PF
Model 1*				
1963 (Reference)	10.45	1.00	0.00	0
1988	6.93	0.66	3.53	34
1990	6.64	0.64	3.81	36
Model 2*				
1963 (Reference)	22.22	1.00	0.00	0
1988	14.05	0.63	8.17	37
1990	13.19	0.59	9.03	41

* Model 1 assumes the rate of maternal Rh sensitization given an Rh-positive, ABO compatible pregnancy to be 7%, while model 2 assumes the same rate to be 17%.

Table 37: Effect of the Rh prophylaxis program on the rate of maternal Rh D sensitization (per 1000 total births). The effects were estimated by contrasting the observed rate of Rh sensitization and the rate predicted by model 1 (i.e., using the 7% assumption for the rate of maternal Rh sensitization) in the absence of an Rh prophylaxis program (racial composition of births adjusted to 1988 values).

Year	Rate of Rh sensitization per 1000 births		RR	RD	PF
	Predicted (No PRG)	Observed			
1988	6.72	1.06	0.16	5.66	84
1990	6.43	0.75	0.12	5.68	88

Figure 40. Conditional probability modeling of data from Manitoba showing the observed rate of maternal Rh sensitization and the rate predicted by the model assuming the absence of an Rh prophylaxis program.

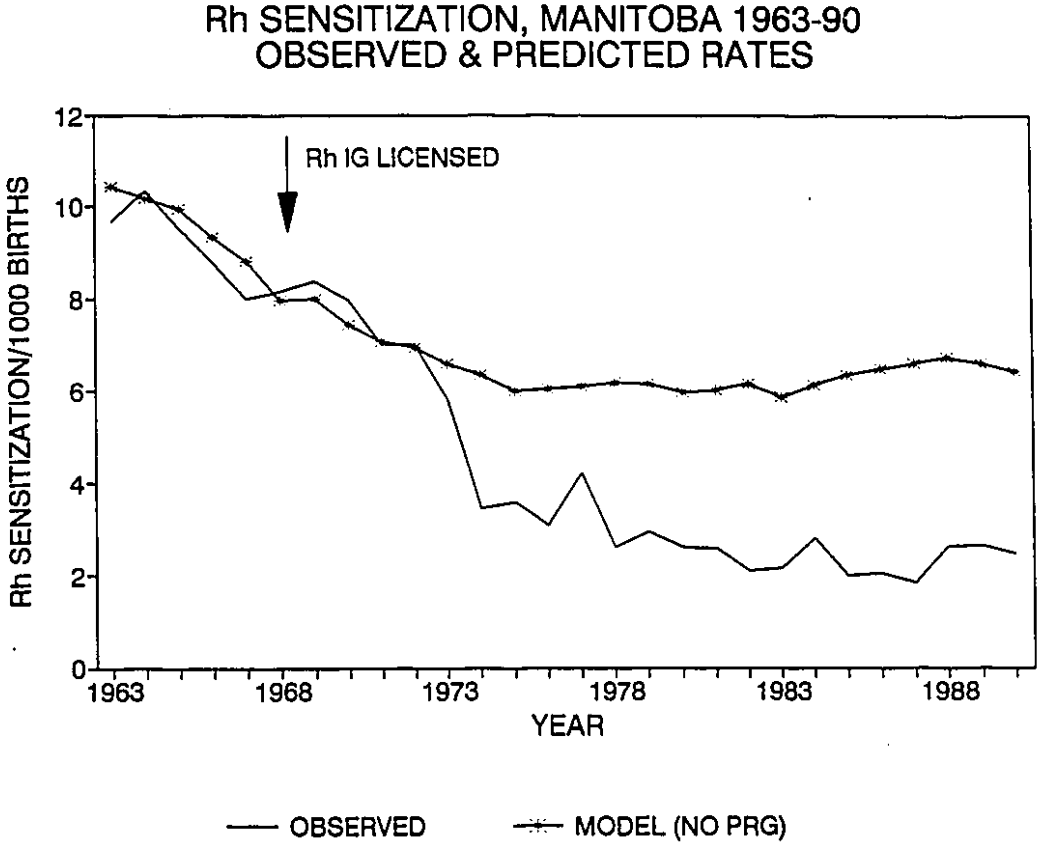


Table 38: Effect of changes in the abortion rate on the rate of maternal Rh sensitization, assuming the absence of an Rh prophylaxis program. Results from both models are presented with effects expressed in terms of risk ratios (RR), risk differences (RD) and etiologic/preventive fractions (EF/PF).

Year	Abortion rate /100 live births	Rate of Rh sensitization per 1000 births	RR	RD	EF/PF
Model 1*					
1963 (ref.)	4.5	10.45	1.00	0.00	0
	16.6	11.81	1.13	-1.36	12
1988 (ref.)	16.6	6.72	1.00	0.00	0
	4.5	5.75	0.86	0.97	14
Model 2*					
1963 (ref.)	4.5	22.22	1.00	0.00	0
	16.6	23.58	1.06	-1.36	6
1988 (ref.)	16.6	13.64	1.00	0.00	0
	4.5	12.67	0.93	0.97	7

* Model 1 assumes the rate of maternal Rh sensitization given an Rh-positive, ABO compatible pregnancy to be 7%, while model 2 assumes the same rate to be 17%.

Note: The RR/RD/PF estimates express the effect of the change in the abortion rate observed between 1963 and 1988. The estimates were made in the context of the background risk observed in 1963 (i.e., the model used the birth order distribution of Manitoba in 1963) and separately in the context of the background risk observed in 1988 (i.e., using the birth order distribution of Manitoba in 1988).

the estimate of abortion effect (Table 38).

4.2.2.4 EFFECT OF CHANGES IN RACIAL COMPOSITION

The effect of changes in the racial composition of births in Manitoba was estimated under the various scenarios of birth order distribution and abortion rate (see Table 39). The changes (i.e., decrease in the proportion of whites from 96.6% to 93.4%) were responsible for a 3% decline in the rate of Rh sensitization. This marginal effect justifies the assumption in the Poisson model (for data from Manitoba), ignoring the effect of changes in the racial composition between 1963 and 1988.

The effect of changes in racial composition in the data sets from Canada and the United States could not be estimated because of a paucity of data on proportion of births according to race, especially for the early years. This effect is most relevant for the interpretation of data on nonwhites. The changes in racial composition among U.S. nonwhites are shown in Tables 40 and 41. The increase in the proportion of Asian births among nonwhites would have been responsible for a slight reduction in infant deaths from hemolytic disease of the newborn (see Table 1A for Rh-negative prevalence rates among different races). The non-inclusion of these changes in racial composition in the Poisson model should have biased the estimate of Rh prophylaxis slightly upward (i.e., towards showing a greater protective effect). In fact, Rh prophylaxis

Table 39: Effect of changes in the racial composition of Manitoba (between 1963 and 1988) on the rate of maternal Rh sensitization (per 1000 births). Results from the two models are presented with effects expressed in terms of risk ratios (RR), risk differences (RD) and preventive fractions (PF). All estimates were made assuming the absence of an Rh prophylaxis program.

Racial composition	Birth order	Abortion rate	Rate of Rh sensitization (per 1000 births)	RR	RD	PF
Model 1*						
1963 (ref.)	1963	1963	10.45	1.00	0.00	0
1988	1963	1963	10.14	0.97	0.31	3
1963 (ref.)	1988	1988	6.93	1.00	0.00	0
1988	1988	1988	6.72	0.97	0.20	3
Model 2*						
1963 (ref.)	1963	1963	22.22	1.00	0.00	0
1988	1963	1963	21.57	0.97	0.66	3
1963 (ref)	1988	1988	14.05	1.00	0.00	0
1988	1988	1988	13.64	0.97	0.41	3

* Model 1 assumes the rate of maternal Rh sensitization given an Rh-positive, ABO compatible pregnancy to be 7%, while model 2 assumes the same rate to be 17%.

Table 40: Racial composition of nonwhite births in the United States for specific years. The African-American category includes births originally classified as Negro or black.

Year	African-American		Other		Total
	Number	Percent	Number	Percent	Number
1951	489,282	95.2	24,496	4.8	513,778
1954	544,288	94.9	29,444	5.1	573,732
1964	607,556	92.3	50,774	7.7	658,330
1968	531,152	90.1	58,188	9.9	589,340
1988	671,976	78.1	188,129	21.9	860,105

Table 41: Racial composition of births which occurred in the United States in 1988. Similar detail was not available for births which occurred in the earlier years.

Race	Number	Percent
All races	3,909,510	100.0
White	3,046,162	77.9
African-American	671,976	17.2
American Indian	45,871	1.2
Chinese	22,904	0.6
Japanese	10,483	0.3
Hawaiian	7,661	0.2
Filipino	24,612	0.6
Other Asian or Pacific Islander	76,598	2.0

effects among nonwhites were unexpectedly low, and the direction of the above-mentioned bias (secondary to racial changes) makes this finding all the more striking.

4.2.2.5 EFFECT OF RACE

The effects of racial factors were estimated by applying race-specific Rh-negative and ABO incompatibility prevalence rates to the Manitoba population. It is seen that whites were about ten times as likely to become Rh-sensitized as Native Indians and about two-and-a-half times as likely to become Rh-sensitized as Asian Indians (Table 42).

4.2.3 PERINATAL DEATHS FROM Rh DISEASE

4.2.3.1 EFFECT OF CHANGES IN BIRTH ORDER DISTRIBUTION

Tables 43 and 44 shows the effect of changes in birth order distribution (observed in Manitoba between 1963 and 1988) on the rate of perinatal death from Rh disease. Effects were estimated for both models 1 and 2, and the results are similar to the previous analysis, where maternal Rh sensitization was the outcome of interest. Both models yield approximately similar risk ratios, though the risk difference estimates are naturally much higher with model 2, which assumes a higher rate of baseline risk.

The estimates of birth order effect were made at different levels of perinatal care quality, since the risk difference associated with birth order change and perinatal

Table 42: Effect of race on the rate of maternal Rh sensitization (per 1000 total births). Results from both models are presented, and effects are estimated using the 1963 and 1988 birth order distributions of Manitoba. Whites were assumed to have an Rh-negative prevalence of 17%, while the prevalence among Native Indians and Asian Indians was assumed to be 1% and 5%, respectively.

Year/ Race	Rate of Rh sensitization per 1000 births	RR	RD	PF
Model 1*				
1963 Whites (ref.)	10.79	1.00	0.00	0
Native Indians	1.01	0.09	9.78	91
Asian Indians	4.25	0.39	6.54	61
1988 Whites (ref.)	7.15	1.00	0.00	0
Native Indians	0.68	0.10	6.47	90
Asian Indians	2.85	0.40	4.30	60
Model 2*				
1963 Whites (ref.)	22.94	1.00	0.00	0
Native Indians	2.10	0.09	20.84	91
Asian Indians	8.93	0.39	14.00	61
1988 Whites (ref.)	14.50	1.00	0.00	0
Native Indians	1.38	0.09	13.12	91
Asian Indians	5.77	0.40	8.73	60

* Model 1 assumes the rate of maternal Rh sensitization given an Rh-positive, ABO compatible pregnancy to be 7%, while model 2 assumes the same rate to be 17%.

deaths from Rh disease was expected to be modified by this third variable (i.e., perinatal care quality). Figure 41 graphically depicts the modification of the risk difference associated with birth order change by perinatal care quality.

4.2.3.2 EFFECT OF CHANGES IN THE QUALITY OF PERINATAL CARE

Tables 45 and 46 show the effect of changes in the quality of perinatal care on the rate of perinatal death from Rh disease. The risk ratio and preventive fraction estimates are constant across models 1 and 2 and show that changes in perinatal care quality were responsible for preventing about 80-90% of perinatal deaths from Rh disease. These estimates were made using perinatal survival given Rh sensitization whether D or non-D. This was because mortality data by Rh status (whether Rh D or non-D) was unavailable for the early years.

The risk difference associated with changes in perinatal care quality is, of course, modified by the background outcome rate. Model 1, which assumes a lower rate of outcome in comparison to model 2, yields a lower risk difference estimate. Birth order distribution, which is a determinant of the rate of perinatal death from Rh disease, also modifies the risk difference associated with perinatal care quality. The risk difference estimates in Table 45 (based on the birth order distribution of Manitoba in 1963) are larger than those in Table 46 (birth order distribution of Manitoba in 1988). This phenomenon of effect modification of

Table 43: Effect of changes in birth order distribution on the rate of perinatal death given Rh sensitization (per 100,000 total births) in Manitoba between 1963 and 1988. Results from two models are presented with effects expressed in terms of risk ratios (RR), risk differences (RD) and preventive fractions(PF). Both models assumed the level of perinatal care quality and racial composition observed in Manitoba in 1963. All estimates were made assuming the absence of an Rh prophylaxis program.

Year	Rate of Rh perinatal deaths /100,000 births	RR	RD	PF
Model 1*				
1963 (Reference)	122.3	1.00	0.00	0
1988	81.0	0.66	41.25	34
1990	77.7	0.64	44.56	36
Model 2*				
1963 (Reference)	260.0	1.00	0.00	0
1988	164.4	0.63	95.63	37
1990	154.4	0.59	105.65	41

Table 44: Effect of changes in birth order distribution on the rate of perinatal death given Rh sensitization (per 100,000 total births) in Manitoba between 1963 and 1988. Note effect modification of the risk difference by the level of perinatal care quality (see also Table 45). Results from two models are presented with effects expressed in terms of risk ratios (RR), risk differences (RD) and preventive fractions (PF). Both models assumed the racial composition of Manitoba, 1963, and the level of perinatal care quality observed in Manitoba in 1988. All estimates were made assuming the absence of an Rh prophylaxis program.

Year	Rate of Rh perinatal deaths /100,000 births	RR	RD	PF
Model 1*				
1963 (Reference)	23.0	1.00	0.00	0
1988	15.2	0.66	7.75	34
1990	14.6	0.64	8.38	36
Model 2*				
1963 (Reference)	48.9	1.00	0.00	0
1988	30.9	0.63	17.98	37
1990	29.0	0.59	19.87	41

* Model 1 assumes the rate of maternal Rh sensitization given an Rh-positive, ABO compatible pregnancy to be 7%, while model 2 assumes the same rate to be 17%.

Figure 41. Conditional probability modeling of data from Manitoba: graphical depiction of the effect of changes in the birth order distribution on the rate of perinatal deaths from Rh disease (per 100,000 total births), with effect modification of the risk difference by the quality of perinatal care. (The Rh prophylaxis program is presumed to be absent).

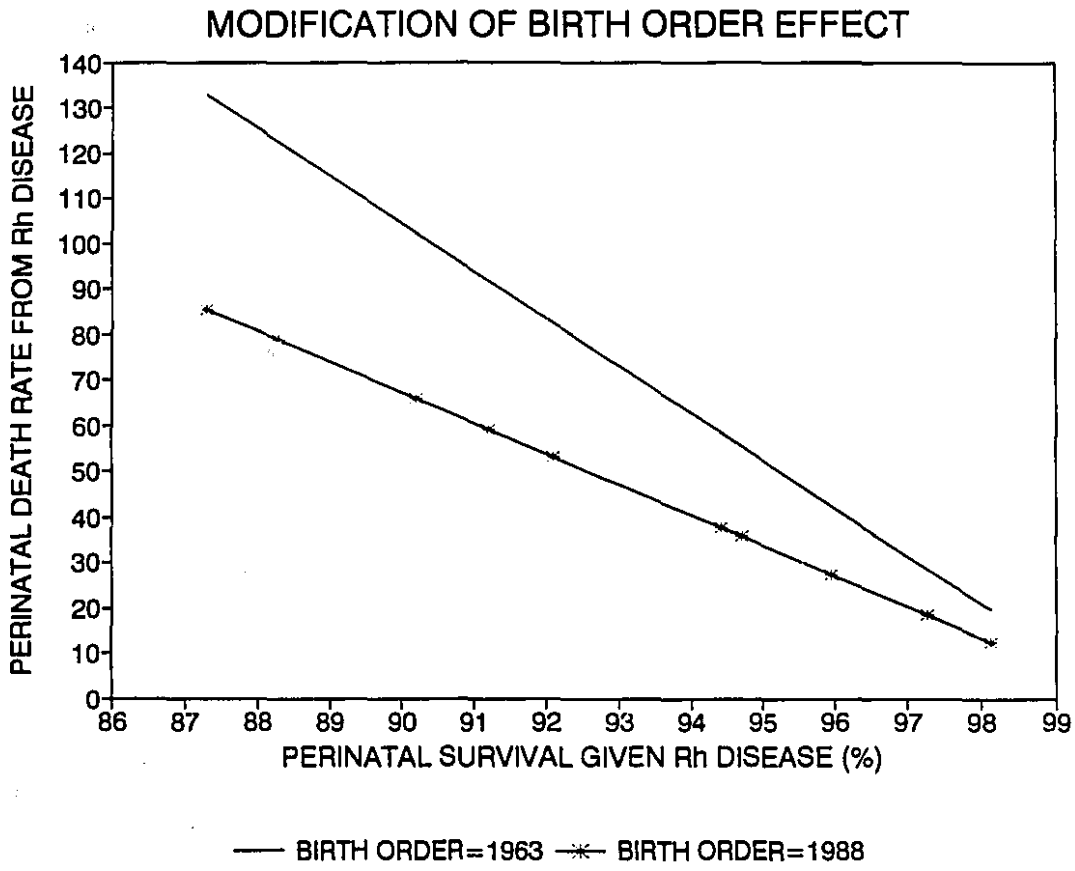


Table 45: Modeling (based on conditional probabilities) of the rate of perinatal deaths from Rh disease (per 100,000 births) in Manitoba, showing the effect of changes in perinatal care quality between 1963 and 1988. Results from two models are presented with effects expressed as risk ratios (RR), risk differences (RD) and preventive fractions (PF). Both models assume the birth order distribution, racial composition and abortion frequency observed in Manitoba in 1963.

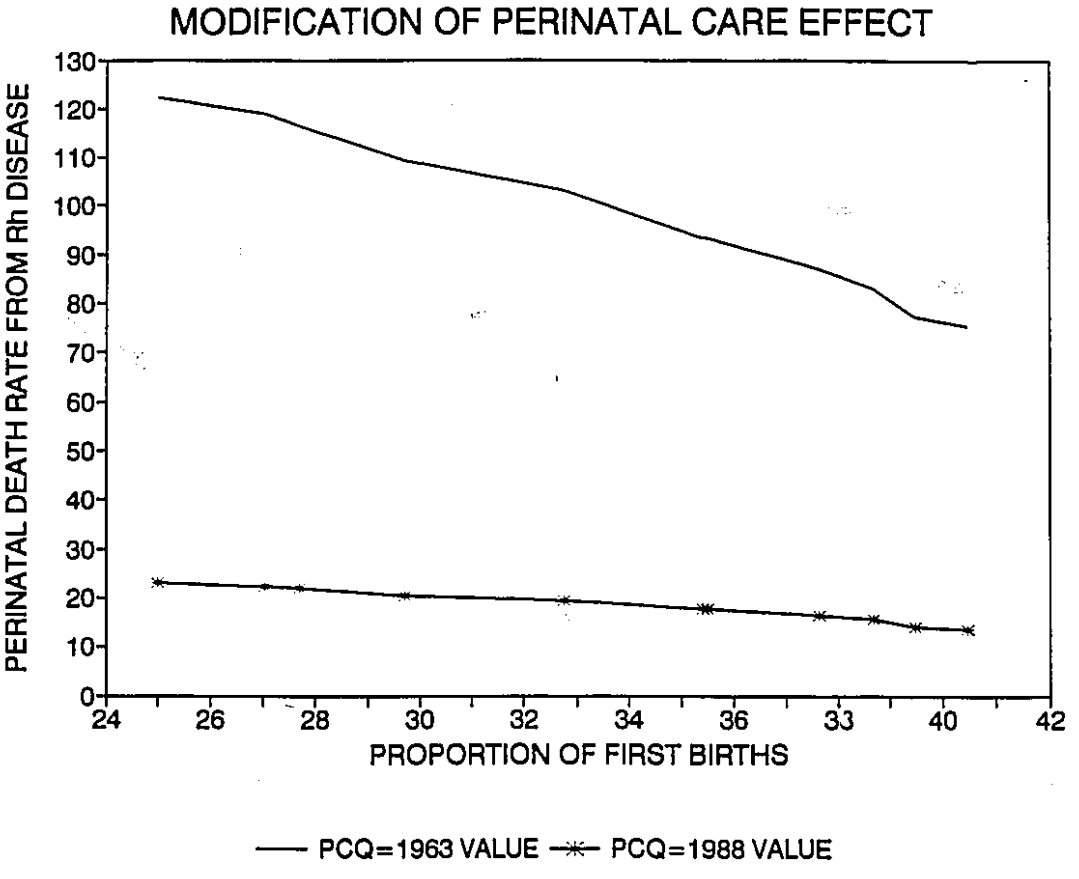
Year	Rh perinatal deaths per 100,000 births	RR	RD	PF
Model 1*				
1963 (ref.)	122.3	1.00	0.00	0
1988	23.0	0.19	99.27	81
1990	9.4	0.08	112.86	92
Model 2 *				
1963 (ref.)	260.0	1.00	0.00	0
1988	48.9	0.19	211.09	81
1990	20.0	0.08	239.98	92

Table 46: Modeling (based on conditional probabilities) of the rate of perinatal deaths from Rh disease (per 100,000 births) in Manitoba, showing the effect of changes in perinatal care quality between 1963 and 1988. Results from two models are presented with effects expressed as risk ratios (RR), risk differences (RD) and preventive fractions (PF). Both models assume the birth order distribution, racial composition and abortion frequency observed in Manitoba in 1988.

Year	Rh perinatal deaths per 100,000 births	RR	RD	PF
Model 1*				
1963 (ref.)	78.6	1.00	0.00	0
1988	14.8	0.19	63.84	81
1990	6.0	0.08	72.58	92
Model 2*				
1963 (ref.)	152.7	1.00	0.00	0
1988	28.7	0.19	124.00	81
1990	11.7	0.08	140.90	92

* Model 1 assumes the rate of maternal Rh sensitization given an Rh-positive, ABO compatible pregnancy to be 7%, while model 2 assumes the same rate to be 17%.

Figure 42. Conditional probability modeling of data from Manitoba: graphical depiction of the effect of changes in perinatal care quality on the rate of perinatal deaths from Rh disease (per 100,000 total births), with effect modification of the risk difference by birth order distribution. (The Rh prophylaxis program is presumed to be absent).



the risk difference associated with perinatal care quality (by birth order distribution) is illustrated in Figure 42.

