Cost-Effectiveness of the Management of Rh-Negative Pregnant Women

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Abstract

Objective: The purpose of this study was to determine the most cost-effective option to prevent alloimmunization against the Rh factor.

Methods: A virtual population of Rh-negative pregnant women in Quebec was built to simulate the cost-effectiveness of preventing alloimmunization. The model considered four options: (1) systematic use of anti-D immunoglobulin; (2) fetal Rh(D) genotyping;

(3) immunological determination of the father's Rh type; (4) mixed screening: immunological determination of the father's Rh type, followed if positive by fetal Rh(D) genotyping. Two outcomes were considered, in addition to the estimated costs: (1) the number of babies without hemolytic disease, and (2) the number of surviving infants.

Results: In a first pregnancy, two options emerged as the most cost-effective options: systematic prophylaxis and immunological Rh typing of the father, with overlapping confidence intervals between them. In a second pregnancy, the results were similar. In all cases (first or second pregnancy or a combination of the two) fetal genotyping was not found to be a cost-effective option.

Conclusion: Routine prophylaxis and immunological Rh typing of the father are the most cost-effective options for the prevention of Rh alloimmunization. Considering that immunological typing of the father would probably not be carried out by the majority of clinicians, routine prophylaxis remains the preferred option. However, this could change if the cost of Rh(D) fetal genotyping fell below $140 per sample.

Key Words: Simulation, Rhesus, genotyping, hemolytic disease, alloimmunization, cost-effectiveness

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INTRODUCTION

Despite the availability of prophylactic measures, alloimmunization to the Rh(D) antigen during pregnancy remains the most common cause of hemolytic disease of the newborn (1: 1000 newborns).[1] Alloimmunization is the occurrence of an immune response to the presence of an antigen (alloantigen) that an individual lacks, but that is present in other individuals of the same species. In humans, this situation is observed only in special circumstances: pregnancy (immunization of an Rh-negative mother by her Rh-positive fetus), blood transfusion, or transplantation of tissues or organs.[2]

Early determination of the fetal Rh blood type in pregnant Rh-negative women allows better monitoring of the risk of alloimmunization and better prevention of its feared consequences (hemolytic disease of the fetus [HDF] and stillbirth, due to the passage of maternal immunoglobulins through the placenta) by the administration of prophylactic anti-D immunoglobulin (IgG).[3]

Currently accepted recommendations for the prevention of alloimmunization are the routine injection of anti-D IgG at 28 weeks' gestation for all Rh-negative non-sensitized women when fetal Rh type is positive or unknown.[4–8] Such a measure is necessary because there is no practical therapeutic intervention that will slow the process of alloimmunization once it has been initiated.[9–11]

Non-invasive determination of fetal Rh status is now possible through the analysis of cell-free circulating fetal DNA in maternal plasma as early as the 10th week of

pregnancy; that is, before the alloimmunization process is triggered. Non-invasive determination of fetal Rh status is expected to reduce the number of women who receive anti-D IgG unnecessarily and undergo surveillance testing according to current recommendations.[4,12]

However, although the diagnostic performance of this new approach is high (clinical sensitivity and specificity approaching 100%), it is not universally available. Its introduction into regular follow-up of pregnancies still requires evidence about its value compared with more traditional approaches. Indeed, two economic studies were performed on non-invasive fetal Rh(D) genotyping. However, those studies should be considered as cost-minimizing studies because they did not estimate clinical outcomes.[13,14] Thus, information on the cost-effectiveness of the various options is still unavailable.

Computer-based simulation modelling is a recognized approach to comparing the putative cost-effectiveness of several clinical interventions for a specific condition.[15–18] It is especially useful to compare the effectiveness of a large number of different interventions in the same cohort of patients, because that would require a very large, costly and sometimes impossible clinical trial.[19]

METHODS

We built a virtual population of 10 000 Rh-negative pregnant women. This number was considered sufficient to perform statistically meaningful simulations given that 150 cases

of Rh(D) incompatibility would be expected. The model assumed that 55% of women will have a second pregnancy,[20] on average 3.15 years after the first.[21] The Rh type of the fetus was established based on the probability of the father being either homozygously or heterozygously Rh positive.[22]

Besides the estimated costs, two clinical outcomes were considered: (1) the number of babies without hemolytic disease, and (2) the number of surviving infants.
Modelling was performed using a previously described agent-based, hybrid-state and time-driven simulator called SCHNAPS.[23,33] Two decision trees were built (Figure 1). The first decision tree applied to the first pregnancy of an Rh negative woman. The second applied to an eventual second pregnancy in 55% of those women.[20]

The first model reflected the natural evolution of a first pregnancy for an Rh negative pregnant woman and the health of her baby up to 28 days after delivery. The choice of a 28-day follow-up neonatal period was based on the fact that the consequences of alloimmunization and hemolytic disease of the newborn are manifest during this period.[25,26] Weekly cycle units were chosen for the time-driven simulations, which correspond to the usual time interval of events in the pregnancy literature.[27]

A probability of being alloimmunized was assigned to each Rh-negative woman depending on (1) the probability of the fetus being Rh positive, (2) the gestational age , and (3) the use of anti-D prophylaxis at 28 weeks and/or after delivery.[4,28] The probability of the fetus being Rh positive was assigned depending on the father's probable Rh type.