4.2.3.3 COMBINED EFFECT OF THE NON-PROGRAM VARIABLES

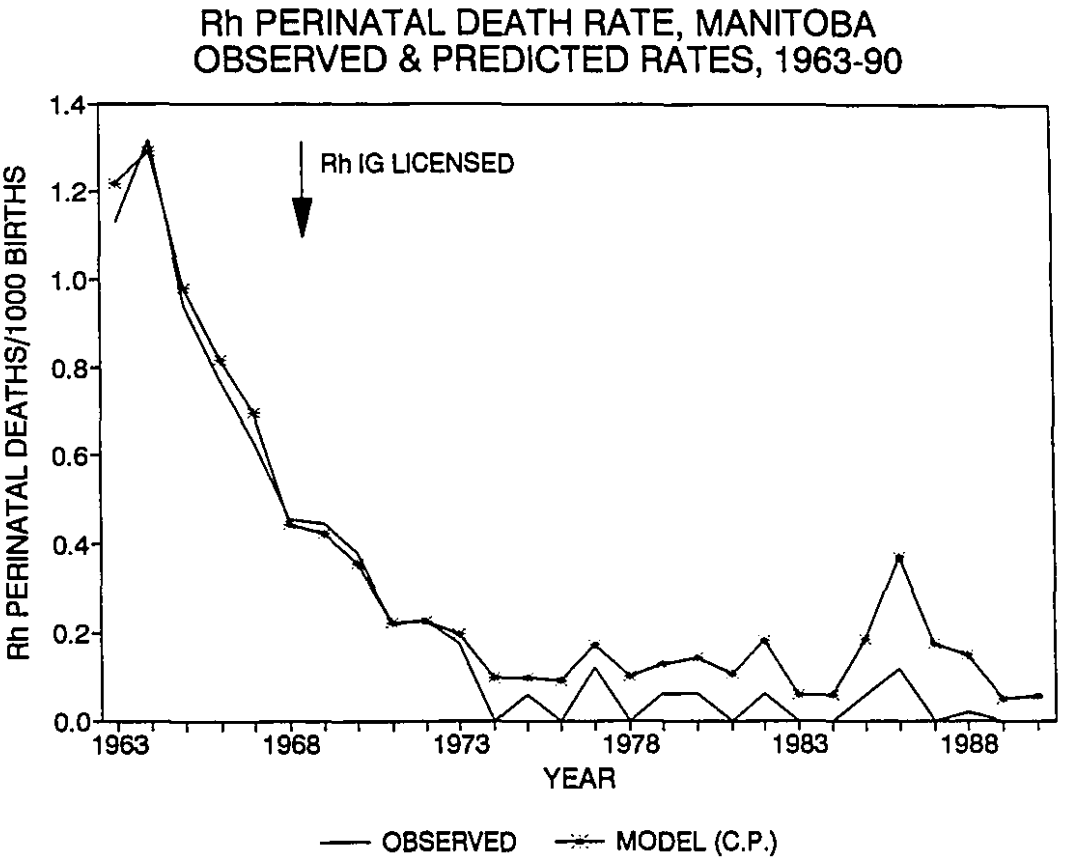
Table 47 shows the combined effect of changes in the non-program variables (birth order distribution, quality of perinatal care, abortion rate and racial composition) on the rate of perinatal deaths given Rh sensitization. Non-program factors were responsible for preventing 88% of perinatal deaths from Rh disease between 1963 and 1988. The Poisson regression estimate of the preventive fraction for non-program factors was 77.6% (95% confidence interval=42.1 to 91.4%, see Table 17). Figure 43 shows the observed rates of perinatal death from Rh disease in Manitoba between 1963 and 1990, along with the rate predicted by the model in the absence of an Rh prophylaxis program. Figure 26A (Appendix) graphically compares the rate of Rh sensitization predicted by the conditional probability model with that predicted by the Poisson regression model. The consistently greater effect of non-program factors seen with the conditional probability model is probably because of the more complete representation of birth order in this model as compared with the Poisson model where birth order distribution was approximated using proportion of first births alone.

Table 47: Effect of changes in non-program variables (changes in the birth order distribution, perinatal care quality, abortion rate and racial composition combined) on the rate of perinatal death from Rh disease (per 100,000 births). Results from both models are presented with effects expressed in terms of risk ratios (RR), risk differences (RD) and preventive fractions (PF).

Year	Rh perinatal deaths per 100,000 births	RR	RD	PF
Model 1				
1963 (ref.)	122.3	1.00	0.00	0
1988	14.8	0.12	107.48	88
1990	5.8	0.05	116.48	95
Model 2				
1963 (ref.)	260.0	1.00	0.00	0
1988	30.0	0.12	229.97	88
1990	11.9	0.05	248.10	92

* Model 1 assumes the rate of maternal Rh sensitization given an Rh-positive, ABO compatible pregnancy to be 7%, while model 2 assumes the same rate to be 17%.

Figure 43. Conditional probability modeling of data from Manitoba, showing the observed rate of perinatal deaths from Rh disease (per 100,000 total births) and the rate predicted by the model assuming the absence of an Rh prophylaxis program.



4.2.4 COST-EFFECTIVENESS OF Rh PROPHYLAXIS

The cost (in terms of the number of doses of Rh immunoglobulin) and cost-effectiveness (in terms of the number of Rh immunoglobulin doses required to prevent one case of maternal Rh sensitization) of various strategies of Rh prophylaxis were assessed using the decision analytic model for Manitoba. As mentioned earlier, Rh sensitization was chosen as the outcome of interest, since it is more directly related to patient management and health care costs in comparison with perinatal death from Rh disease. 2,237 doses of Rh immunoglobulin were required for post-delivery Rh prophylaxis in Manitoba in 1963, while 1,609 doses were required in 1988 (Table 48). The cost-effectiveness estimates (Table 48) showed that changes in the birth order distribution of Manitoba witnessed between 1963 and 1988 were responsible for reducing the cost-effectiveness of such Rh prophylaxis. Under model 1, 12 doses of Rh immunoglobulin were required to prevent one maternal Rh sensitization in 1963, while 22 doses were required in 1988. Under model 2, 6 doses of Rh immunoglobulin were required to prevent one maternal Rh sensitization in 1963, while 10 doses were required in 1988.

A program of Rh prophylaxis covering both post-delivery and post-abortion Rh-negative women would be slightly less cost-effective (relative to postpartum prophylaxis alone, Table 49). For instance, under such a program 19 doses of Rh immunoglobulin would have been required to prevent one case of

Rh sensitization (in Manitoba in 1963) compared with 12 doses required under a program of postpartum Rh prophylaxis. Table 50 shows the cost and cost-effectiveness of restricting post-delivery Rh prophylaxis to ABO compatible pregnancies. The total number of Rh immunoglobulin doses would be reduced, and the cost-effectiveness of the strategy would be marginally greater in comparison with an Rh prophylaxis program covering all postpartum women. Finally, a program of post-delivery prophylaxis restricted to first births would drastically reduce the total number of Rh immunoglobulin doses required while being most cost-effective (Table 51).

Tables 52-54 shows a comparison of the cost-effectiveness of the various strategies of Rh prophylaxis according to race. These cost-effectiveness estimates are very similar. The total cost, in terms of the program's annual requirement of Rh immunoglobulin, is very different, however (Table 54), because of racial variations in the prevalence of the Rh-negative phenotype.

Tables 55 and 56 show the cost and cost-effectiveness of the various Rh prophylaxis options in India. The birth order distribution and stillbirth and abortion rates of India (1981) were integrated into the decision analytic model for this analysis. It is seen that large numbers of Rh immunoglobulin doses are required for the various programs. The most cost-effective and least costly option appears to be the one with Rh prophylaxis restricted to first births. It

should be noted that a shift to the left in the birth order distribution (i.e., a move towards smaller families) will cause Rh prophylaxis programs to become less cost-effective (see cost-effectiveness estimates for Manitoba for 1963 and 1988, Tables 48-54). For this reason, the cost-effectiveness estimates (Tables 55 and 56) made using the 1981 birth order distribution of India are likely to be more favourable than a contemporary or future program of Rh prophylaxis. The effect of birth order changes between 1961 and 1981 on the rate of maternal Rh sensitization in India are shown in Figure 28A Appendix).

4.2.5 SENSITIVITY ANALYSES

The results of the Monte Carlo sensitivity analyses are presented in Table 57. The point estimates are almost the same as those obtained in the analysis previously presented. The 95% confidence intervals constructed using centiles 2.5 and 97.5 from the 10,000 random iterations performed are fairly precise inspite of the fairly wide range of values entertained for the sensitivity analysis. This is because of the relative nature of most of the estimates. The confidence intervals constructed around the cost-effectiveness estimates for the different Rh prophylaxis options are fairly wide, however, because of the wide range of probabilities entertained with regard to the prevalence of Rh types. Nevertheless, the hierarchy of cost-effectiveness options is unchanged.

Table 48: Cost-effectiveness of post-delivery Rh prophylaxis in Manitoba in preventing maternal Rh sensitization, with cost-effectiveness assessed in terms of the number of Rh immunoglobulin (Ig) doses required to prevent one case of maternal Rh sensitization. 'No PRG' refers to the absence of any Rh prophylaxis, while 'PRG' refers to a program of post-partum Rh prophylaxis.

Year	Rate of Rh sensitization per 1000 births		Ig doses required annually	Ig doses/Rh sensitization averted
	No PRG	PRG		
Model 1*				
1963	10.45	2.60	2237	12
1988	6.72	2.44	1609	22
Model 2*				
1963	22.22	5.35	2237	6
1988	13.64	3.95	1609	10

Table 49: Cost-effectiveness of post-abortion Rh prophylaxis in preventing maternal Rh sensitization in Manitoba, with cost-effectiveness assessed in terms of the number of Rh immunoglobulin (Ig) doses required to prevent one case of maternal Rh sensitization. 'No PRG' refers to post-delivery Rh prophylaxis only, while 'PRG' refers to a Rh prophylaxis program which includes both post-abortion and post-delivery prophylaxis.

Year	Rate of Rh sensitization per 1000 births		Ig doses required annually	Ig doses/Rh sensitization averted
	No PRG	PRG		
Model 1*				
1963	2.60	2.19	174	19
1988	2.44	1.37	450	25
Model 2*				
1963	5.35	4.94	174	19
1988	3.95	2.88	450	25

* Model 1 assumes the rate of maternal Rh sensitization given an Rh-positive, ABO compatible pregnancy to be 7%, while model 2 assumes the same rate to be 17%.

Table 50: Cost-effectiveness of post-delivery Rh prophylaxis for ABO compatible pregnancies only, with cost-effectiveness assessed in terms of the number of Rh immunoglobulin (Ig) doses required to prevent one case of maternal Rh sensitization. 'No PRG' refers to the absence of an Rh prophylaxis program, while 'PRG' refers to a restricted post-delivery Rh prophylaxis program which covers ABO compatible pregnancies only.

Year	Rate of Rh sensitization per 1000 births		Ig doses required annually	Ig doses/Rh sensitization averted
	No PRG	PRG		
Model 1*				
1963	10.45	2.87	1901	11
1988	6.72	2.59	1368	19
Model 2*				
1963	22.22	5.98	1901	5
1988	13.64	4.30	1368	9

Table 51: Cost-effectiveness of post-delivery Rh prophylaxis restricted to first births, with cost-effectiveness assessed in terms of the number of Rh immunoglobulin (Ig) doses required to prevent one case of maternal Rh sensitization. 'No PRG' refers to the absence of any Rh prophylaxis, while 'PRG' refers to a program of Rh prophylaxis restricted to first births.

Year	Rate of Rh sensitization per 1000 births		Ig doses required annually	Ig doses/Rh sensitization averted
	No PRG	PRG		
Model 1*				
1963	10.45	7.40	559	8
1988	6.72	4.23	647	15
Model 2*				
1963	22.22	15.53	559	4
1988	13.64	7.91	647	7

* Model 1 assumes the rate of maternal Rh sensitization given an Rh-positive, ABO compatible pregnancy to be 7%, while model 2 assumes the same rate to be 17%.

Table 52: Comparison of the cost-effectiveness of various forms of Rh prophylaxis, according to race. The birth order distribution of Manitoba for 1963/1988 was used in the model. These results were obtained for model 1.

Type of Rh prophylaxis	Year	Ig doses per Rh sensitization averted		
		Whites	Native Indians	Asian Indians
Postpartum (vs none)	1963	12	11	12
	1988	22	20	21
Post-abortion & postpartum (vs postpartum only)	1963	18	11	13
	1988	25	15	18
Postpartum, restricted to ABO compatible births (vs none)	1963	11	11	11
	1988	19	19	19
Postpartum, restricted to first-order births (vs none)	1963	8	7	8
	1988	15	17	15

Table 53: Comparison of the cost-effectiveness of various forms of Rh prophylaxis, according to race. The birth order distribution of Manitoba for 1963/1988 was used in the model. These results were obtained for model 2.

Type of Rh prophylaxis	Year	Ig doses per Rh sensitization averted		
		Whites	Native Indians	Asian Indians
Postpartum (vs none)	1963	6	5	6
	1988	10	9	9
Post-abortion & postpartum (vs post partum only)	1963	18	11	13
	1988	25	15	18
Postpartum, restricted to ABO compatible births (vs none)	1963	5	5	5
	1988	9	8	8
Postpartum, restricted to first-order births (vs none)	1963	4	3	4
	1988	7	7	6

Table 54: Model estimated requirements for Rh immunoglobulin for Manitoba in 1963/1988 under the assumption that the entire population had the Rh type and ABO blood group distributions of (1) whites, (2) Native Indians and (3) Asian Indians.

Type of Rh prophylaxis	Year	Total number of Ig doses required/year		
		Whites	Native Indians	Asian Indians
Postpartum	1963	2309	207	894
	1988	1711	154	662
Post-abortion & postpartum	1963	2483	217	945
	1988	2191	182	803
Postpartum, restricted to ABO compatible births	1963	1962	182	742
	1988	1455	135	550
Postpartum, restricted to first-order births	1963	577	52	223
	1988	688	62	266

Table 55: Comparison of the cost-effectiveness of various forms of Rh prophylaxis in India. The birth order distribution of India in 1981 was used in the model. These results were obtained for model 1 (see Table 57 for results from model 2).

Type of Rh prophylaxis	Rate of Rh sensitization per 1000 births		Ig doses required (for PRG)	Ig doses/Rh sensitization averted
	No PRG	PRG		
Postpartum (vs none)	4.08	1.63	33,540	16
Post-abortion & postpartum (vs postpartum)	1.63	0.84	10,706	15
Postpartum, restricted to ABO compatible births (vs none)	4.08	1.78	27,838	14
Postpartum, restricted to first-order births (vs none)	4.08	2.92	9,387	9

Table 56: Comparison of the cost-effectiveness of various forms of Rh prophylaxis in India. The birth order distribution of India in 1981 was used in the model. These results were obtained for model 2 (see Table 56 for results from model 1).

Type of Rh prophylaxis	Rate of Rh sensitization per 1000 births		Ig doses required (for PRG)	Ig doses/Rh sensitization averted
	No PRG	PRG		
Postpartum (vs none)	7.88	2.50	33,540	7
Post-abortion & postpartum (vs postpartum)	2.50	1.72	10,706	16
Postpartum, restricted to ABO compatible births (vs none)	7.88	2.85	27,838	6
Postpartum, restricted to first-order births (vs none)	7.88	5.30	9,387	4

Table 57. Mont Carlo sensitivity analyses for some key indices estimated by the conditional probability model (model 1).

Variable	Centiles 2.5	50	97.5
Rh sensitization rate (per 1000 births)			
Manitoba 1963	8.57	10.37	12.23
Manitoba 1988	5.66	6.68	7.75
Effect of birth order on Rh sensitization			
Preventive fraction	32.57	35.60	38.05
Risk difference (per 1000 births)	2.86	3.69	4.54
Effect of perinatal care quality on perinatal deaths from Rh disease			
(1) Baseline 1963			
Preventive fraction	66.44	81.13	93.54
Risk difference (per 100,000 births)	63.54	97.86	136.91
(2) Baseline 1988			
Preventive fraction	66.44	81.13	93.54
Risk difference (per 100,000 births)	41.31	63.16	87.57
Cost-effectiveness of Rh prophylaxis (Number of Rh immunoglobulin doses required to avert one case of Rh sensitization)			
Post partum prophylaxis			
Manitoba 1963	10	12	15
Manitoba 1988	18	22	27
Post-abortion prophylaxis			
Manitoba 1963	16	19	22
Manitoba 1988	21	25	30
Prophylaxis for ABO compatible pregnancies only			
Manitoba 1963	9	11	13
Manitoba 1988	16	19	24
Prophylaxis for first births only			
Manitoba 1963	7	8	10
Manitoba 1988	13	15	19

5 DISCUSSION

5.1 EPIDEMIOLOGIC ANALYSIS

5.1.1 VALIDITY ASSURANCE

5.1.1.1 NON-EXPERIMENTAL METHODS FOR EFFICACY ASSESSMENT

As mentioned earlier (Section 3.1), the non-experimental assessment of drug/treatment efficacy is generally considered infeasible because of uncontrollable confounding by indication. This is because drug/treatment use is inherently associated with the severity of the indication, and the latter is difficult to quantify in precise terms. However, this problem does not plague the non-experimental assessment of Rh immunoglobulin effect, because the indication for Rh immunoglobulin is of the all-or-none type [85].

5.1.1.2 ECOLOGICAL FALLACY

The design of the study was ecological, with the outcome rate in the population (at any particular time) modeled as a function of the prevailing determinant levels. Ecological studies of this nature are susceptible to a unique problem, called the ecological fallacy, which was first described by Selvin [134]. If the disease rate in a population is found to increase simultaneously with increases in the level of some determinant, it remains uncertain whether the excess disease in fact occurred among those with the determinant. This problem is especially relevant in the context of exploratory studies. In the context of Rh disease and related outcomes,

however, the possibility of an ecological fallacy can be excluded, because the general understanding of the biologic processes associated with Rh disease is well developed, especially at the level of the individual patient. For example, if two populations apparently distinguished on the basis of birth order distribution show differences in the rate of some Rh disease-related outcome, then these differences in disease rates can be attributed to birth order differences. The supposition that later birth orders give rise to higher disease rates is supported by *a priori* hypotheses based on clinical and biologic experience.

5.1.1.3 CHOICE OF OUTCOME

All three outcomes considered in the analyses of data from Manitoba (and the combined data from Manitoba and Nova Scotia) included both Rh D and Rh non-D cases. Since Rh immunoglobulin is directed specifically against Rh D sensitization, it was inevitable that the choice of the more general outcome would lead to a diminished estimate of Rh immunoglobulin effect. Two reasons dictated the choice of all Rh cases as against Rh D-related cases alone. First, once sensitization has occurred, management of pregnancy does not radically differ across cases of Rh D and Rh non-D sensitization. Thus, costs to the health care system would arise in both situations, with the magnitude of cost more a function of the degree of sensitization, rather than the antigen against which sensitization has occurred. The

second reason for combining both Rh D and Rh non-D cases was that data from Manitoba in the pre-prophylaxis years do not allow such a differentiation. This latter reason was also responsible for the choice of all cases of hemolytic disease of the newborn for the analyses pertaining to national data for Canada and the United States.

5.1.1.4 CHARACTERIZATION OF BIRTH ORDER DISTRIBUTION

The birth order distribution of each population-year was characterized in the regression model by the proportion of first births. Analyses were also performed using other birth orders (such as the second or third birth order), both alone and simultaneously. The results of exploratory analyses using such alternative representations of birth order distribution did not yield any significant advantages over the use of first birth order. Simultaneous entry of multiple birth order terms into the regression model resulted in problems of collinearity.

Nevertheless, it is clear that the proportion of first births does not completely describe the birth order distribution of a population, because populations can show changes in later birth orders without concomitant change in the proportion of first births. These changes can have significant effects on the rate of Rh disease and related outcomes.

5.1.1.5 CHARACTERIZATION OF MEDICAL CARE QUALITY

Two different variables were used for characterizing the quality of medical care. When perinatal deaths from Rh disease was the outcome at issue, quality of care was represented by the rate of perinatal survival given Rh disease. Infant survival rate, the complement of the infant mortality rate, was used to represent quality of care when infant deaths from hemolytic disease was the outcome of interest.

While the change from perinatal survival rates given Rh disease to infant survival rates was clearly justified by a similar change in the outcomes considered, these two variables used to characterize quality of medical care are different conceptually. This is because perinatal survival given Rh disease quantifies medical care with specific regard to Rh disease, while infant survival rate is a more general index of infant care. Since perinatal survival given Rh disease is an Rh disease-specific index, it better approximates perinatal care quality as it pertains to Rh disease. On the other hand, if the severity of presentation of Rh disease has been changing (decreasing) over the last three decades, then perinatal survival given Rh disease would be a poorer measure of true medical care quality in comparison with infant survival rate. It should be noted in this connection, however, that perinatal and infant deaths from Rh disease represent outcomes that are similar in some respects but distinct in others. For instance, stillbirths (which not

infrequently occurred as a consequence of Rh disease) are included among perinatal deaths but not among infant deaths. For this reason, it is not intuitively clear whether the effect of a given factor (for instance, Rh prophylaxis) should be identical across the two outcomes. In fact, Rh prophylaxis effects were approximately the same across both outcomes (PF=83% in Manitoba, Table 14; and PF=85% among U.S. Whites, Table 28).

5.1.2.6 BIAS DUE TO CONFOUNDING

The issue of properly characterizing birth order distribution and quality of medical care has been discussed in the previous sections. Incomplete characterization of these two confounding variables (akin to non-differential misclassification) would have led to residual confounding, i.e., overestimation of the Rh prophylaxis effect. The estimates of the effects of the confounders (birth order and quality of medical care) themselves would have been biased towards the null. Some insight into the magnitude of the bias with regard to the birth order variable may be obtained from an examination of the results of the conditional probability model. The effect of birth order distribution, as assessed by the conditional probability model, is slightly greater than that estimated by the Poisson model. Conversely, the effects of Rh prophylaxis are slightly smaller in magnitude in the conditional probability model.

The Poisson model did not account for some of the other determinants of Rh disease-related outcomes, including changes in abortion rates and changes in the racial composition of the population across the study period. These variables were not included in the model because of collinearity between these variables and others already in the model. The effect of birth order, as estimated by the regression model, was expected to subsume the smaller effect associated with changes in the abortion rate. Changes in the racial composition of Manitoba were not expected to affect outcome rates significantly, because the changes were minor. The conditional probability model provides estimates of the effect of these two determinants. The effect of changing birth order (i.e., including the effect of changing abortion rates) as assessed by the two different approaches is similar, though the point estimates from the conditional probability model are higher. The effect of changes in racial composition of the population in Manitoba is small, as anticipated.

The changes in racial composition of births in the United States were not minor changes, however, especially with regard to births among U.S. nonwhites. Tables 42 and 43 show that the proportion of African-American births within this category of all nonwhite births changed substantially between 1964 and 1988. The change is due to an increased number of Asian-Americans births. Given the lower rate of Rh-negative prevalence among Asian-Indians compared with African-

Americans, this change should have led to a lower rate of hemolytic disease in 1988. Such a change would have biased the regression estimates of Rh prophylaxis and other determinants towards showing greater effects. However, the regression estimates of the Rh prophylaxis effect are smaller among U.S. nonwhites than among U.S whites. Two possible explanations exist for the unexpectedly low estimates of Rh prophylaxis effect among U.S. nonwhites. The first explanation involves differential access to Rh prophylaxis across racial categories, with a smaller proportion of nonwhites receiving Rh prophylaxis in comparison to whites. This does not necessarily imply differences in access to Rh prophylaxis in the period 1982-1988 but could be secondary to low prophylaxis rates among nonwhites in the late 1970's. The second possibility is that rates of infant deaths from hemolytic disease of the newborn were grossly underestimated among nonwhites in the 1960's.

5.1.2.7 INFORMATION BIAS

The data from the Manitoba surveillance program, while likely to have some of the informational inaccuracies inherent in any large population screening program, were not expected to contain serious problems with regard to the diagnosis of Rh disease-related outcomes. This is because of the availability of relevant antigen and antibody testing. The fact that the same levels of test sensitivity were preserved throughout the

study period means that the validity of the risk ratio estimates is assured. True risk difference estimates, on the other hand, are likely to be higher if Rh sensitization rates were underestimated as a result of the less sensitive tests used.

A similar issue applies with regard to over-diagnosis of infant deaths from hemolytic disease of the newborn as reported by the vital statistics publications of Canada and the United States. Although estimates of the risk ratio are unlikely to be biased, true risk differences estimates are likely to be smaller than estimated. The general direction of the effect modification scenarios noted is unlikely to have been affected by such a possibility, however.

The possibility that infant deaths from hemolytic disease of the newborn were grossly underestimated among nonwhites in the 1960's was mentioned earlier as a possible explanation for the low effectiveness of Rh prophylaxis seen among U.S. nonwhites.

5.2 CONDITIONAL PROBABILITY MODEL

5.2.1 VALIDITY ASSURANCE

5.2.1.1 RESULTS OF MODEL VALIDATION

Although the results of model validation show fairly close agreement between observed outcome rates and those predicted by model 1 (Section 4.2.1.2), the concordance is only approximate. In the conditional probability model, only Rh D

sensitizations were modeled, while the observed data from Manitoba used for model validation also contained Rh non-D sensitizations. This implies that the conditional probability model is only approximately valid.

Also, the magnitude of the differences in rates predicted by model 1 and model 2 (probability of maternal Rh sensitization given an ABO compatible Rh-positive fetus 7% and 17%, respectively) are difficult to reconcile. On the other hand, the medical literature documents wide variations in the rates of Rh sensitization following Rh-positive, ABO compatible pregnancies (Table 1). It should be noted that since the main objectives of this study relate to the relative magnitudes of outcome rates, the two models provide similar results in most instances. For instance, the preventive fraction for the effect of changing birth order is 35% across both models. Since cost-effectiveness of various Rh prophylaxis options also involves relative comparisons, the hierarchy of cost-effective options is again the same across both models.

5.2.1.2 VALIDITY OF MODEL ASSUMPTIONS

Most assumptions used in the conditional probability model were based on best estimates of the relevant probabilities as deduced from medical literature. Some of the assumptions, however, were either based on scanty data or were extrapolated from allied but distinct situations. These assumptions include

those for abortion rates in Manitoba prior to 1971, abortion rates for India, birth order distribution of Native Indians in Manitoba and the racial composition of births in Manitoba. The latter assumption was obtained from the population proportions of whites and Native Indians as documented in census statistics. These crude assumptions were made in the absence of better estimates but are not expected to bias the results significantly (see Monte Carlo sensitivity analyses, Section 4.2.5). It should be noted in this context that as far as the validity of risk ratio and preventive fraction estimates is concerned, what matters is not the absolute value of the parameter assumed, but the changes to which it is subjected over time. As we have seen, however, this general rule does not apply to risk difference estimates.

Approximations were also made with regard to denominators when calculating the rates of Rh disease related outcomes in Manitoba. Specifically, the number of births in a given year (January to December) was obtained from vital statistics publications, while the numerators for the rates, obtained from the surveillance program of Manitoba were counted from the November of the previous year to October of the relevant year.

5.2.1.3 CHOICE OF COST MEASURE

The choice of number of Rh immunoglobulin doses as the measure of "cost" was made for several reasons. Rh immunoglobulin is

the most critical component of any Rh prophylaxis program, which is not only because of its cost. As discussed in the earlier sections, limits exist on its production. Further, costs of other components of an Rh prophylaxis program (such as administrative and infrastructure costs) were considered to be necessary for other aspects of perinatal care unrelated to Rh disease. Finally, since costs were estimated for the purpose of comparing alternative strategies of Rh prophylaxis, administrative and infrastructure costs were typically considered to be shared between the various Rh prophylaxis options.

5.2.1.4 CHOICE OF EFFECT MEASURE

As mentioned previously, Rh sensitization among pregnant women was considered the outcome of interest in the cost-effectiveness analysis, because health care costs are more directly linked to this outcome, rather than to perinatal deaths from Rh disease. Cost-effectiveness analyses based on perinatal deaths would have provided similar results, however, albeit with some distinct differences. First, given the infrequent nature of perinatal deaths from Rh disease (relative to maternal Rh sensitization), the number of doses of Rh immunoglobulin required to prevent each such event would have been larger and estimated with less precision. Since the cost-effectiveness analyses were carried out for comparative purposes, however, this difference is not an issue;

comparative analyses based on perinatal deaths from Rh disease would have provided similar results to the analyses utilizing Rh sensitization as the outcome. One major difference would have been the modification of cost-effectiveness by the quality of perinatal care.

5.3 CONCLUSIONS

5.3.1 EFFECT OF BIRTH ORDER

The changes in birth order distribution witnessed in Manitoba between 1963 and 1988 were responsible for about 35% of the decrease in Rh sensitization rates observed during that period. This estimate is consistent with the results of both Poisson and conditional probability models, although closer to the point estimate obtained by the latter method. The preference for the result of the conditional probability model was dictated by the fact that the model integrated the entire birth order distribution of the population, whereas the Poisson model limited the birth order representation to the proportion of first births.

The conditional probability model yielded a similar estimate for the preventive fraction associated with birth order when perinatal deaths from Rh disease was considered as the outcome of interest. This is far higher then the point estimate obtained from the Poisson regression model for perinatal deaths from Rh disease in Manitoba. However, the Poisson estimate was affected by collinearity problems (point

estimate of PF for BO1=3.9, 95% confidence interval= -80.3 to 81.8). For these reasons, the conditional probability model estimate for birth order effect was considered a better estimate of the true effect. The results of Poisson regression of data from Canada and the United States also suffered from similar collinearity problems, which hindered the quantification of the isolated birth order effect. These analyses were used mainly for obtaining estimates of the effect of Rh prophylaxis and combined non-program effects.

5.3.2 EFFECT OF MEDICAL CARE QUALITY

The Poisson model estimated that changes in the quality of perinatal care observed in Manitoba between 1963 and 1988 were responsible for a 77% decline in the occurrence of perinatal deaths from Rh disease (95% confidence interval=4 to 94%). Similar estimates were obtained from regression of Canadian and U.S. data on infant deaths from hemolytic disease. The preventive fraction associated with the quality of infant care was 77% (95% confidence interval wide due to collinearity) in the Canadian analysis and 71% (95% confidence interval=27 to 88%) in the U.S. data (total population). The conditional probability model estimate for the effect of perinatal care quality between 1963 and 1988 was 81%. This estimate was considered the best estimate because of the above-mentioned collinearity problems associated with the Poisson model.

5.3.3 EFFECT OF Rh PROPHYLAXIS

The conditional probability model showed that Rh prophylaxis prevented 84-88% of Rh D sensitization and 61-62% of all Rh sensitizations (D and non-D) in Manitoba. The Poisson estimate for the effect of Rh prophylaxis on all Rh sensitizations was about the same (PF=69%, 95% confidence interval=61 to 76%). With perinatal death from Rh disease as the outcome variable, the Poisson model for Manitoba yielded a preventive fraction of 83% (95% confidence interval=44 to 95%) for Rh prophylaxis. The estimate of Rh prophylaxis effect on perinatal deaths given Rh D sensitization was not made using the conditional probability model because of the absence of required data. Analysis of the data on infant deaths from hemolytic disease from Canada and the United States (total population) showed Rh prophylaxis effects of 90% (95% confidence interval=67 to 97%) and 88% (95% confidence interval=78 to 93%), respectively.

One could speculate that the effects of Rh prophylaxis are greater when mortality outcomes are considered in contrast to Rh sensitization rates. This argument supposes that Rh non-D sensitization, which is not prevented by Rh prophylaxis, is a less serious threat to the fetus/infant in comparison to Rh D sensitization. This is not a totally convincing argument, however, since the indices used for the quality of medical care accounted for possible time trends in disease severity at birth. If the argument is valid, the analysis should have resulted in overestimates of the effect

for medical care quality rather than for Rh prophylaxis.

5.3.4 EFFECT OF CHANGES IN ABORTION RATES

This estimate was made using the conditional probability model only. Model 1 assumptions showed that changes in abortion rates in Manitoba between 1963 and 1988 (i.e., an increase from 4.5 to 16.6 per 100 livebirths) were responsible for a 12-14% increase in the rate of maternal Rh sensitization. Model 2 assumptions showed these changes were responsible for a 6-7% increase in the rate of maternal Rh sensitization. These estimates assume the absence of an Rh prophylaxis program, but given constancy of preventive fraction estimates across varying background rates of outcomes, are also applicable in a situation where Rh prophylaxis is routine.

5.3.5 EFFECT OF CHANGES IN RACIAL COMPOSITION

Changes in the racial composition of Manitoba births between 1963 and 1988 were found to have led to a 3% decline in the rate of maternal Rh sensitization. Changes in the racial composition of births among U.S. nonwhites, however, may have had a slightly larger effect, though its magnitude could not be estimated in the absence of data on the racial composition of births for the early years under study.

5.3.6 EFFECT OF RACE

The Poisson regression model using data from the United States

showed that white infants were at a 6-7 times greater risk of death from hemolytic disease of the newborn than nonwhite infants in the pre-prophylaxis years. The risk ratio declined to 2.5 in the post-prophylaxis period. Conditional probability modeling showed that whites were at 10-fold greater risk of maternal Rh sensitization than Native Indians and at a 2.5-fold greater risk than Asian Indians. Results from the conditional probability model are more trustworthy, since extraneous factors like differential access to Rh prophylaxis may have been responsible for the results seen with Poisson regression.

5.3.7 EFFECT OF Rh-SPECIFIC BLOOD TRANSFUSIONS

The introduction of Rh type-specific blood transfusions was responsible for a 22% (95% confidence interval=2 to 38%) decline in infant deaths from hemolytic disease in Canada, while the results of the analysis of U.S data (total population) showed a preventive fraction of 19% (95% confidence interval=13 to 25%) associated with the introduction of this service.

5.3.8 EFFECT OF NON-PROGRAM FACTORS

Poisson regression showed that non-program factors were responsible for a 78% (95% confidence interval=42 to 91%) decline in perinatal deaths from Rh disease in Manitoba between 1963 and 1988, while 73% (95% confidence interval=

51 to 85%) of the decline in infant deaths from hemolytic disease in Canada was due to non-program factors. The corresponding estimate for the United States (total population) was 76% (95% confidence interval=54 to 88%). The conditional probability model showed that non-program factors were responsible for 88% of the decline in perinatal deaths from Rh disease in Manitoba between 1963 and 1988. This point estimate lies within the 95% confidence bounds of the estimate obtained by Poisson regression. A better representation of the birth order distribution and a clear separation of the effects of abortion and changes in racial composition were probably responsible for the higher point estimate obtained from the conditional probability model.

5.3.9 MODIFICATION OF Rh PROPHYLAXIS EFFECT BY RACE

The low rate of Rh prophylaxis effectiveness seen among U.S. nonwhites as compared with U.S. whites is one of the most provocative findings of this study. Possible explanations include differential access to Rh prophylaxis by race and under-reporting of infant deaths from hemolytic disease of the newborn among nonwhites in the pre-prophylaxis years. A study of Rh prophylaxis coverage rates by race is indicated to resolve this issue and correct possible shortcomings in the delivery of this cost-effective intervention. The interpretation that the approximately similar rates of hemolytic disease among whites and nonwhites imply identical

Rh prophylaxis benefits across the racial categories [36] is not justified by the available evidence.

5.3.10 COST-EFFECTIVENESS OF Rh PROPHYLAXIS

This analysis was undertaken for the purpose of comparing alternative strategies of Rh prophylaxis in terms of cost and cost-effectiveness. The cost-effectiveness of Rh prophylaxis relative to a curative strategy is not questioned. Rather, the attempt is to optimise Rh prophylaxis options in terms of cost (a feasibility issue) and cost-effectiveness. In this context, it should be noted that most of the morbidity and mortality associated with Rh disease in Third-world countries does not constitute a significant burden on health care costs, principally because no significant medical interventions are attempted in these situations. While developed countries view cost-effective preventive options as inexpensive, these same options represent expensive alternatives in third world countries.

In terms of cost and cost-effectiveness, the option of providing Rh prophylaxis to first births appears to be the most financially feasible and efficient option. The annual requirements for Rh immunoglobulin under this option are 3-4 times less than the requirements under the other options. This option also offers the greatest effect on reduction in Rh sensitization per dose of Rh immunoglobulin administered. These recommendations apply especially to countries such as

India and those of Africa where Rh-negative prevalence rates range between 5% and 8%. The unconfirmed finding of Thornton et al [135] that effects of Rh immunoglobulin administered in the first pregnancy persist into subsequent pregnancies would be an additional advantage of this strategy. Thus, administration of Rh prophylaxis (postpartum) for first births under a national health care program would be the most effective starting point for an Rh prophylaxis program. This could be extended to unrestricted postpartum prophylaxis (for subsequent pregnancies) at a later stage. Post-abortion prophylaxis would be a third-stage option which could be introduced as a final measure.

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APPENDIX

Table 1A. Showing the wide variation in the prevalence of the three different Rh genotypes according to country and race. (Data from Mourant et al [53] and Tills et al [54]).
* indicating extremely low prevalence (ie. < 1%) not a total absence of said phenotype).

	COUNTRY (RACE)	PREVALENCE OF Rh GENOTYPE Rh dd	Rh Dd	Rh DD
EUROPE	France	0.16	0.48	0.36
	Germany	0.18	0.49	0.33
	Greece	0.11	0.45	0.44
	Italy	0.16	0.48	0.36
	Sweden	0.17	0.49	0.34
	England	0.18	0.49	0.33
	USSR	0.16	0.48	0.36
ASIA	Siberia	0.01	0.21	0.78
	Uzbekistan	0.06	0.37	0.57
	Iran	0.09	0.42	0.49
	India	0.04	0.30	0.66
	Vietnam	0.00*	0.03	0.97
	China	0.00*	0.08	0.92
	Japan	0.01	0.20	0.79
	Korea	0.00	0.00	1.00
AFRICA	Nigeria	0.05	0.36	0.59
	Madagascar	0.01	0.19	0.80
	Rhodesia(Zim)	0.04	0.32	0.64
	Congo	0.04	0.32	0.64
	Senegal	0.07	0.38	0.55
N AMERICA	Canada	0.16	0.48	0.36
	Cree	0.02	0.22	0.76
	USA-White	0.17	0.48	0.35
	Puerto Rico	0.10	0.44	0.46
S.AMERICA	Argentina	0.08	0.41	0.51
	Brazil-White	0.15	0.48	0.37
	Indian	0.01	0.16	0.83
AUSTRALIA	White	0.18	0.49	0.33
	Aborigine	0.00*	0.00*	1.00

Table 2A. List of exclusion criteria used for the compilation of annual statistics on Rh disease related outcomes in Manitoba and Nova Scotia.

1. Non-residents of Manitoba (or Nova Scotia).
2. Passive Rh immune globulin (WinRho contaminants).
3. Sensitization due to blood group antibodies which rarely or never produce clinical erythroblastosis (eg M, Wr^a, LW^b, s, Le, weak autoantibodies etc.).
4. Miscarriages and abortions.
5. Antibody very weak being demonstrable only by an enzyme or Autoanalyser techniques and representing a degree of sensitization which carries no risk to fetus (Note: These new techniques of testing were introduced in Manitoba in 1967 [87, annual report for 1974]).

Table 3A. Changes in the International Classification of Diseases (ICD) codes for Rh hemolytic disease of the newborn from the sixth to the ninth revisions [97-100].

ICD Sixth Revision 1948

770 Hemolytic disease of newborn (erythroblastosis).

- 770.0 Erythroblastosis, without mention of nervous affection or immaturity.
- 770.1 Kernicterus, without mention of immaturity.
- 770.2 Erythroblastosis, with disorder of liver other than icterus gravis, without mention of immaturity.
- 770.5 Erythroblastosis, without mention of nervous affection but with immaturity.
- 770.6 Kernicterus with immaturity.
- 770.7 Erythroblastosis, with disorder of liver other than icterus gravis, with immaturity.

ICD Seventh Revision 1955 (no change)

770 Hemolytic disease of newborn (erythroblastosis).

- 770.0 Erythroblastosis, without mention of nervous affection or immaturity.
- 770.1 Kernicterus, without mention of immaturity.
- 770.2 Erythroblastosis, with disorder of liver other than icterus gravis, without mention of immaturity.
- 770.5 Erythroblastosis, without mention of nervous affection but with immaturity.
- 770.6 Kernicterus with immaturity.
- 770.7 Erythroblastosis, with disorder of liver other than icterus gravis, with immaturity.

Table 3A (cont.) Changes in the International Classification of Diseases (ICD) codes for Rh hemolytic disease of the newborn from the sixth to the ninth revisions [97-100].

ICD Eighth Revision 1965

774 Hemolytic disease of the newborn with kernicterus.

- 774.0 With Rh incompatibility.
- 774.1 With ABO incompatibility.
- 774.2 With other or unspecified incompatibility.
- 774.3 Without mention of cause.

775 Hemolytic disease of the newborn, without mention of kernicterus.

- 775.0 With Rh incompatibility.
- 775.1 With ABO incompatibility.
- 775.2 With other or unspecified incompatibility.
- 775.3 Without mention of cause.

ICD Ninth Revision 1975

773 Hemolytic disease of fetus or newborn, due to isoimmunization.

- 773.0 Hemolytic disease due to Rh isoimmunization.
- 773.1 Hemolytic disease due to ABO isoimmunization.
- 773.2 Hemolytic disease due to other and unspecified isoimmunization.
- 773.3 Hydrops fetalis due to isoimmunization.
- 773.4 Kernicterus due to isoimmunization.
- 773.5 Late anemia due to isoimmunization.

774 Other perinatal jaundice

- 774.1 Perinatal jaundice from herditary haemolytic anaemias
- 774.2 Perinatal jaundice from other excessive haemolysis
- 774.3 Neonatal jaundice associated with preterm delivery
- 774.4 Perinatal jaundice due to hepatocellular damage
- 774.5 Perinatal jaundice from other causes
- 774.6 Unspecified fetal and neonatal jaundice
- 774.7 Kernicterus nor due to isoimmunization

Note: Other perinatal jaundice (coded 774 under the Ninth Revision) did not receive a 3 digit code untill the Ninth revision. Such cases were coded under hemolytic disease of the newborn codes in the Sixth, Seventh and Eighth ICD revisions. See sections 3.1.12 and 4.1.8 for the implications of such misclassifcation.

Table 4A. Range of values considered at each chance node in the conditional probability model for the Monte Carlo sensitivity analysis.

Variable	Point Estimate	Range
Prevalence of the Rh negative phenotype		
Whites	0.17	0.15-0.19
Native Indians	0.01	0.005-0.015
Prevalence of ABO compatibility		
Whites	0.85	0.83-0.87
Native Indians	0.88	0.86-0.90
Probability of maternal Rh sensitization following		
Abortion	0.045	0.035-0.055
Delivery	0.07	0.05-0.09
Magnitude of protection due to ABO incompatibility		
A incompatibility	0.90	0.85-0.95
B incompatibility	0.55	0.45-0.65
Abortion rate in Manitoba, 1963	4.5/100 livebirths	2.0-7.0
Perinatal survival given Rh sensitization		
Manitoba, 1963	88.3%	84.0-92.5
Manitoba, 1988	97.8%	95.6-99.9
Proportion of white births		
Manitoba, 1963	96.5%	94.0-99.0
Manitoba, 1988	93.4%	91.0-95.8
Rh immunoglobulin efficacy	80.0%	70.0-90.0

Table 5A: Data for Poisson regression: changes in the three factors affecting Rh disease outcome occurrence and the rates of the three Rh disease-related outcomes in Manitoba between 1963-68 and 1982-88. BO1 = Proportion of first births (%), PCQ = Perinatal Care Quality i.e., perinatal survival given Rh hemolytic disease of the newborn and PRG = Presence or absence of Rh prophylaxis program.

Year	BO1	PCQ	PRG	Rh sensiti-zation	Rh HDN	Perinatal deaths from Rh disease
1963	25.0	86.2	0	9.61	8.10	1.12
1964	27.1	84.3	0	10.33	8.38	1.31
1965	27.7	88.1	0	8.39	7.76	0.92
1966	29.7	89.0	0	8.61	6.83	0.75
1967	32.8	90.2	0	8.06	6.49	0.64
1968	35.5	93.0	0	8.19	6.48	0.46
1982	41.1	96.4	1	2.10	1.73	0.06
1983	42.5	100.0	1	2.16	1.44	0.00
1984	41.8	100.0	1	2.80	1.97	0.00
1985	39.9	96.3	1	1.99	1.58	0.06
1986	40.5	93.6	1	2.04	1.81	0.12
1987	39.7	100.0	1	1.82	1.24	0.00
1988	40.2	97.4	1	2.64	2.23	0.06

Note: Although rates of the 3 outcomes are shown above, actual outcome counts and numbers of births were used in the regression.

Table 6A: Numbers and rates (per 1000 total births) of three Rh disease outcomes observed in Manitoba in 1963 and 1990.

Year	Rh sensitization		Rh hemolytic disease		Perinatal deaths from Rh disease	
	Number	Rate	Number	Rate	Number	Rate
1963	223	9.61	188	8.10	26	1.12
1990	43	2.46	36	2.06	0	0.00

Table 7A: Changes in the three factors affecting Rh disease occurrence in Manitoba between 1963 and 1990 (Rh HDN = Rh hemolytic disease of the newborn).

Year	First births (percent)	Perinatal survival given Rh HDN	Program
1963	25.0	86.2	0
1990	41.6	100.0	1

Table 8A: Changes in the frequency of Rh disease outcomes between 1963 and 1990 as estimated using 3 different measures of impact (RD=risk difference per 1000 total births, RR=risk ratio and PF=preventive fraction).

Year	Rh sensitization	Rh hemolytic disease	Perinatal deaths from Rh disease
RD	7.14	6.04	1.12
RR	0.26	0.25	0.00
PF	0.74	0.75	1.00

Table 9A: Result of Poisson regression using data from Manitoba 1963-68 and 1982-90 with rate of Rh sensitization as the outcome. BETA=beta coefficient for unit change in the independent variable, SE=standard error of the beta coefficient estimate, RR=risk ratio (for the observed change in the independent variable between 1963 and 1988), PF=preventive fraction and 95% CI=95% confidence interval on the preventive fraction.

OUTCOME=Rh SENSITIZATION

VARIABLE (MODEL)	BETA	SE	RR	PF	95% CI on PF
BO1	-0.0912	0.0042	0.22	77.9	74.7-80.7
DEVIANCE=95.7, df=13, p<0.001					
PRG	-1.356	0.0615	0.26	74.2	70.9-77.2
DEVIANCE=16.7, df=13, p>0.2					
BO1	-0.0176	0.0088	0.75	25.2	0.6-43.8
PRG	-1.1490	0.1210	0.32	68.3	59.8-75.0
DEVIANCE=12.61, df=12, p>0.3					

Table 10A: Result of Poisson regression using data from Manitoba 1963-68 and 1982-90 with rate of Rh hemolytic disease of the newborn as the outcome.

OUTCOME=Rh HEMOLYTIC DISEASE

VARIABLE (MODEL)	BETA	SE	RR	PF	95% CI on PF
BO1	-0.0960	0.0047	0.20	79.6	76.2-82.4
DEVIANCE=73.8, df=13, p<0.001					
PRG	-1.41	0.0688	0.24	75.6	72.1-78.7
DEVIANCE=18.9, df=13, p>0.1					
BO1	-0.0257	0.0097	0.65	34.6	10.4-52.3
PRG	-1.1060	0.1352	0.33	66.9	56.9-74.6
DEVIANCE=11.82, df=12, p>0.4					

Table 11A: Result of Poisson regression using data from Manitoba 1963-68 and 1982-90 with rate of perinatal deaths from Rh hemolytic disease of the newborn as the outcome.

OUTCOME=PERINATAL DEATHS FROM Rh HEMOLYTIC DISEASE

VARIABLE (MODEL)	BETA	SE	RR	PF	95% CI on PF
BO1	-0.1915	0.0198	0.04	95.8	92.0-97.8
DEVIANCE=24.3, df=13, p<0.05					
PCQ	-0.2359	0.0241	0.04	96.1	92.6-98.0
DEVIANCE=18.0, df=13, p>0.1					
PRG	-3.3110	0.4572	0.04	96.4	91.1-98.5
DEVIANCE=20.2, df=13, p>0.05					
BO1	-0.0934	0.0310	0.21	78.7	41.7-92.2
PRG	-2.1720	0.6025	0.11	88.6	62.9-96.5
DEVIANCE=10.3, df=12, p>0.5					
PCQ	-0.1361	0.0369	0.15	84.7	58.6-94.4
PRG	-1.9310	0.5929	0.16	85.5	53.7-95.5
DEVIANCE=5.8, df=12, p>0.9					
BO1	0.0032	0.0559	1.01	-5.5	-84.5-82.8
PCQ	-0.1391	0.0643	0.15	85.3	19.7-97.4
PRG	-1.9410	0.6145	0.14	85.6	52.1-95.7
DEVIANCE=5.79, df=11, p>0.8					
BO1, PCQ	-1.8660	0.5448	0.15	84.5	55.0-94.7
PRG	-1.9410	0.6145	0.14	85.6	52.1-95.7

BO1, PCQ represents the combined effects of BO1 and PCQ. The beta coefficient was calculated using the formula

$$\text{Beta} = (B_1 * (\text{BO1}(1963) - \text{BO1}(1988))) + (B_2 * (\text{PCQ}(1963) - \text{PCQ}(1988)))$$

The risk ratio thus represents the combined effects of changes observed in BO1 and ISR between 1963 and 1988.

Table 12A: Result of logistic regression using data from Manitoba 1963-68 and 1982-88, with rate of Rh sensitization as the outcome. The regression model used the logistic link with error specified as binomial (OR=odds ratio).

OUTCOME=Rh SENSITIZATION

VARIABLE (MODEL)	BETA	SE	OR	PF	95% CI on PF
BO1	-0.0914	0.0045	0.25	75.0	71.4-78.2
DEVIANCE=95.8, df=11, p<0.001					
PRG	-1.3990	0.0691	0.25	75.3	71.7-78.4
DEVIANCE=15.1, df=11, p>0.1					
BO1	-0.0182	0.0088	0.76	24.1	1.4-41.7
PRG	-1.1880	0.1246	0.30	69.5	61.1-76.1
DEVIANCE=10.80, df=10, p>0.3					

Table 13A: Result of logistic regression using data from Manitoba 1963-68 and 1982-88, with rate of Rh disease as the outcome. The regression model used the logistic link with error specified as binomial (OR=odds ratio).

OUTCOME=Rh HEMOLYTIC DISEASE

VARIABLE (MODEL)	BETA	SE	OR	PF	95% CI on PF
BO1	-0.0973	0.0051	0.23	77.2	73.5-80.4
DEVIANCE=73.6, df=11, p<0.001					
PRG	-1.4730	0.0781	0.23	77.1	73.3-80.3
DEVIANCE=16.1, df=11, p>0.1					
BO1	-0.0266	0.0098	0.67	33.2	10.6-50.1
PRG	-1.1620	0.1396	0.31	68.7	58.9-76.2
DEVIANCE=8.61, df=10, p>0.5					

Table 14A: Result of logistic regression using data from Manitoba 1963-68 and 1982-88 with rate of perinatal deaths from Rh disease as the outcome. The regression model used the logistic link with error specified as binomial (OR=odds ratio).

OUTCOME=PERINATAL DEATHS FROM Rh HEMOLYTIC DISEASE

VARIABLE (MODEL)	BETA	SE	OR	PF	95% CI on PF
BO1	-0.1785	0.0203	0.07	93.4	87.9-96.4
DEVIANCE=19.1, df=11, p>0.05					
PCQ	-0.2241	0.0249	0.08	91.9	86.0-95.3
DEVIANCE=14.8, df=11, p>0.1					
PRG	-3.0530	0.4574	0.05	95.3	88.4-98.1
DEVIANCE=17.6, df=11, p>0.05					
BO1	-0.0928	0.0310	0.24	75.6	38.5-90.3
PRG	-1.9360	0.5992	0.14	85.6	53.3-95.5
DEVIANCE=7.8, df=10, p>0.6					
PCQ	-0.1326	0.0369	0.23	77.4	49.1-89.9
PRG	-1.779	0.5806	0.17	83.1	47.3-94.6
DEVIANCE=3.93, df=10, p>0.95					
BO1	-0.0026	0.0559	0.99	3.84	-80.3-81.8
PCQ	-0.1302	0.0647	0.23	76.7	3.9-94.4
PRG	-1.771	0.6085	0.17	83.0	43.9-94.8
DEVIANCE=3.92, df=9, p>0.9					

Table 15A: Result of Poisson regression, Manitoba 1963-68 and 1982-88, with rate of perinatal deaths from Rh hemolytic disease of the newborn as the outcome: exploratory analysis using various alternatives for quantifying birth order distribution.
OUTCOME=PERINATAL DEATHS FROM Rh HEMOLYTIC DISEASE

VARIABLE (MODEL)	BETA	SE	RR	PF EF	95% CI on PF
BO1	-0.1784	0.0203	0.07	93.4	87.8-96.4
BO2	-0.3152	0.0435	0.05	95.2	89.2-97.9
BO3	0.8301	0.1099	2.29	59.2	48.5-67.7
BO1	-0.0026	0.0559	0.96	3.9	-80.3-81.8
PCQ	-0.1301	0.0647	0.23	76.7	3.8-94.4
PRG	-1.7710	0.6084	0.17	83.0	43.9-94.8
DEVIANCE= 3.93, df=9, p>0.9					
BO1—┐ *	-1.4960	0.4851	0.22	77.6	42.1-91.4
PCQ—┘					
PRG	-1.7710	0.6084	0.17	83.0	43.9-94.8
BO2	0.0854	0.2299	2.28	-56.2	-99.4-97.1
PCQ	-0.1576	0.0772	0.17	82.9	7.4-96.9
PRG	-2.3970	1.7620	0.09	90.9	-65.2-99.7
DEVIANCE=3.79, df=9, p>0.9					
BO3	0.0019	0.1918	0.99	0.2	50.4-49.8
PCQ	-0.1320	0.0682	0.23	77.2	-1.8-94.9
PRG	-1.7830	0.6634	0.17	83.2	38.3-95.4
DEVIANCE=3.93, df=9, p>0.9					
BO3—┐ *	-1.4800	0.5995	0.23	77.3	26.3-93.0
PCQ—┘					
PRG	-1.7830	0.6634	0.17	83.2	38.3-95.4
BO1	-0.0119	0.0823	0.83	16.5	-89.7-92.8
BO2	0.1537	0.3037	4.41	-77.3	-99.9-98.6
BO3	0.0541	0.3102	0.94	5.8	-81.9-51.1
PCQ	-0.1503	0.0801	0.86	81.4	-7.1-96.8
PRG	-2.943	2.5300	0.05	94.7	-86.7-99.9
DEVIANCE=3.67, df=7 p>0.8					
BO1	-0.0047	0.0816	0.99	6.9	-90.6-91.8
BO3	-0.0099	0.2808	1.01	-1.1	-83.1-79.3
PCQ	-0.1310	0.0702	0.23	76.9	-7.1-95.1
PRG	-1.7480	0.8993	0.17	82.6	-1.5-97.0
DEVIANCE=3.92, df=8, p>0.8					

* See footnote to Table 11A for explanation.

Figure 1A. Poisson regression of Manitoba data: graphical depiction of the effect of birth order changes on the rate of perinatal deaths from Rh disease (per 100,000 total births), with effect modification of the risk difference by the quality of perinatal care (Rh prophylaxis program present).

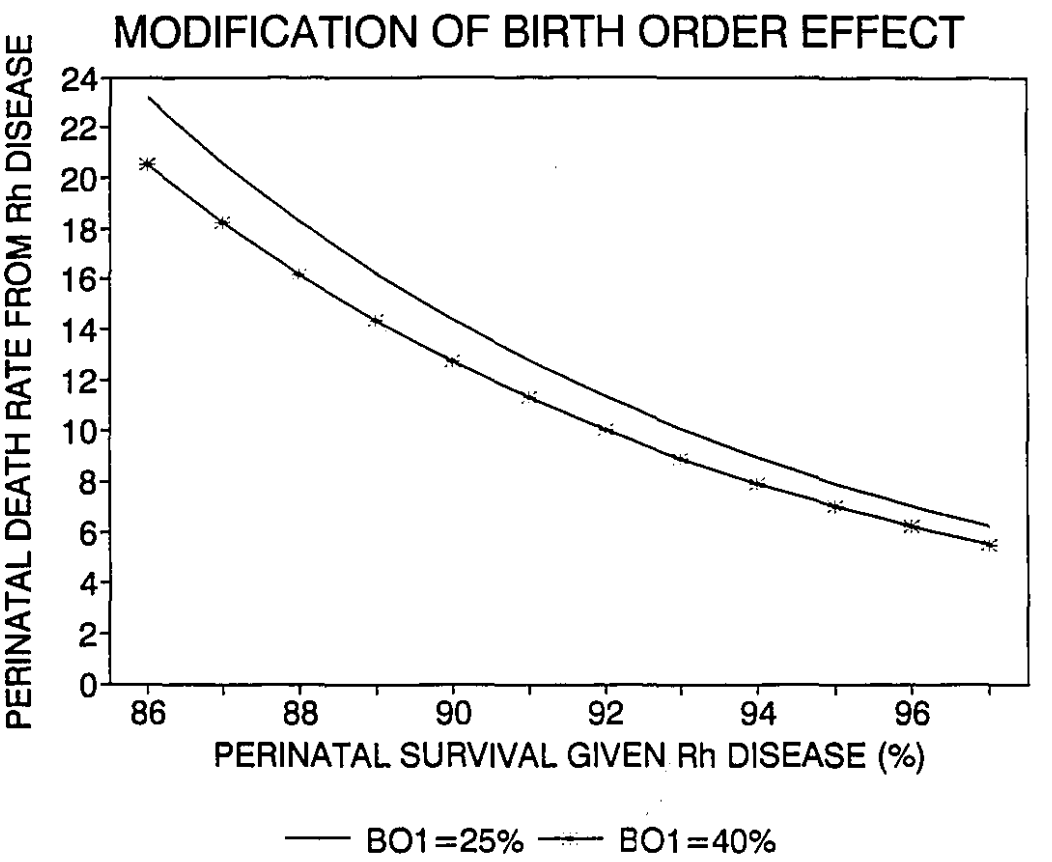


Figure 2A. Poisson regression of Manitoba data: graphical depiction of the effect of birth order changes on the rate of perinatal deaths from Rh disease (per 100,000 total births), with effect modification of the risk difference by the presence/absence of an Rh prophylaxis program (quality of perinatal care kept constant at the 1963 level).

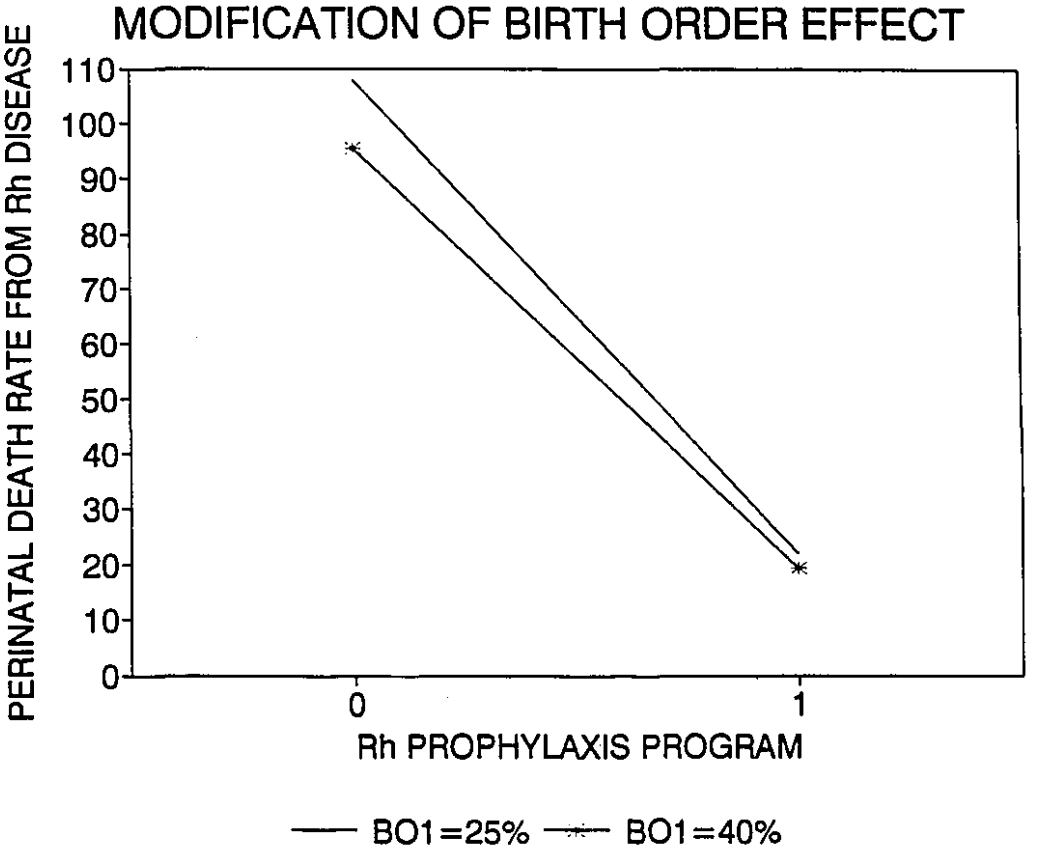


Figure 3A. Poisson regression of Manitoba data: graphical depiction of the effect of birth order changes on the rate of perinatal deaths from Rh disease (per 100,000 total births), with effect modification of the risk difference by the presence/absence of an Rh prophylaxis program (quality of perinatal care kept constant at the 1988 level).

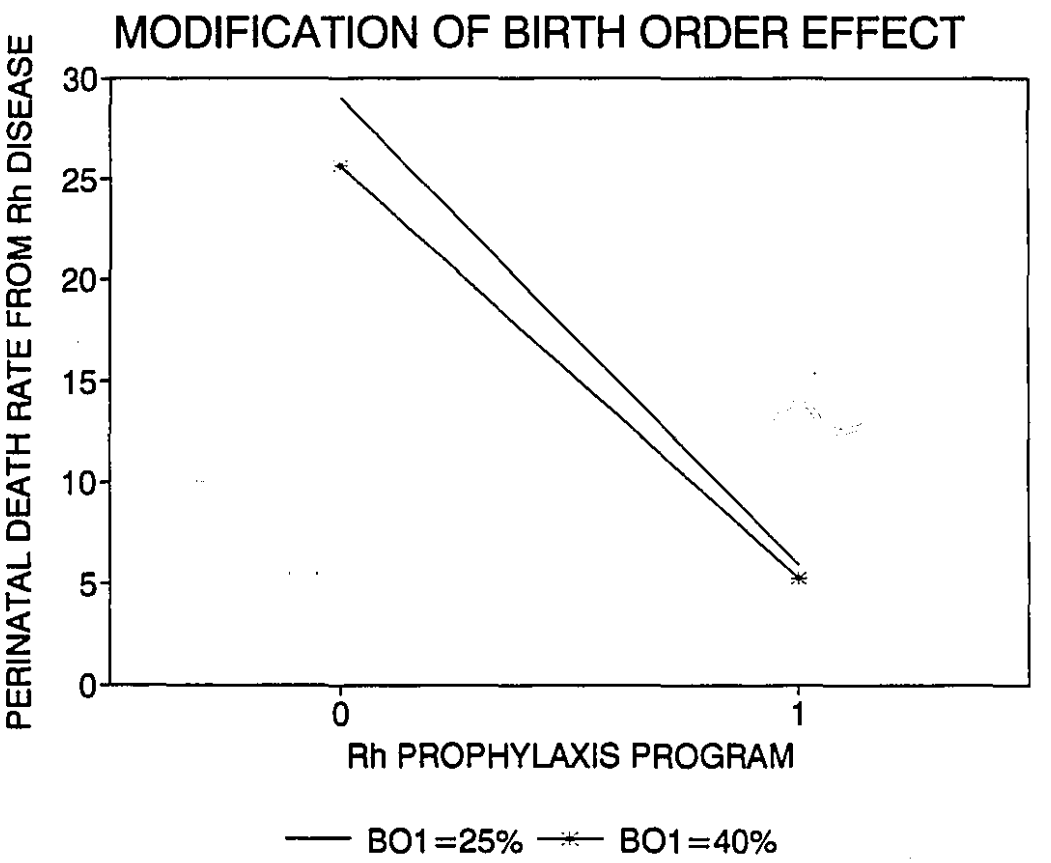


Figure 4A. Poisson regression of Manitoba data: graphical depiction of the effect of the quality of perinatal care on the rate of perinatal deaths from Rh disease (per 100,000 total births), with effect modification of the risk difference by the presence or absence of a program of Rh prophylaxis (proportion of first births kept constant at the 1988 level).

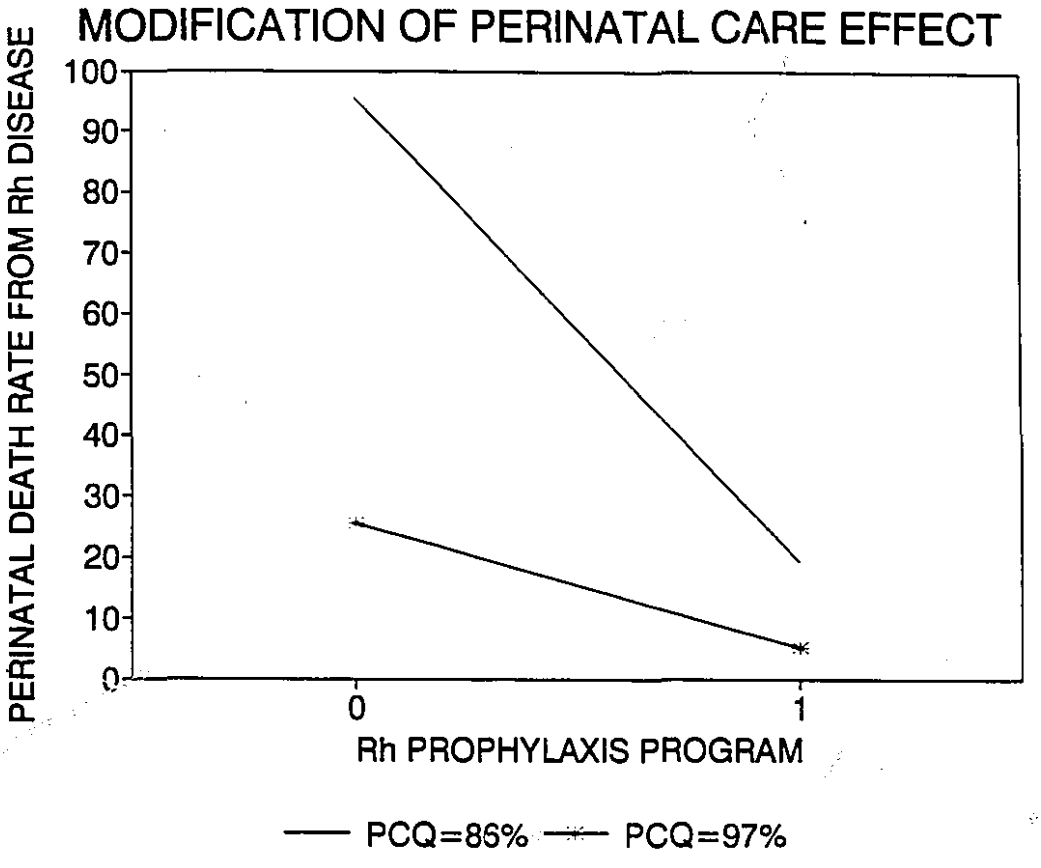


Figure 5A. Poisson regression of Manitoba data: graphical depiction of the effect of the quality of perinatal care on the rate of perinatal deaths from Rh disease (per 100,000 total births), with effect modification of the risk difference by the proportion of first births in the population (Rh prophylaxis program absent).

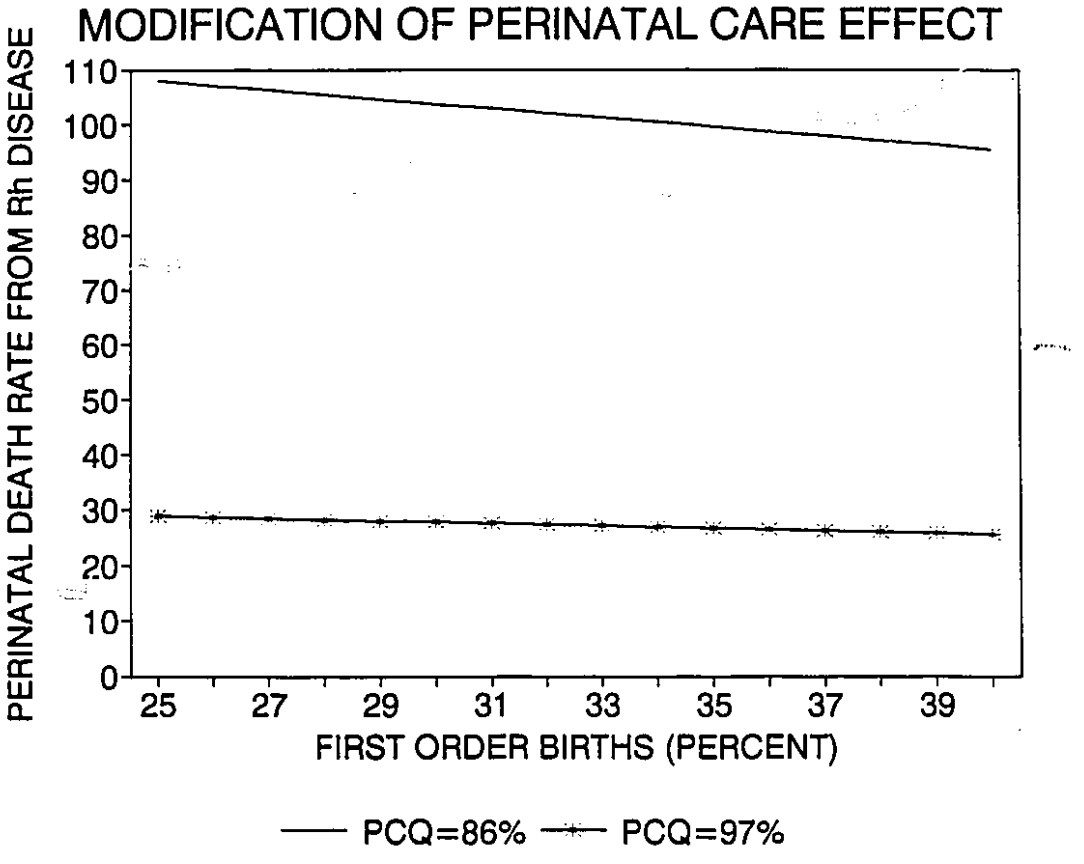


Figure 6A. Poisson regression of Manitoba data: graphical depiction of the effect of the quality of perinatal care on the rate of perinatal deaths from Rh disease (per 100,000 total births), with effect modification of the risk difference by the proportion of first births in the population (Rh prophylaxis program present).

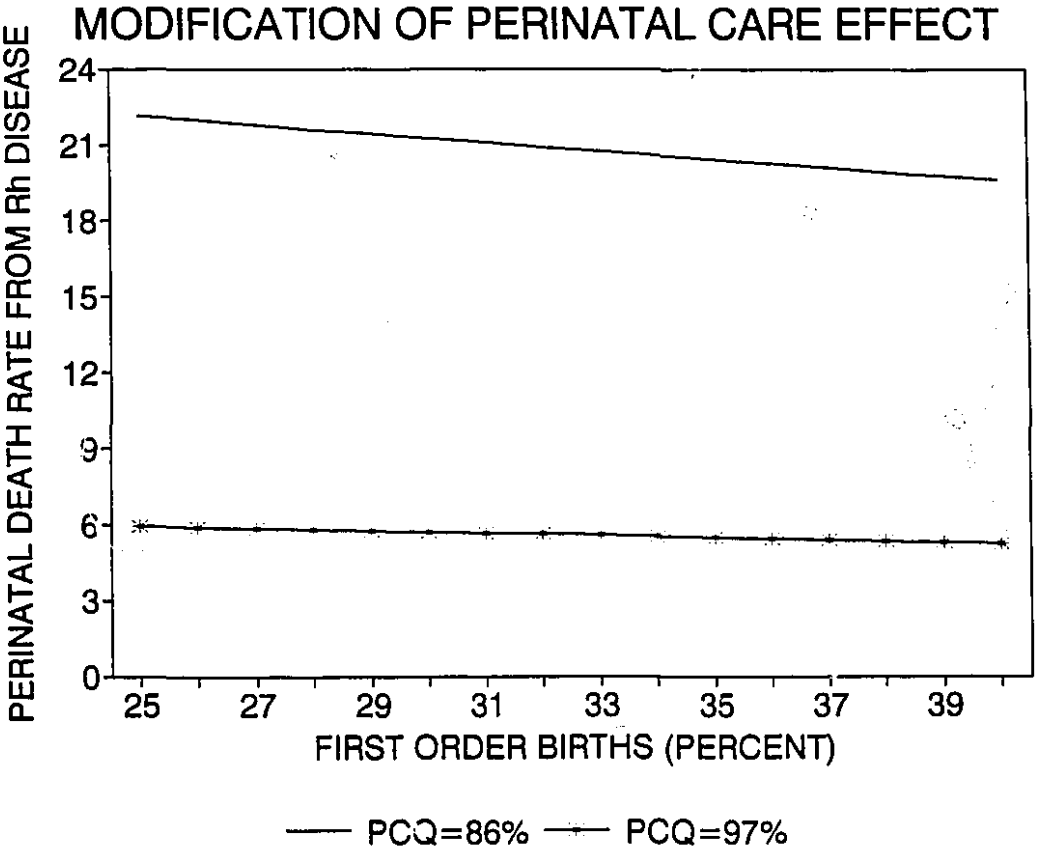


Figure 7A. Poisson regression of Manitoba data: graphical depiction of the effect of a program of Rh prophylaxis on the rate of perinatal deaths from Rh disease (per 100,000 total births), with effect modification of the risk difference by the quality of perinatal care (proportion of first births kept constant at the 1988 level).

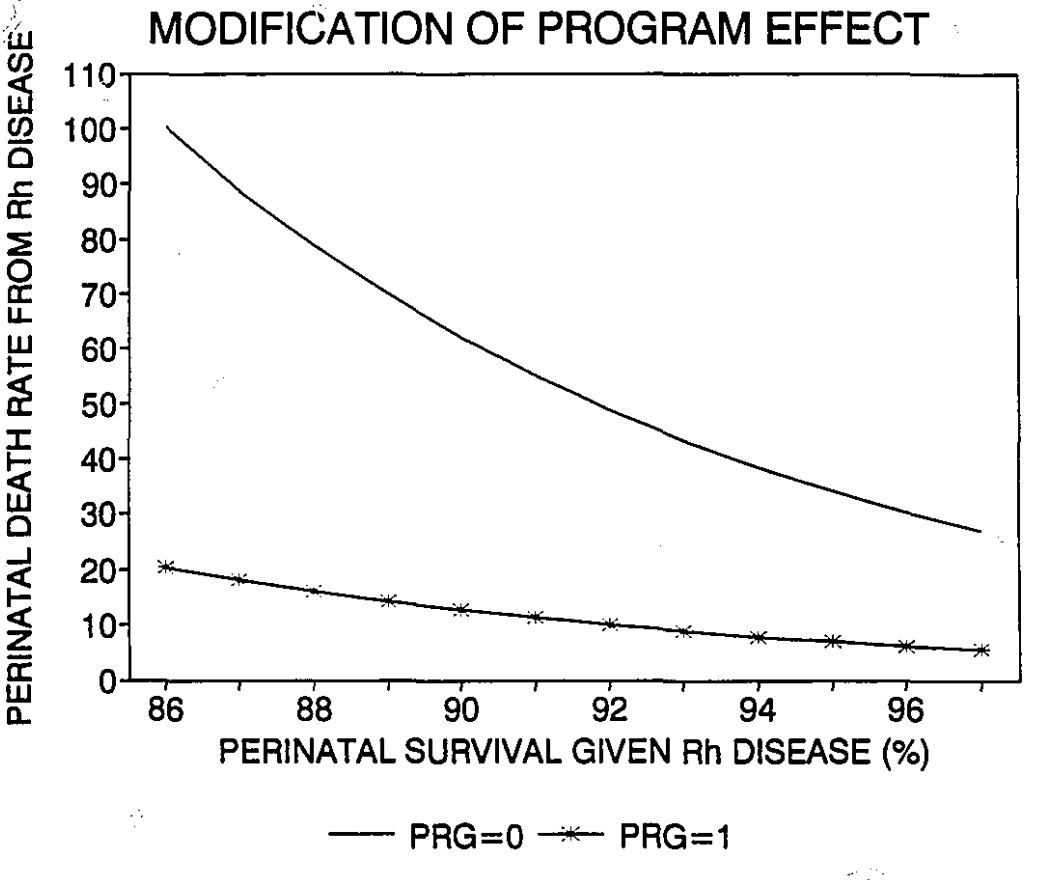


Figure 8A. Poisson regression of Manitoba data: graphical depiction of the effect of a program of Rh prophylaxis on the rate of perinatal deaths from Rh disease (per 100,000 total births), with effect modification of the risk difference by the proportion of first births in the population (quality of perinatal care kept constant at the 1963 level).

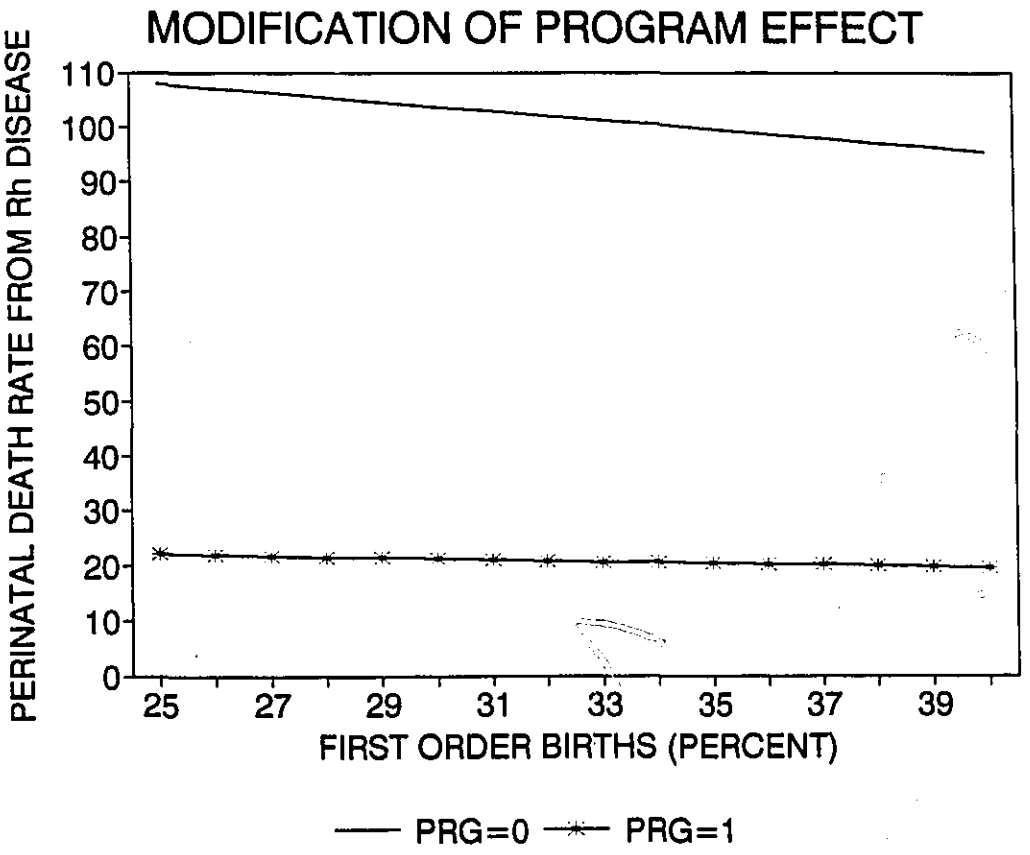


Figure 9A. Poisson regression of Manitoba data: graphical depiction of the effect of a program of Rh prophylaxis on the rate of perinatal deaths from Rh disease (per 100,000 total births), with effect modification of the risk difference by the proportion of first births in the population (quality of perinatal care kept constant at the 1988 level).

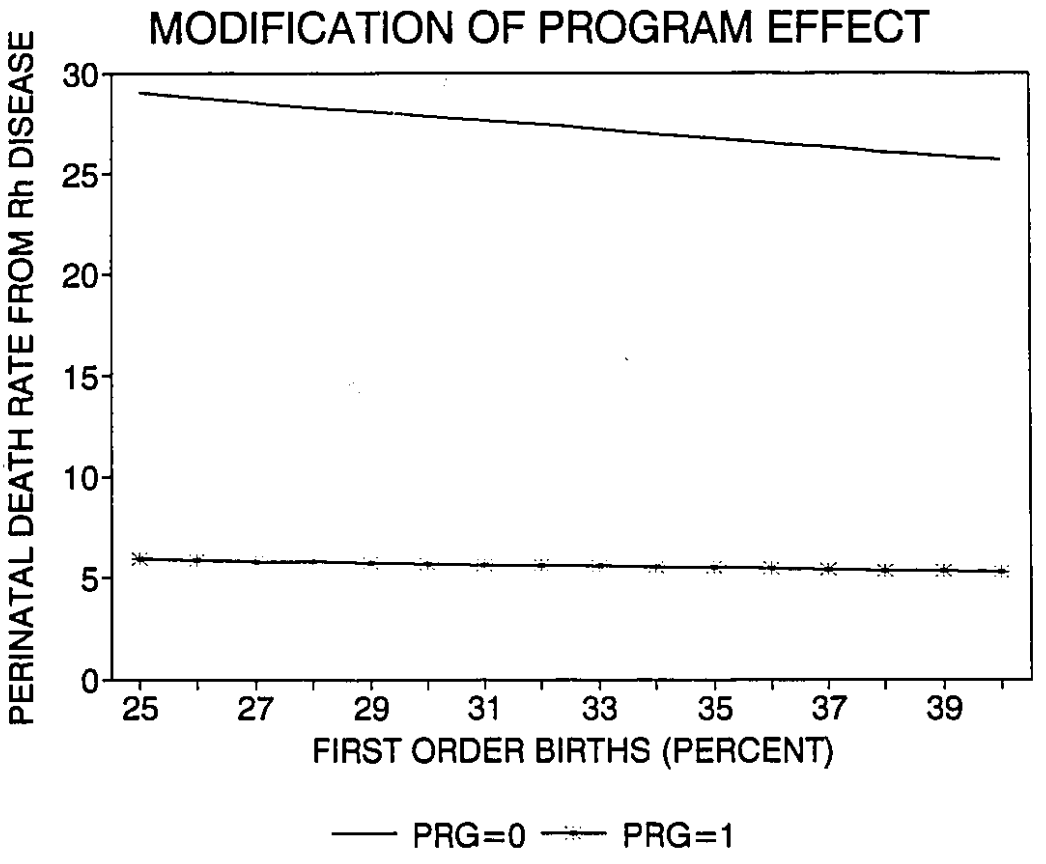


Table 16A: Numbers and rates (per 1000 total births) of three Rh disease outcomes observed in Manitoba in 1963 and Nova Scotia in 1988.

Year	Rh sensitization		Rh hemolytic disease		Perinatal deaths from Rh disease	
	Number	Rate	Number	Rate	Number	Rate
1963 Manitoba	223	9.61	188	8.10	26	1.12
1988 Nova Scotia	47	3.84	15	1.23	0	0.00

Table 17A: Changes in the frequency of Rh disease outcomes between 1963 (Manitoba) and 1988 (Nova Scotia) as estimated using 3 different measures of impact (RD=risk difference, RR=risk ratio and PF=preventive fraction).

	Rh sensitization	Rh hemolytic disease	Perinatal deaths from Rh disease
RD	5.76	6.87	1.12
RR	0.40	0.15	(0)
PF(%)	59.98	84.85	100.0

Table 18A: Changes in the three factors affecting Rh disease occurrence in Manitoba (1963) and Nova Scotia (1988).

Year	First births (percent)	Perinatal survival given Rh HDN	Program
1963 Manitoba	25.0	86.2	0
1988 Nova Scotia	43.91	100.0	1

Table 19A: Data for Poisson regression: Changes in the three factors affecting Rh disease outcome occurrence and the rates of the three Rh disease related outcomes in Manitoba (between 1963-68) and Nova Scotia (between 1982-88). BO1 = proportion of first births (%), PCQ = perinatal care quality ie. perinatal survival given Rh hemolytic disease of the newborn and PRG = presence/presence of an Rh prophylaxis program.

Year	BO1	PCQ	PRG	Rh sensiti -zation	Rh HDN	Perinatal deaths from Rh disease
1963	25.01	86.2	0	9.61	8.10	1.12
1964	27.06	84.3	0	10.33	8.38	1.31
1965	27.70	88.1	0	8.39	7.76	0.92
1966	29.70	89.0	0	8.61	6.83	0.75
1967	32.76	90.2	0	8.06	6.49	0.64
1968	35.50	93.0	0	8.19	6.48	0.46
1982	44.53	94.1	1	4.03	1.37	0.08
1983	44.90	95.8	1	5.37	1.92	0.08
1984	43.51	94.7	1	2.97	1.53	0.08
1985	43.34	91.7	1	3.04	0.96	0.08
1986	42.85	100.0	1	3.62	0.97	0.00
1987	42.47	100.0	1	3.37	1.40	0.00
1988	43.91	100.0	1	3.84	1.23	0.00

Note: Although rates of the 3 outcomes are shown above, actual outcome counts and numbers of births were used in the regression.

Figure 10A. Data from Manitoba (1963-81) and Nova Scotia (1982-88) showing rates of Rh sensitization, Rh hemolytic disease and perinatal deaths from Rh disease per 1000 total births.

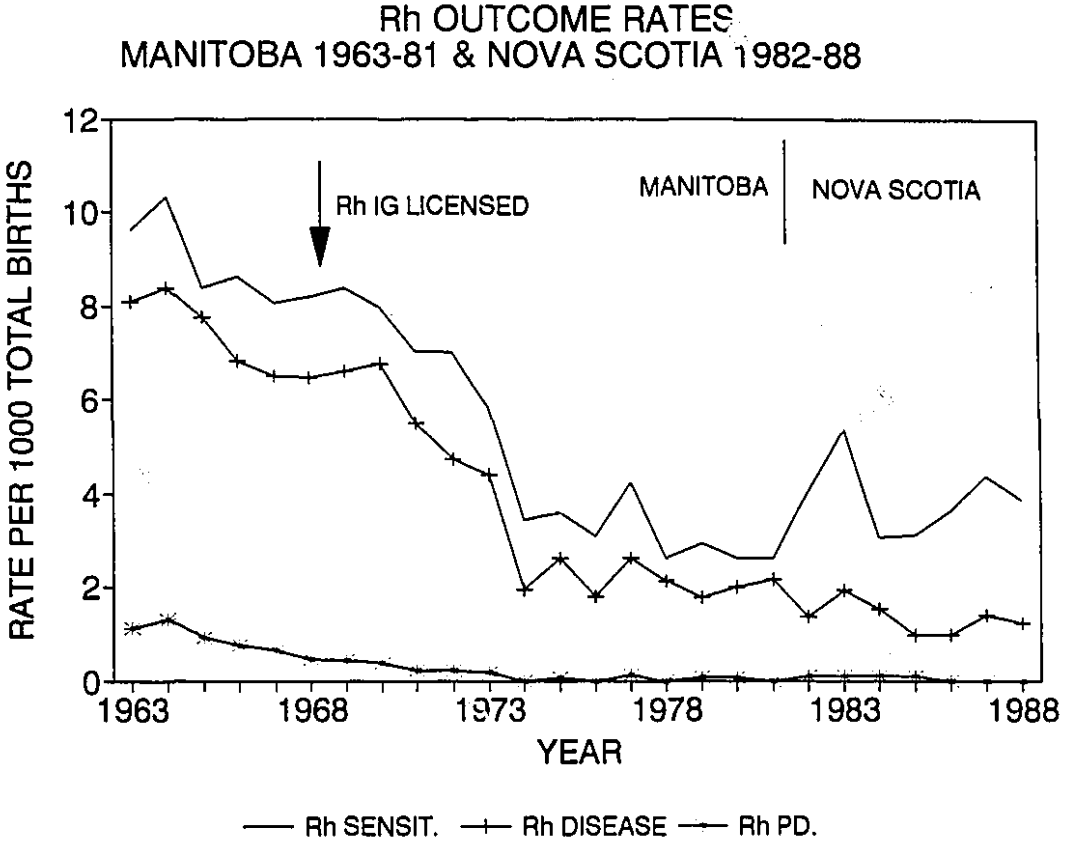


Table 20A: Result of Poisson regression using data from Manitoba for the years 1963-68 and Nova Scotia 1982-88 with rate of Rh sensitization as the outcome and effects expressed in terms of risk ratios and preventive fractions.

MANITOBA 1963-68, NOVA SCOTIA 1982-88
OUTCOME=Rh SENSITIZATION

VARIABLE (MODEL)	BETA	SE	RR	PF	95% CI on PF
BO1	-0.0514	0.0038	0.38	62.2	56.5-67.1
DEVIANCE=37.22, df=11, p<0.01					
PRG	-0.8686	0.0634	0.42	58.1	52.5-62.9
DEVIANCE=21.8, df=11, p<0.05					
BO1	-0.0163	0.0088	0.74	26.4	-1.8-46.9
PRG	-0.6331	0.1429	0.53	46.9	29.7-59.9
DEVIANCE=18.35, df=10, p<0.05					

Table 21A: Result of Poisson regression using data from Manitoba for the years 1963-68 and Nova Scotia 1982-88 with rate of Rh hemolytic disease of the newborn as the outcome and effects expressed as risk ratios and preventive fractions.

MANITOBA 1963-68, NOVA SCOTIA 1982-88
OUTCOME=Rh HEMOLYTIC DISEASE

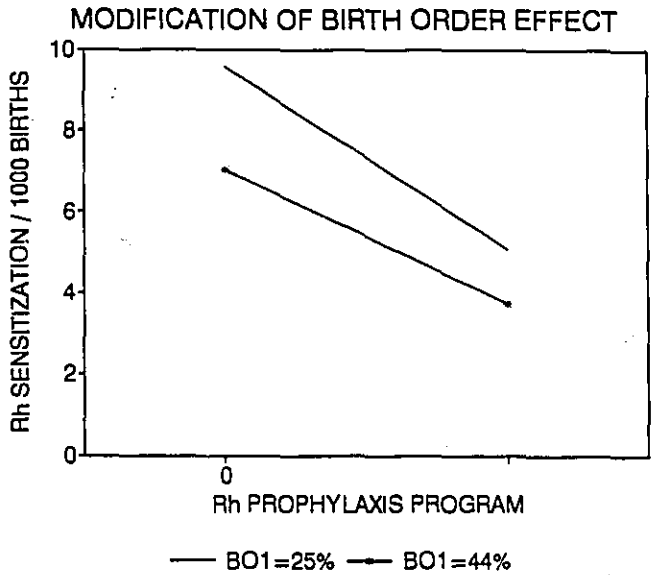
VARIABLE (MODEL)	BETA	SE	RR	PF	95% CI on PF
BO1	-0.0915	0.0050	0.18	82.3	78.6-85.3
DEVIANCE=65.32, df=11, p<0.001					
PRG	-1.7130	0.0987	0.18	82.0	78.1-85.1
DEVIANCE=15.70, df=11, p>0.1					
BO1	-0.0256	0.0098	0.62	38.4	11.4-57.1
PRG	-1.3410	0.1744	0.26	73.8	63.2-81.4
DEVIANCE=8.73, df=10, p>0.5					

Table 22A: Result of Poisson regression using data from Manitoba 1963-68 and Nova Scotia 1982-88 with rate of perinatal deaths from Rh hemolytic disease of the newborn as the outcome and effects expressed in terms of risk ratios and preventive fractions.

MANITOBA 1963-68, NOVA SCOTIA 1982-88
OUTCOME=PERINATAL DEATHS FROM Rh HEMOLYTIC DISEASE

VARIABLE (MODEL)	BETA	SE	RR	PF	95% CI on PF
BO1	-0.1504	0.0195	0.06	94.2	88.0-97.3
DEVIANCE=12.68, df=11, p>0.3					
PCQ	-0.2199	0.0274	0.05	95.2	89.9-97.7
DEVIANCE=16.48, df=11, p>0.1					
PRG	-2.9660	0.5091	0.05	94.6	86.0-98.1
DEVIANCE=15.95, df=11, p>0.1					
BO1	-0.0895	0.0309	0.18	81.6	42.2-94.1
PRG	-1.6350	0.6950	0.19	80.5	23.9-95.0
DEVIANCE=6.78, df=10, p>0.7					
PCQ	-0.1292	0.0365	0.17	83.2	54.8-93.7
PRG	-1.9010	0.5885	0.15	85.1	52.7-95.3
DEVIANCE=2.72, df=10, p>0.9					
BO1	-0.0015	0.0544	0.97	2.7	-86.3-87.0
PCQ	-0.1279	0.0627	0.17	82.9	6.7-96.9
PRG	-1.8900	0.7299	0.15	84.9	36.8-96.4
DEVIANCE=2.72, df=9, p>0.9					

Figure 11A. Poisson regression of data from Manitoba and Nova Scotia: graphical depiction of the effect of birth order changes (upper figure) and presence/absence of Rh prophylaxis (lower figure) on the rate of Rh sensitization (per 1000 total births), with effect modification of the risk difference by presence/absence of Rh prophylaxis (upper figure) and proportion of first births (lower figure), respectively.



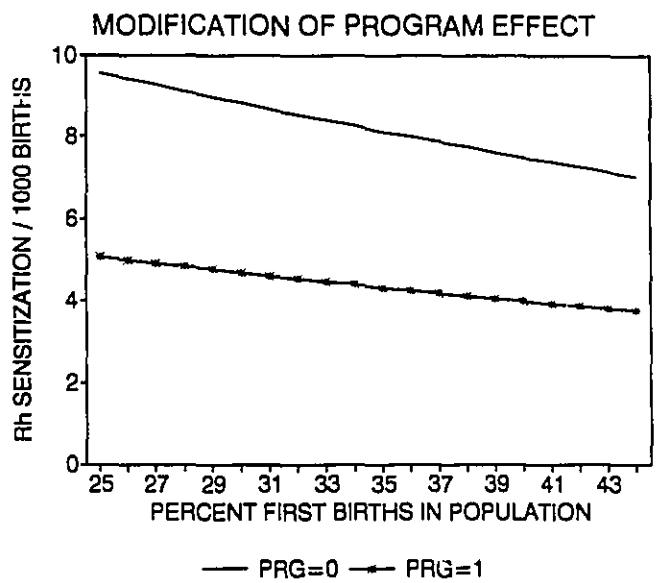
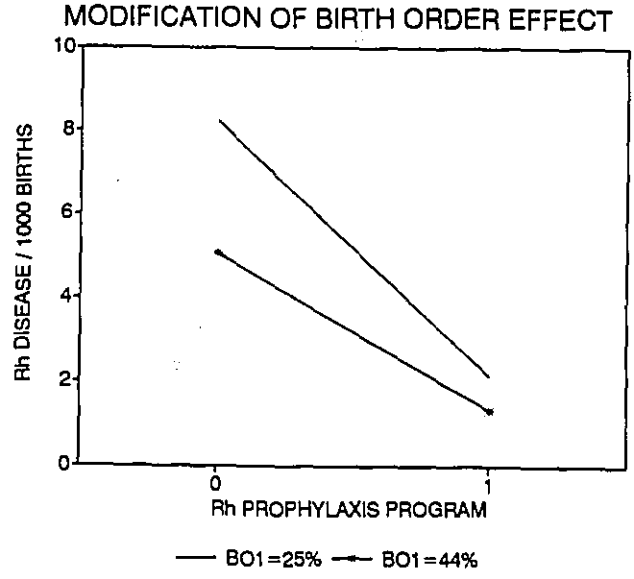


Figure 12A. Poisson regression of data from Manitoba and Nova Scotia: graphical depiction of the effect of birth order changes (upper figure) and presence/absence of Rh prophylaxis (lower figure) on the rate of Rh disease (per 1000 total births), with effect modification of the risk difference by presence/absence of Rh prophylaxis (upper figure) and proportion of first births (lower figure), respectively.



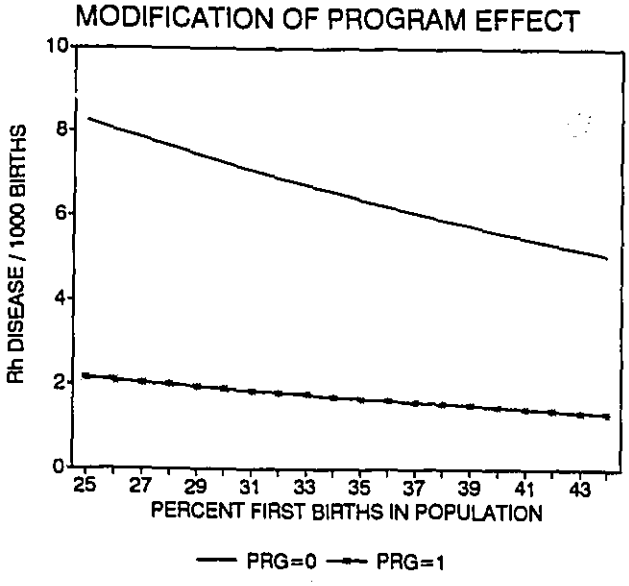


Figure 13A. Poisson regression of data from Manitoba and Nova Scotia: graphical depiction of the effect of birth order on the rate of perinatal deaths from Rh disease (per 100,000 total births), with effect modification of the risk difference by
1. the quality of perinatal care (upper panel).
2. the presence/absence of a program of Rh prophylaxis (lower panel).
In the upper two graphs the Rh prophylaxis program was absent and present, respectively, while in the lower two graphs the quality of perinatal care was kept constant at the 1963 and 1988 levels, respectively.

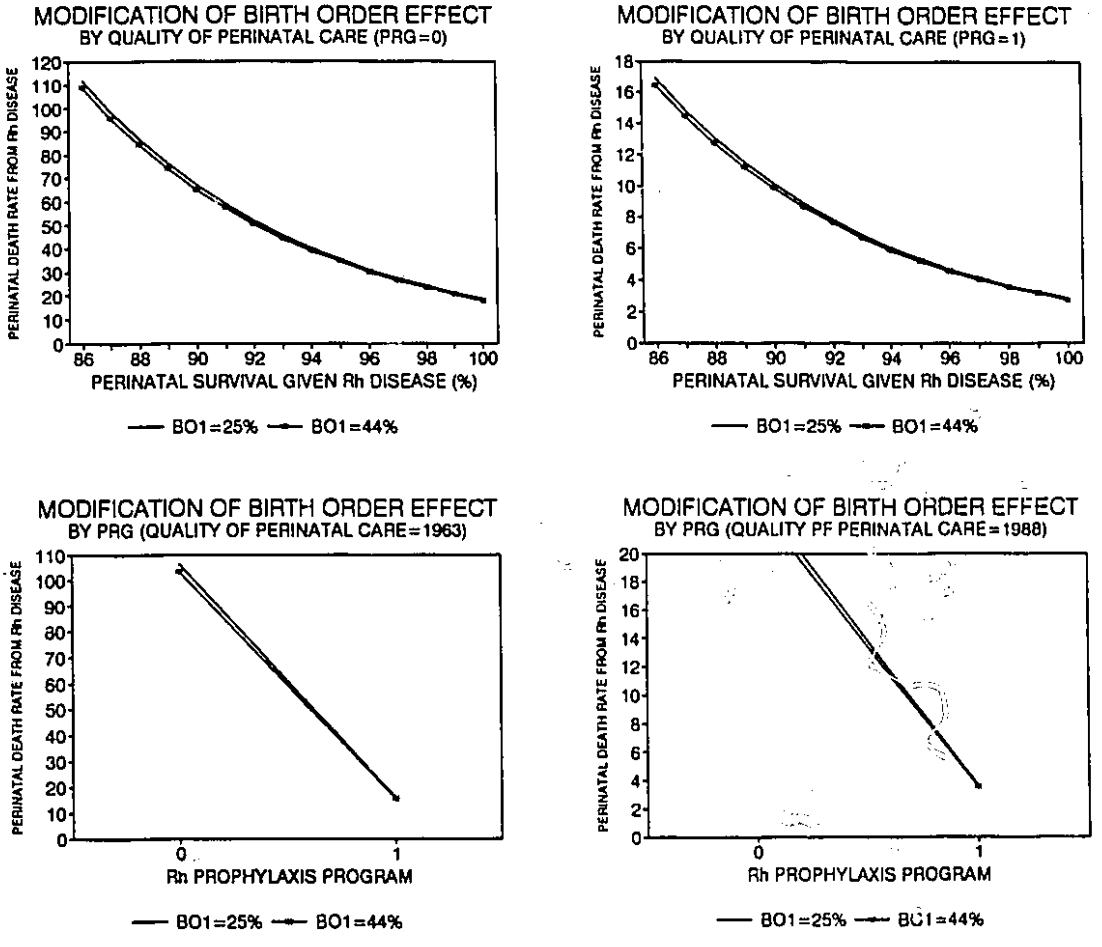
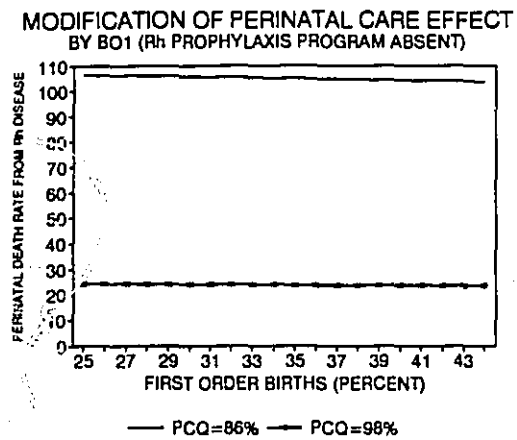
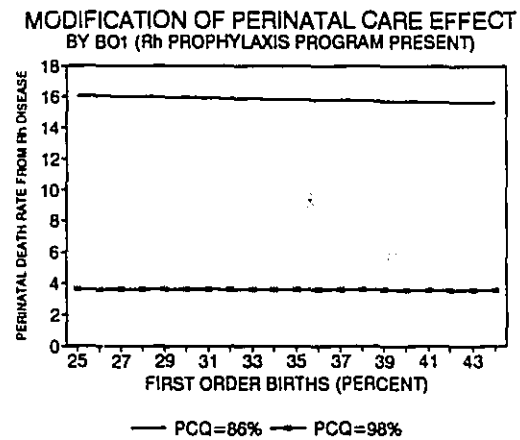


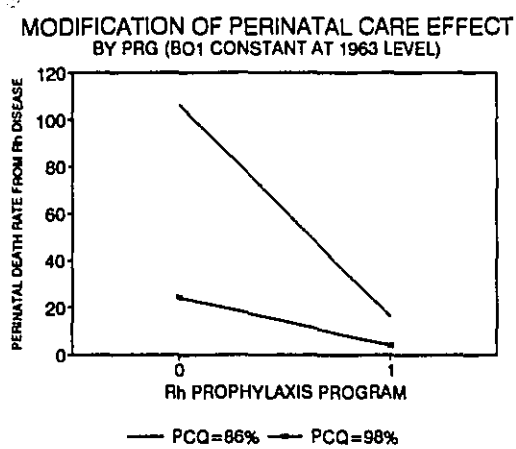
Figure 14A. Poisson regression of data from Manitoba and Nova Scotia: graphical depiction of the effect of the quality of perinatal care on the rate of perinatal deaths from Rh disease (per 100,000 total births), with effect modification of the risk difference by

1. the proportion of first order births (upper panel).
2. the presence/absence of a program of Rh prophylaxis (lower panel).

In the upper two graphs the Rh prophylaxis program was absent and present, respectively, while in the lower two graphs the proportion of first order births was kept constant at the 1963 and 1988 levels, respectively.







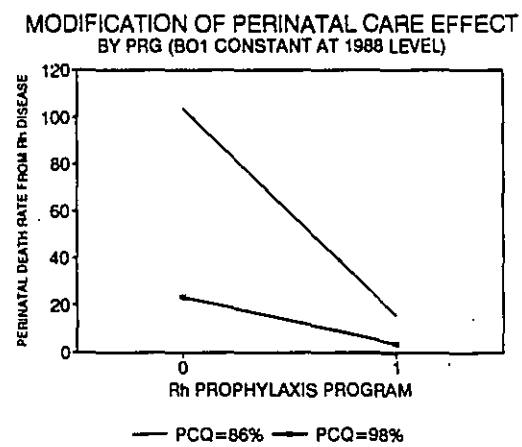
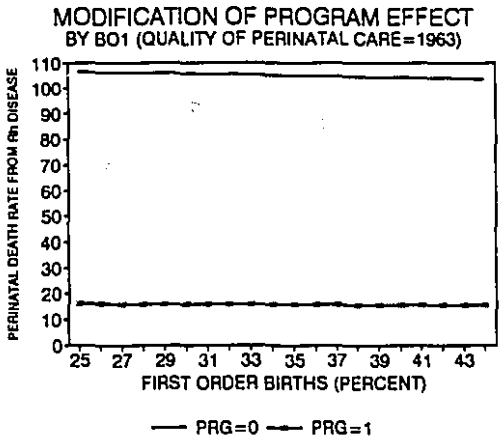
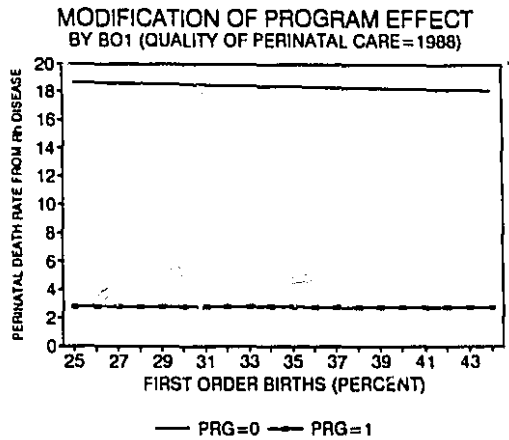


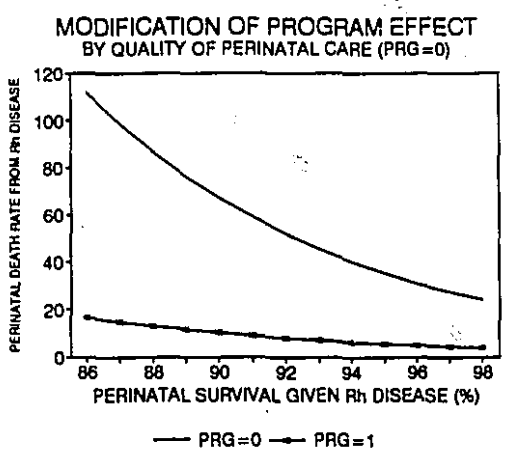
Figure 15A. Poisson regression of data from Manitoba and Nova Scotia: graphical depiction of the effect of an Rh prophylaxis program on the rate of perinatal deaths from Rh disease (per 100,000 total births), with effect modification of the risk difference by

1. the proportion of first order births (upper panel).
2. the quality of perinatal care (lower panel).

In the upper two graphs the quality of perinatal care was kept constant at the 1963 and 1988 levels, respectively, while in the lower two graphs the Rh prophylaxis program was absent and present, respectively.







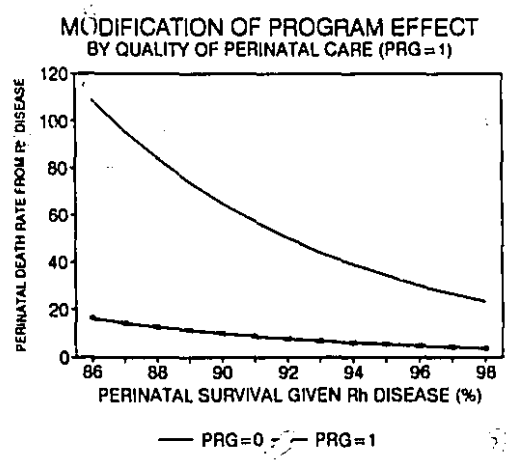


Figure 16A. Poisson regression of data from Manitoba and Nova Scotia: graphical depiction of the goodness of fit. The goodness of fit of the model using Rh sensitization as the outcome is shown in the figure on the upper left while the figure on the upper right shows the model using Rh disease as the outcome. The lower figure shows the goodness of fit of the model using perinatal deaths from Rh disease as the outcome variable.

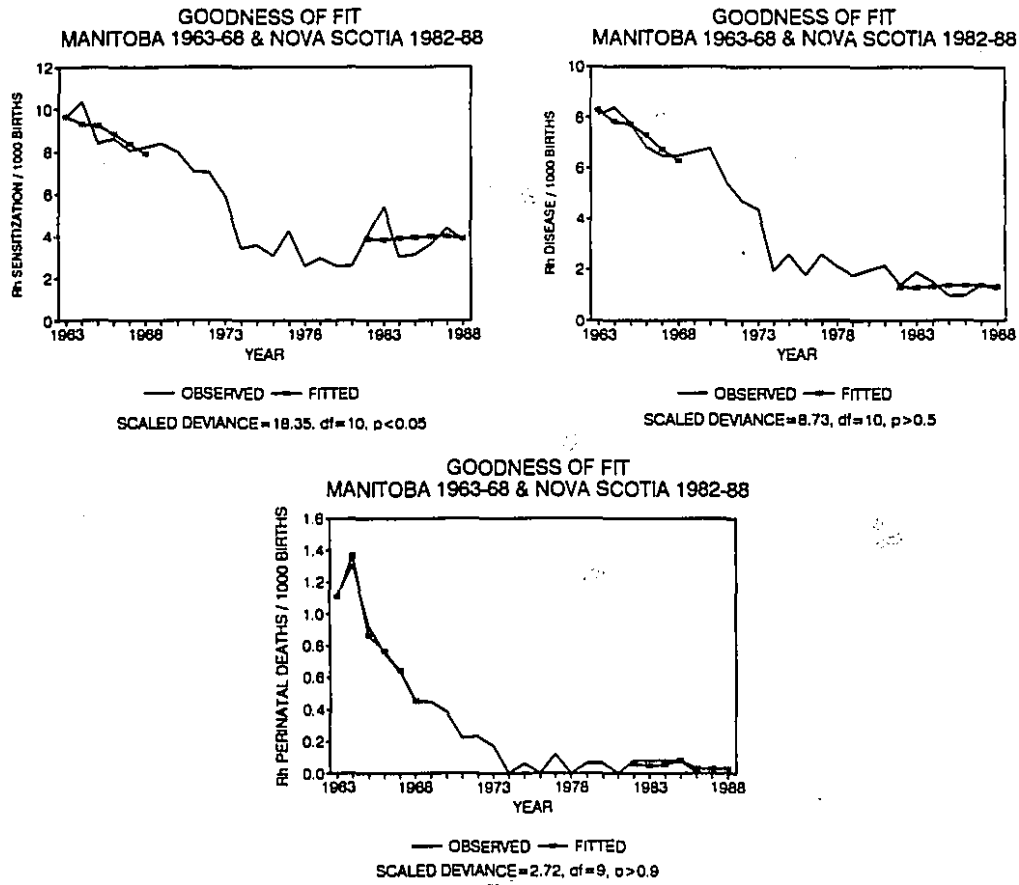


Table 23A: Poisson regression using data from Manitoba for the years 1963-68 and Nova Scotia for 1982-88: correlation of parameter estimates.

OUTCOME=Rh SENSITIZATION

	BO1	PRG
BO1	1.000	-0.896
PRG	1.000	

OUTCOME=Rh HEMOLYTIC DISEASE OF THE NEWBORN

	BO1	PRG
BO1	1.000	-0.824
PRG		1.000

OUTCOME=PERINATAL DEATHS FROM Rh DISEASE

	BO1	PRG
BO1	1.000	-0.681
PRG		1.000

	PCQ	PRG
PCQ	1.000	-0.501
PRG		1.000

	BO1	PCQ
BO1	1.000	-0.862
PCQ		1.000

	BO1	PCQ	PRG
BO1	1.000	-0.812	-0.591
PCQ		1.000	0.243
PRG			1.000

Table 24A: Result of Poisson regression using data from Canada for the years 1963-68 and 1982-88 with rate of infant deaths from hemolytic disease of the newborn (per 100,000 live births) as the outcome and effects expressed as risk differences.

CANADA 1963-68, 1982-88
OUTCOME=INFANT DEATHS FROM HEMOLYTIC DISEASE

VARIABLE (MODEL)	BETA	B_0 INTERCEPT	P_0	P_1	RD
Background 1963					
ISR	-0.068	59.05	60.8	16.6	44.2
PRG	-2.409		60.8	5.5	55.3
Background 1988					
ISR	-0.068	59.05	5.5	1.5	4.0
PRG	-2.409		16.6	1.5	15.1

Table 25A: Poisson regression using Canadian data for the years 1963-68 and 1982-88: correlations among parameter estimates.

	PRG
BO1	-0.500

	PRG
ISR	-0.844

	ISR	PRG
BO1	-0.965	0.886
ISR		-0.958

Table 26A: Poisson regression using Canadian data for the years 1951-54, 1963-68 and 1982-88: correlations among parameter estimates.

	TRA	BO1	ISR	PRG
TRA	1.000	0.277	-0.928	0.501
BO1		1.000	-0.456	-0.157
ISR			1.000	-0.499
PRG				1.000

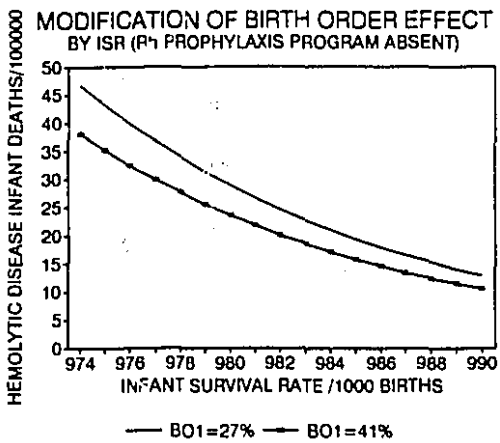
Table 27A: Result of Poisson regression using data from the United States (total population) for the years 1963-68 and 1982-88, with rate of infant deaths from hemolytic disease of the newborn as the outcome and effects expressed as risk differences per 100,000 live births.

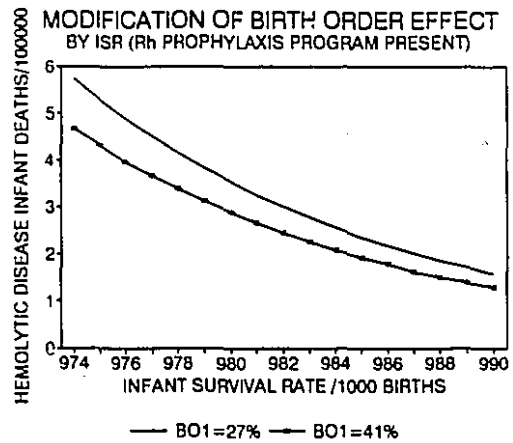
UNITED STATES TOTAL POPULATION 1963-68, 1982-88

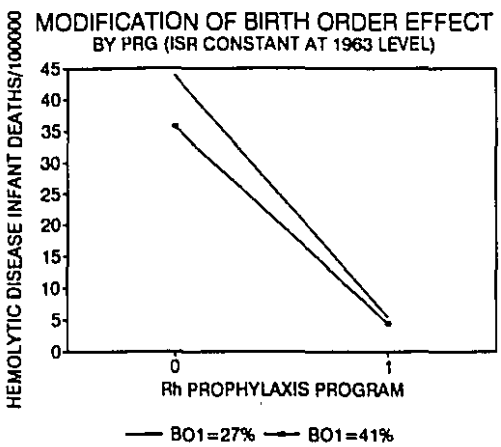
VARIABLE (MODEL)	BETA	B_0 INTERCEPT	P_1	P_0	RD
Background 1963					
ISR	-0.1218	111.0	43.9	6.9	37.0
PRG	-1.7080		43.9	7.9	36.0
Background 1988					
ISR	-0.1218	111.0	7.9	1.2	6.7
PRG	-1.7080		6.8	1.2	5.6
Background 1963					
BO1	-0.0153	71.41	44.1	35.9	8.2
ISR	-0.0808		44.1	12.9	31.2
PRG	-2.1020		44.1	5.4	38.7
Background 1988					
BO1	-0.0153	71.11	1.6	1.3	0.3
ISR	-0.0808		4.4	1.3	3.1
PRG	-2.1020		10.5	1.3	9.2

Figure 17A. Poisson regression of U.S. data (total population): graphical depiction of the effect of birth order on the rate of infant death from hemolytic disease (per 100,000 live births), with effect modification of the risk difference by
1. the quality of infant care (upper panel).
2. the presence/absence of a program of Rh prophylaxis (lower panel).

In the upper two graphs the Rh prophylaxis program was absent and present, respectively, while in the lower two graphs the quality of infant care was kept constant at the 1963 and 1988 levels, respectively.







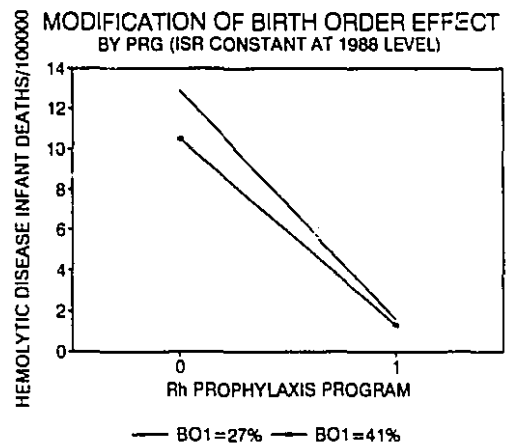
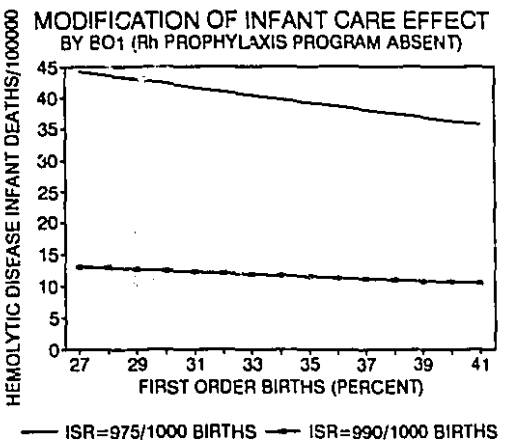
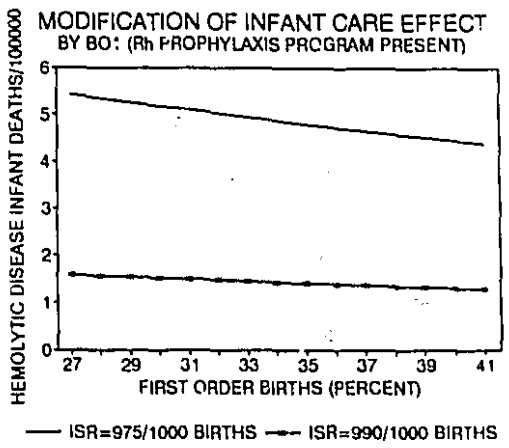
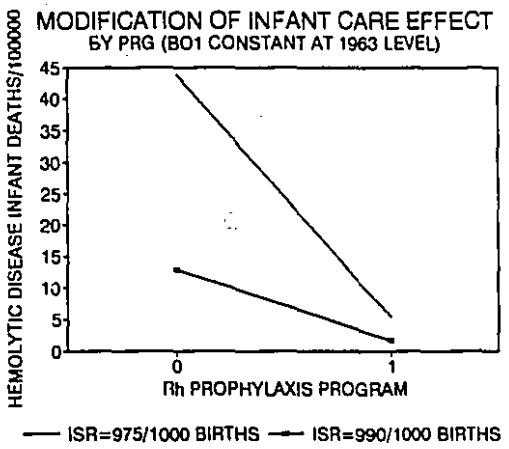


Figure 18A. Poisson regression of U.S. data (total population): graphical depiction of the effect of the quality of infant care on the rate of infant death from hemolytic disease (per 100,000 live births), with effect modification of the risk difference by
1. the proportion of first order births (upper panel).
2. the presence/absence of a program of Rh prophylaxis (lower panel).
In the upper two graphs the Rh prophylaxis program was absent and present, respectively, while in the lower two graphs the proportion of first births was kept constant at the 1963 and 1988 levels, respectively.







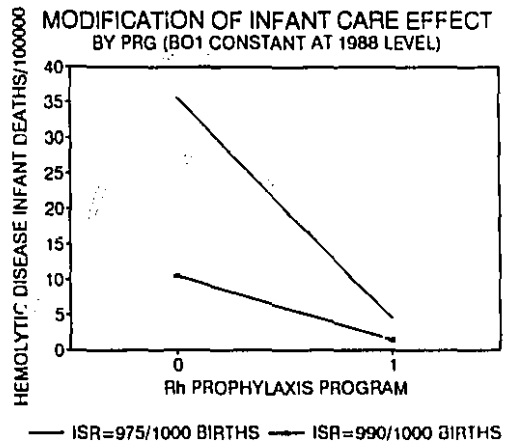
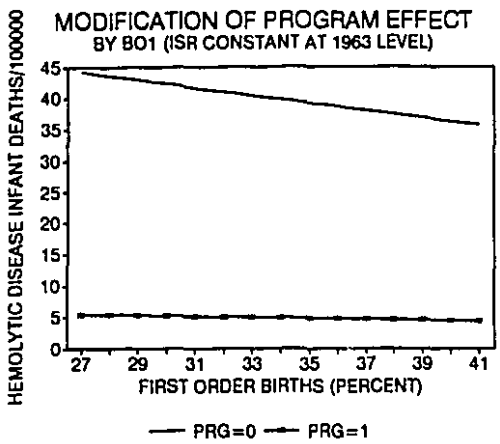
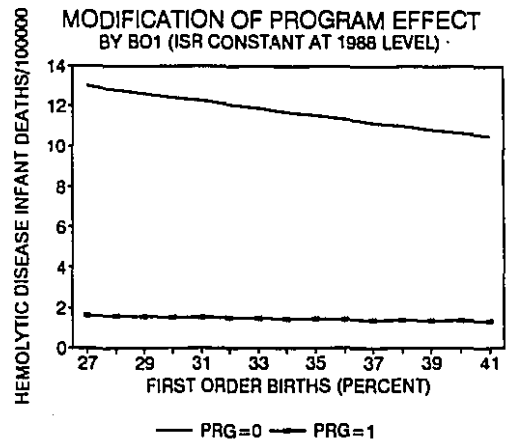
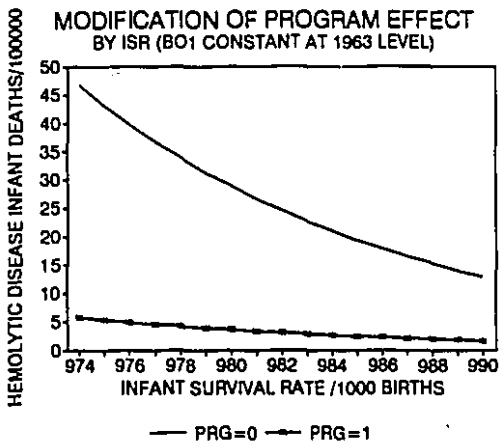


Figure 19A. Poisson regression of U.S. data (total population): graphical depiction of the effect of a program of Rh prophylaxis on the rate of infant death from hemolytic disease (per 100,000 live births), with effect modification of the risk difference by
1. the proportion of first order births (upper panel).
2. the quality of infant care (lower panel).
In the upper two graphs the quality of infant care was kept constant at the 1963 and 1988 levels, respectively, while in the lower two graphs the proportion of first births was fixed at the 1963 and 1988 levels, respectively.







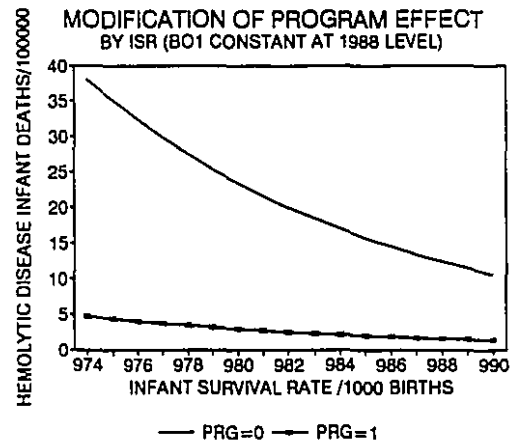


Table 28A: Poisson regression using United States data (total population) for 1963-68 and 1982-88: correlations among parameter estimates.

	BO1	PRG
BO1	1.000	-0.509
PRG		1.000

	ISR	PRG
ISR	1.000	-0.911
PRG		1.000

	BO1	ISR	PRG
BO1	1.000	-0.956	0.906
ISR		1.000	-0.979
PRG			1.000

Table 29A: Poisson regression using United States data (total population) for 1951-54, 1963-68 and 1982-88: correlations among parameter estimates.

	TRA	BO1	ISR	PRG
TRA	1.000	0.420	-0.896	0.777
BO1		1.000	-0.606	0.315
ISR			1.000	-0.855
PRG				1.000

Table 30A: Result of Poisson regression using data from the United States (whites only) for the years 1963-68 and 1982-88, with rate of infant deaths from hemolytic disease of the newborn as the outcome and effects expressed as risk differences.

UNITED STATES, WHITES ONLY, 1963-68, 1982-88

VARIABLE (MODEL)	BETA	B_0 INTERCEPT	P_1	P_0	RD
Background 1963					
ISR	-0.1417	131.000	48.1	7.5	40.6
PRG	-1.858		48.1	7.5	40.6
Background 1988					
ISR	-0.1417	131.000	7.5	1.2	6.3
PRG	-1.8580		7.5	1.2	6.3
Background 1963					
BO1	-0.0016	126.400	45.8	44.9	0.9
ISR	-0.1370		45.8	7.6	38.2
PRG	-1.8980		45.8	6.9	38.9
Background 1988					
BO1	-0.0016	126.400	1.2	1.1	0.1
ISR	-0.1370		6.7	1.1	5.6
PRG	-1.898		7.5	1.1	6.3

Figure 20A. Poisson regression of U.S. data (whites only): graphical depiction of the effect of birth order on the rate of infant death from hemolytic disease (per 100,000 live births), with effect modification of the risk difference by

1. the quality of infant care (upper panel).
2. the presence/absence of a program of Rh prophylaxis (lower panel).

In the upper two graphs the Rh prophylaxis program was absent and present, respectively, while in the lower two graphs the quality of infant care was kept constant at the 1963 and 1988 levels, respectively.

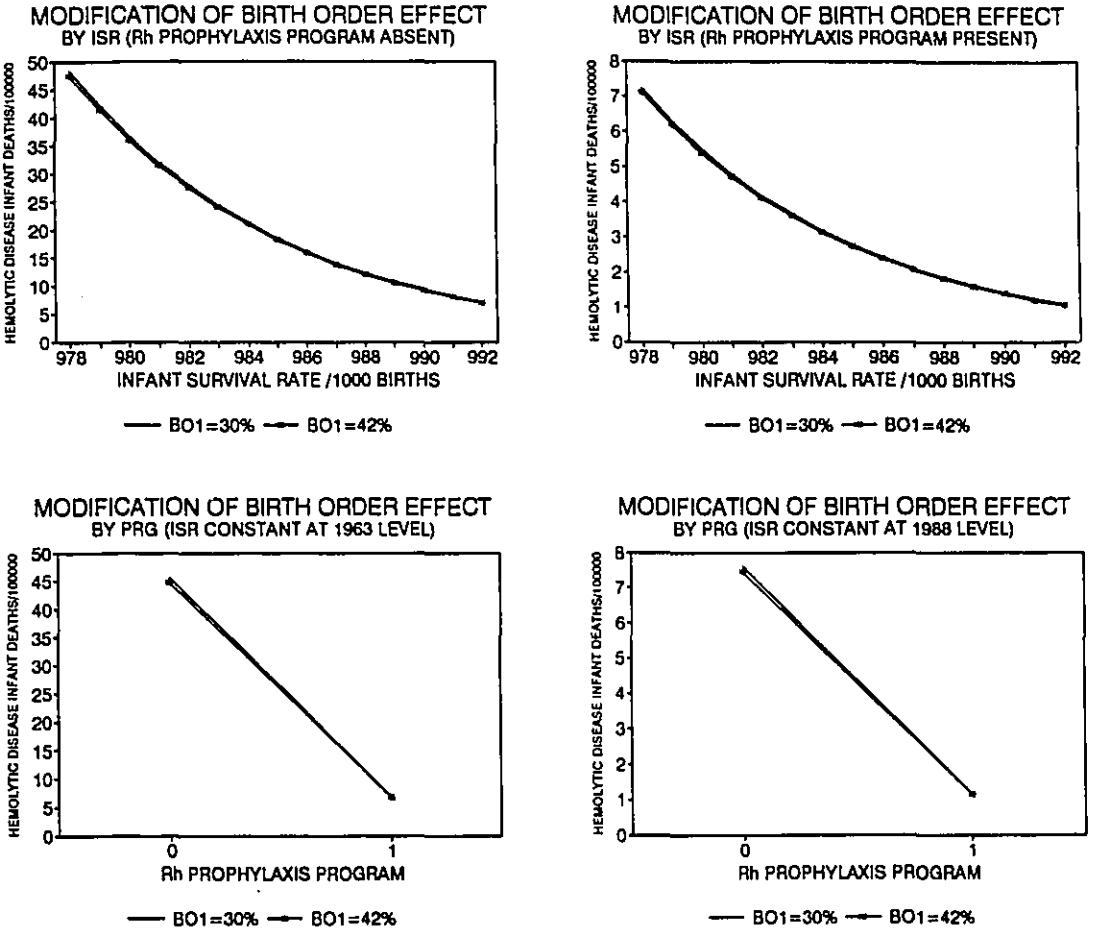
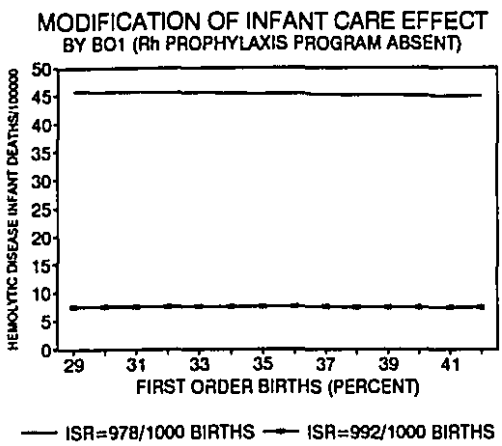
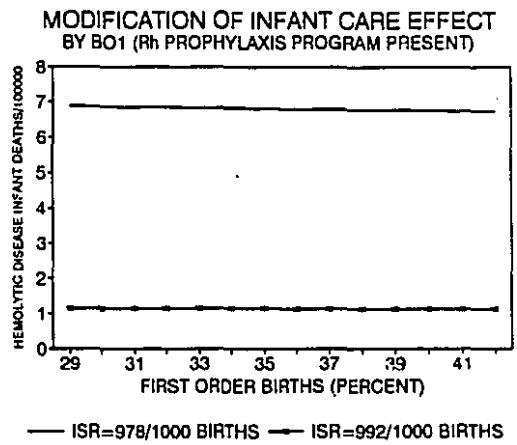
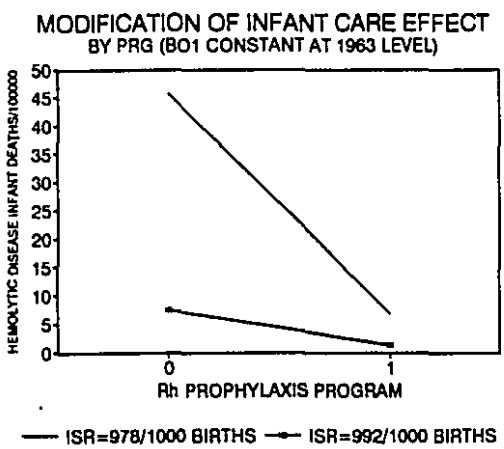


Figure 21A. Poisson regression of U.S. data (whites only): graphical depiction of the effect of the quality of infant care on the rate of infant death from hemolytic disease (per 100,000 live births), with effect modification of the risk difference by
1. the proportion of first order births (upper panel).
2. the presence/absence of a program of Rh prophylaxis (lower panel).
In the upper two graphs the Rh prophylaxis program was absent and present, respectively, while in the lower two graphs the proportion of first births was kept constant at the 1963 and 1988 levels, respectively.







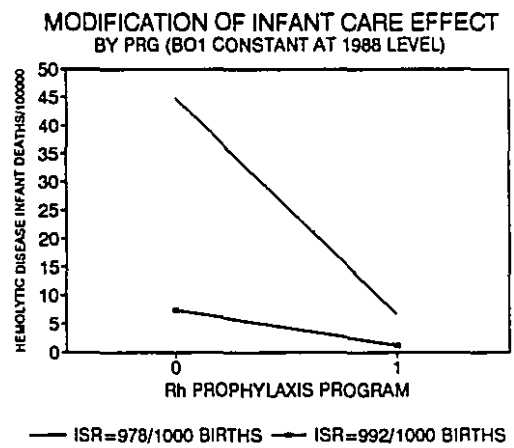


Figure 22A. Poisson regression of U.S. data (whites only): graphical depiction of the effect of a program of Rh prophylaxis on the rate of infant death from hemolytic disease (per 100,000 live births), with effect modification of the risk difference by
1. the proportion of first order births (upper panel).
2. the quality of infant care (lower panel).
In the upper two graphs the quality of infant care was kept constant at the 1963 and 1988 levels, respectively, while in the lower two graphs the proportion of first births was fixed at the 1963 and 1988 levels, respectively.

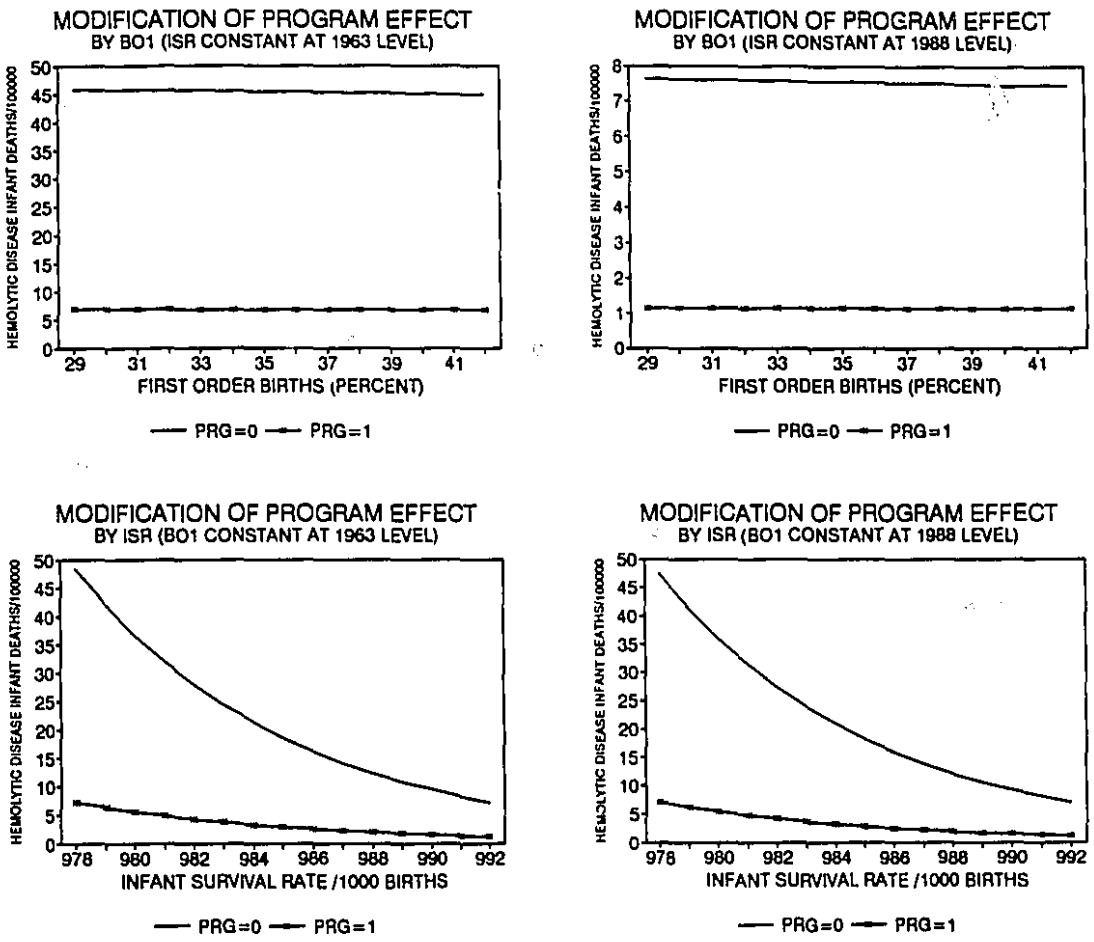
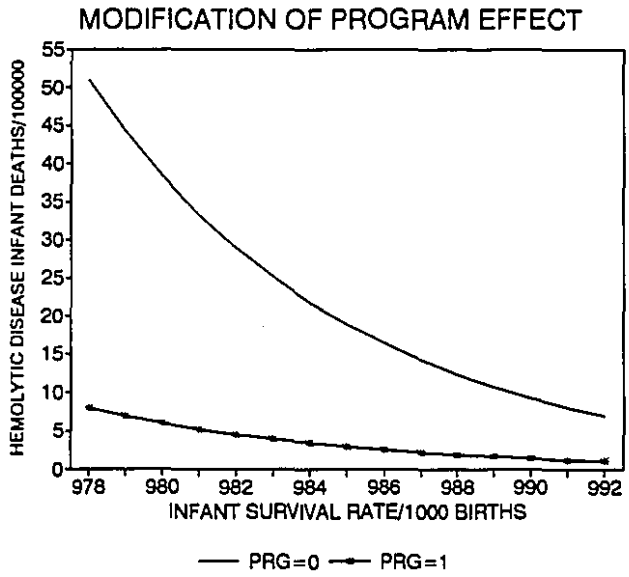


Figure 23A. Poisson regression of U.S. data (whites only). The upper figure shows the effect of an Rh prophylaxis program on the rate of infant deaths from hemolytic disease (per 100,000 live births) with effect modification of the risk difference by non-program factors (BO1 and ISR). The lower figure depicts modification of the risk difference associated with non-program factors by the presence/absence of an Rh prophylaxis program.



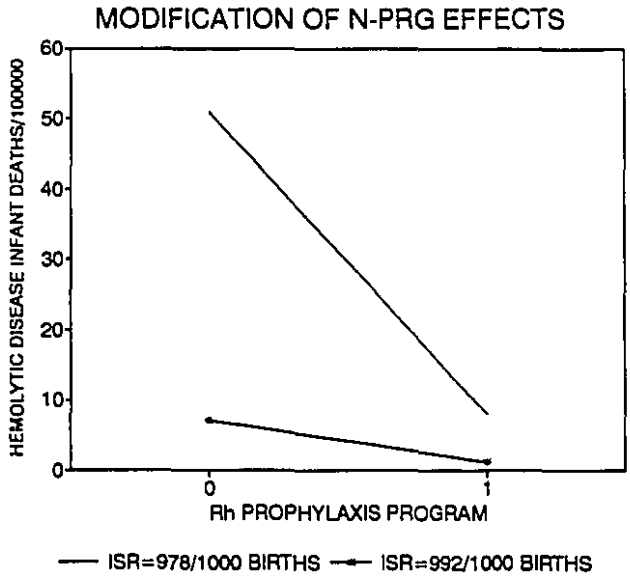


Table 31A: Poisson regression using United States data (whites only) for the years 1964-68 and 1982-88: correlations among parameter estimates.

	PRG
BO1	-0.509

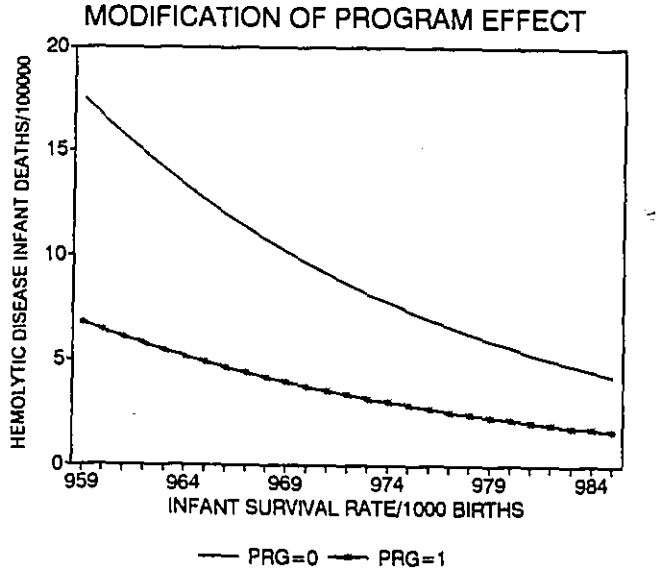
	PRG
ISR	-0.911

	ISR	PRG
BO1	-0.956	0.906
ISR		-0.979

Table 32A: Poisson regression using United States data (whites only) for 1951-54, 1963-68 and 1982-88: correlations among parameter estimates.

	TRA	BO1	ISR	PRG
TRA	1.000	0.420	-0.896	0.777
BO1		1.000	-0.606	0.315
ISR			1.000	-0.855
PRG				1.000

Figure 24A. Poisson regression of U.S. data (nonwhites only). The upper figure shows the effect of an Rh prophylaxis program on the rate of infant deaths from hemolytic disease (per 100,000 live births) with effect modification of the risk difference by non-program factors (BO1 and ISR). The lower figure depicts modification of the risk difference associated with non-program factors by the presence/absence of an Rh prophylaxis program.



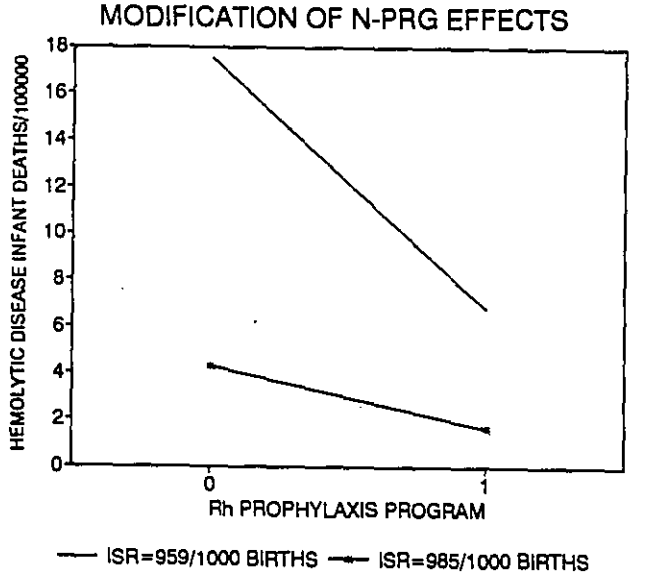


Table 33A: Result of Poisson regression using data from the United States (nonwhites only) for the years 1963-68 and 1982-88, with rate of infant deaths from hemolytic disease of the newborn as the outcome and effects expressed as risk differences.

UNITED STATES, NONWHITES ONLY, 1963-68, 1982-88

VARIABLE (MODEL)	BETA	B_0 INTERCEPT	P_1	P_0	RD
Background 1963					
ISR	-0.0541	43.270	17.6	4.3	13.3
PRG	-0.9488		17.6	6.8	10.8
Background 1988					
ISR	-0.0541	43.270	06.8	1.7	5.2
PRG	-0.9488		04.3	1.7	2.6

Table 34A: Poisson regression using United States data (nonwhites only) for the years 1964-68 and 1982-88: correlations among parameter estimates.

		PRG
BO1		-0.758
		PRG
ISR		-0.966
	ISR	PRG
BO1	-0.972	0.938
ISR		-0.991

Table 35A: Poisson regression using United States data (nonwhites only) for 1951-54, 1963-68 and 1982-88: correlations among parameter estimates.

	TRA	BO1	ISR	PRG
TRA	1.000	0.132	-0.626	0.705
BO1		1.000	-0.784	0.524
ISR			1.000	-0.913
PRG				1.000

Table 36A: Result of Poisson regression using data from Manitoba for the years 1963-68 and 1982-88, with rate of perinatal death from Rh hemolytic disease of the newborn as the outcome and effects expressed in terms of preventive fractions. This analysis was carried out as a check for over/under dispersion in the data (cf. Table 14).

OUTCOME=PERINATAL DEATHS FROM Rh HEMOLYTIC DISEASE

VARIABLE (MODEL)	BETA	SE	PF	95% CI
BO1	-0.1784	0.0267	93.4	85.3-97.0
DISPERSION PARAMETER=1.74				
PCQ	-0.2240	0.0289	91.9	84.7-95.7
DISPERSION PARAMETER=1.35				
PRG	-3.0520	0.5788	95.3	85.3-98.5
DISPERSION PARAMETER=1.60				
BO1	-0.0927	0.0274	75.6	38.5-90.3
PRG	-1.9360	0.5292	85.6	59.3-94.9
DISPERSION PARAMETER=0.78				
PCQ	-0.1325	0.0231	77.3	62.4-86.3
PRG	-1.7790	0.3638	83.1	65.6-91.7
DISPERSION PARAMETER=0.78				
BO1	-0.0026	0.0369	3.9	-65.3-67.9
PCQ	-0.1301	0.0427	76.7	68.2-90.9
PRG	-1.7710	0.4018	83.0	62.6-92.3
DISPERSION PARAMETER=0.44				

Table 37A. Summary of the findings of studies [109,110] showing the extent of inaccuracies in the number of registered deaths from hemolytic disease of the newborn in England and Wales for specific years. For the years 1953 and 1955 the deaths refer to infant deaths while for 1977-89 deaths include all perinatal deaths.

YEAR	REGISTERED HDN DEATHS		
	TOTAL	DUE TO HDN	
		NUMBER	%
1953	411	312	76
1955	400	315	79
1977	155	110	71
1978	140	91	65
1979	111	90	81
1980	103	76	74
1981	57	44	77
1982	67	48	72
1983	55	38	69
1984	49	30	61
1985	52	37	71
1986	52	34	65
1987	35	27	77
1988	31	24	77
1989	23	13	57

Table 38A. Poisson regression of data from the U.S. (total population) 1963-68 and 1982-88. The data set used for regression is shown; upper rows contain the actual data, while the lower rows indicate the observed number of HDN infant deaths reduced by a factor of ten.

YEAR	LIVE BIRTHS	HDN DEATHS	BO1	ISR	PRG
Original data					
1963	4146422	1835	27.59	974.8	0
1964	4076993	1659	28.97	975.2	0
.					
.					
1987	3827087	27	41.33	989.9	1
1988	3927119	45	41.04	990.0	1
Decimated data					
1963	4146422	183.5	27.59	974.8	0
1964	4076993	165.9	28.97	975.2	0
.					
.					
1987	3827087	2.7	41.33	989.9	1
1988	3927119	4.5	41.04	990.0	1

Table 39A. Poisson regression of U.S. data (total population), 1963-68 and 1982-88. Beta coefficients obtained from data set with decimated rates (table 32A) are similar to those obtained when the actual rates are employed for regression. Goodness of fit is markedly improved, while standard errors increase in size because of smaller numbers of outcome events.

VARIABLE	BETA	SE
Original data		
BO1	-0.0153	0.0110
ISR	-0.0808	0.0308
PRG	-2.1020	0.3120
DEVIANCE=28.97, df=9, p<0.01		
Decimated data		
BO1	-0.0153	0.0346
ISR	-0.0805	0.0975
PRG	-2.0980	0.9867
DEVIANCE=2.89, df=9, p>0.9		

Table 40A: Model validation using data from the surveillance program of Manitoba between 1963 and 1988. Model 1 assumed a rate of 7% for the probability of maternal Rh sensitization following the delivery of a Rh-positive, ABO compatible infant, while Model 2 assumed a value of 17% for the same probability.

Year	Rate of maternal Rh sensitization		
	Observed	Model 1	Model 2
1963	9.69	10.45	22.22
1964	10.35	10.16	21.60
1965	9.54	9.95	21.14
1966	8.79	9.34	19.90
1967	8.00	8.81	18.75
1968	8.17	7.98	17.07

Table 41A: Effect of changes in birth order distribution in Manitoba between 1963 and 1988 (and 1963 and 1990) on the rate of maternal Rh sensitization assuming the absence of an Rh prophylaxis program. The racial composition of the births and the abortion rates were kept constant at the 1963 value. Results from both models are presented and effects are presented in terms of risk ratios (RR), risk differences (RD) and preventive fractions (PF).

Year	Rate of Rh sensitization/1000 total births	RR	RD	PF
Model 1*				
1963 (Reference)	10.45	1.00	0.00	0
1988	5.92	0.57	4.53	43
1990	5.81	0.56	4.64	44
Model 2*				
1963 (Reference)	22.22	1.00	0.00	0
1988	13.05	0.59	9.17	41
1990	12.79	0.58	9.43	42

* Model 1 assumes the rate of maternal Rh sensitization given an Rh-positive, ABO compatible pregnancy to be 7%, while model 2 assumes the same rate to be 17%.

Figure 25A. Comparison of conditional probability model predicted rates of maternal Rh sensitization and Poisson regression model predicted rates of maternal Rh sensitization (per 1000 total births) for Manitoba, with both models assuming the absence of an Rh prophylaxis program. Also shown are the observed rates of maternal Rh sensitization in Manitoba between 1963 and 1990.

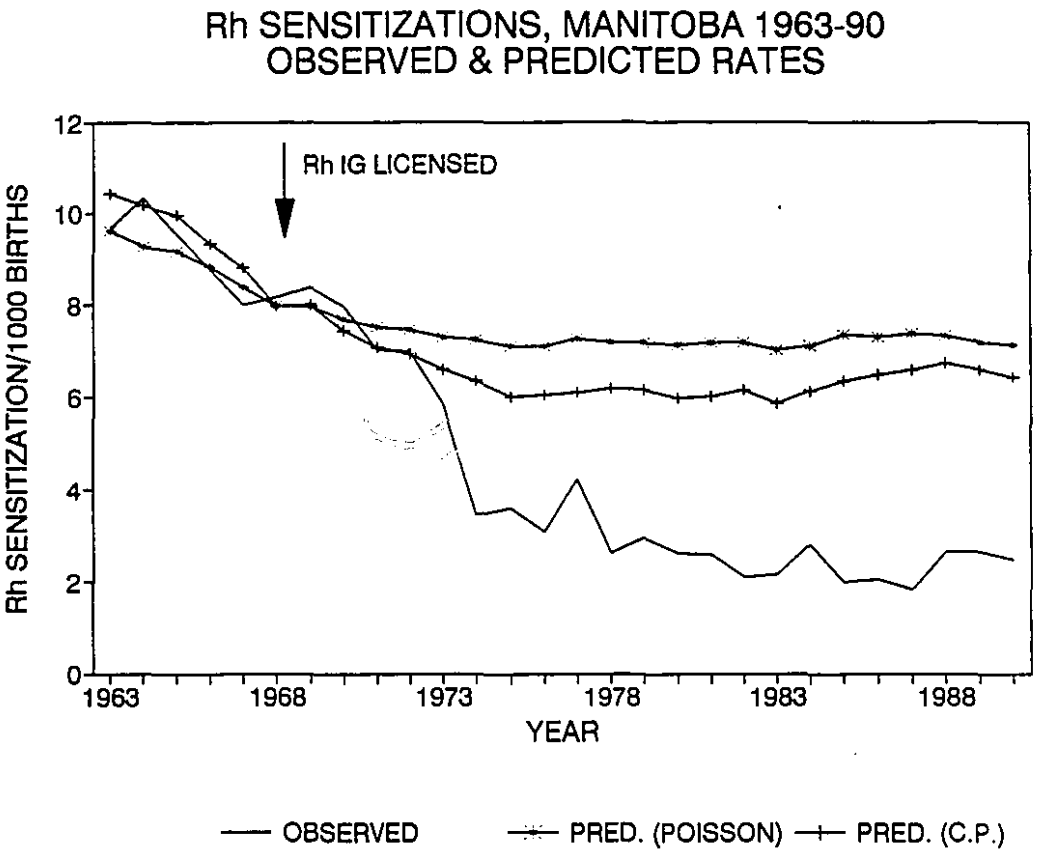


Figure 26A. Comparison of conditional probability model predicted rates of perinatal deaths from Rh disease and Poisson regression model predicted rates of perinatal deaths from Rh disease (per 100,000 total births) for Manitoba, with both models assuming the absence of an Rh prophylaxis program. Also shown are the observed rates of perinatal deaths from Rh disease in Manitoba between 1963 and 1990.

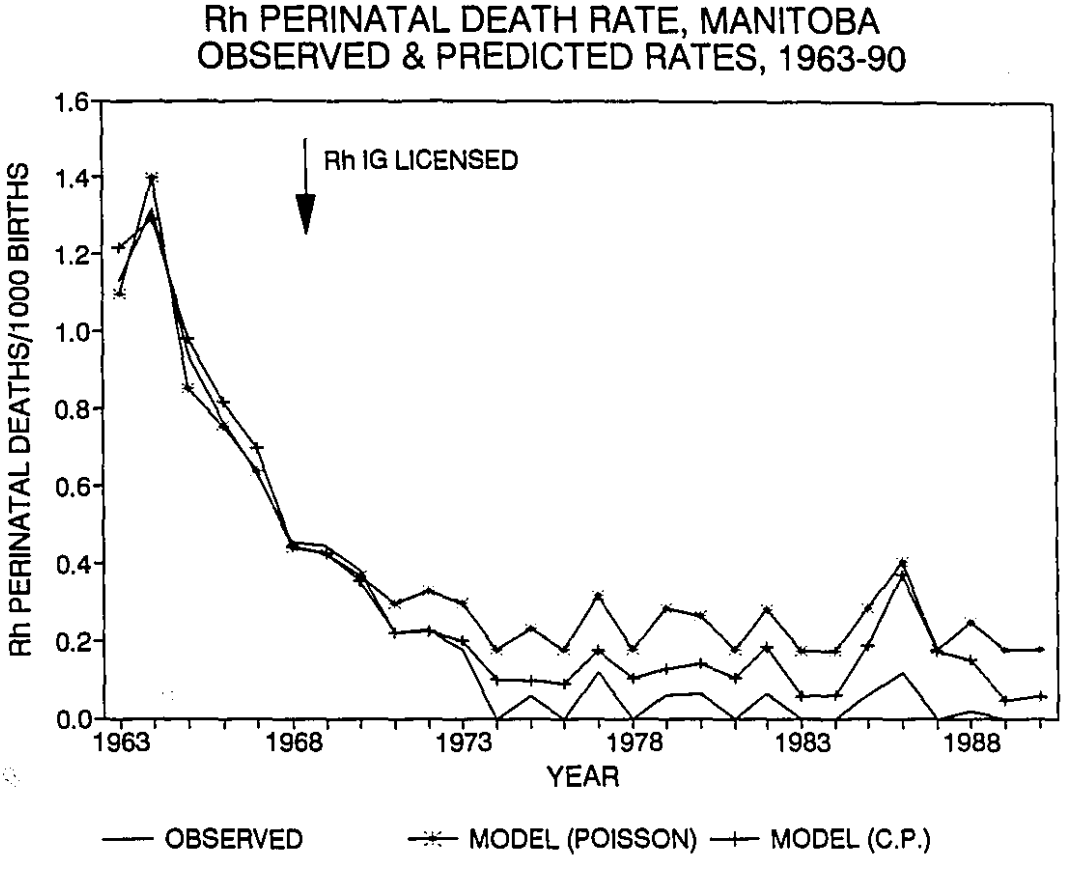


Figure 27A. Conditional probability model predicted rates of Rh sensitization in India between 1961 and 1981. Model 1 assumed a rate of 7% for the probability of Rh sensitization following a Rh positive, ABO-compatible pregnancy, while model 2 assumed the same rate to be 17%.

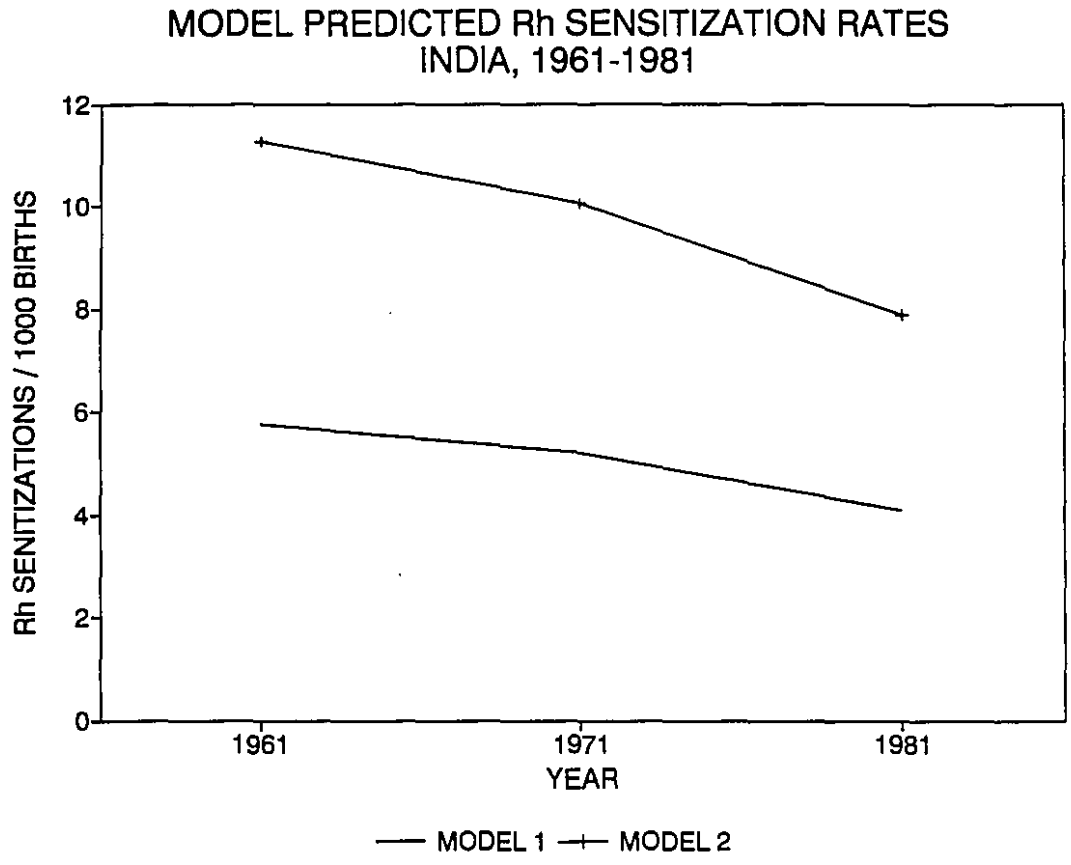


Table 42A: Effect of the Rh prophylaxis program on the rate of maternal Rh sensitization (per 1000 total births). The effects were estimated by contrasting the observed rate of Rh sensitization and the rate predicted by model 1 (i.e., using the 7% assumption for the rate of maternal Rh sensitization) in the absence of an Rh prophylaxis program (racial composition of births adjusted to 1988 values). Both Rh D and Rh non-D sensitizations were included for calculating the observed rate.

Year	Rate of Rh sensitization per 1000 births		RR	RD	PF
	Predicted (No PRG)	Observed			
1988	6.72	2.64	0.39	4.08	61
1990	6.43	2.46	0.38	3.97	62