Following clinical guidelines, a non-alloimmunized woman had nine prenatal visits, one ultrasound examination, an indirect Coombs test, and administration of prophylactic anti-D IgG at 28 weeks' gestation.[4,11,29,30] If the indirect Coombs test is positive, the woman is followed from 28 weeks as an alloimmunized woman.[4] Alloimmunized women (those with a positive indirect Coombs test at 12 or 28 weeks), are monitored by measuring the level of anti-D antibodies, and have an ultrasound examination every four weeks until 28 weeks, every two weeks from 28 to 37 weeks, and thereafter weekly until delivery, as suggested by the Canadian guidelines.[4] This close monitoring is maintained even if the Coombs test becomes negative.

In cases of HDF, medical consultation including ultrasound assessment is performed every four weeks until 20 weeks' gestation, every two weeks from 20 to 37 weeks, and weekly thereafter until delivery.[31] In addition, between 15 and 35 weeks, three Doppler ultrasound are permed to measure the peak systolic velocity in the middle cerebral artery.[3] HDF is categorized into three levels of severity,[9,11,31,32,] and the distribution of severity follows Canadian data.[9,33] In cases of severe HDF, the model considers four intrauterine transfusions.[34] At its birth, a baby with moderate or severe HDF is monitored in NICU for 21 days, and subsequently for a further seven days in hospital.[35]

The probability of a newborn being premature (born between 34 and 37 weeks' gestation[35-37]) was assigned to each fetus according to its status, i.e., HDF versus non-HDF.[36,37,] A premature baby is hospitalized for 21 days in NICU, and then followed-up for seven days in a pediatric ward.[35] Finally, the probability of death for each baby was assigned depending on whether the baby was healthy, was premature, or had HDF, and if

the mother was already alloimmunized.[38]

In the model of the second pregnancy the probability of being alloimmunized was dependent on the state of alloimmunization at the end of the first pregnancy, the prophylaxis given during the first pregnancy and the uptake of prophylaxis at 28 weeks in the second pregnancy.[4] The model assumed that if a woman had a baby with HDF during her first pregnancy, her second baby would also have the disease if Rh positive.

All scenarios considered were in agreement with the Canadian guidelines for the prevention of maternal-fetal Rh alloimmunization.[4,30]

Four scenarios were compared: (1) the current situation, i.e., the routine use of anti-D immunoglobulin at 28 weeks' gestation without determination of fetal Rh type; (2) fetal Rh(D) genotyping by PCR of fetal free circulating DNA in maternal blood; (3) immunological determination of the father's Rh type; and (4) mixed screening: immunological determination of the father's Rh type, followed, if the result is positive, by fetal Rh(D) genotyping by PCR on fetal free circulating DNA in maternal blood.

In the first scenario, there are two possible outcomes depending on the results of the indirect Coombs test done at 12 weeks. If the result is positive, the woman is considered alloimmunized and at risk of HDF if the titre is $\geq 1/16$. If the result is negative, monitoring continues as for a healthy pregnancy, with a repeat indirect Coombs test at 28 weeks and the administration of prophylactic anti-D IgG if negative. After delivery, non-

alloimmunized mothers receive an additional dose of anti-D IgG.

In the second scenario, fetal genotyping is offered. If the woman refuses the test, the course of treatment will be the same as for the first scenario. If she accepts and the test is positive, follow-up indirect Coombs tests are performed as described in the first scenario. If fetal genotyping is negative, the course of treatment is the same as for a healthy pregnancy (Figure 2).

In the third scenario, the father's Rh type is routinely determined. If the father is Rh positive, the response is the same as described in the second scenario with positive fetal genotyping. If the father is Rh negative, there is no need for prophylactic administration of anti-D IgG or an indirect Coombs test. The model considers the probability (2.6%) that the father is unknown or undeclared.[39] In this case, women are followed as described in the first scenario.

In the fourth scenario, if the father is Rh positive, fetal Rh genotyping of fetal DNA circulating in maternal plasma is performed by PCR. If the test shows that the fetus is Rh negative, no further action is taken and follow-up is as for a healthy pregnancy.[2,4,11,40,41]

In the second, third, and fourth scenarios, the model considers the acceptance rate for screening (including fetal genotyping and/or immunological Rh typing of the father) reported in the literature.[16,17,42] As specific information about the acceptance of genetic testing for fetal Rh and the Rh type of the father has not been published to date, we made

assumptions based on the values found in recent Canadian studies on topics considered relevant for this study.[15–17,42] In addition, our model includes an estimate of the likelihood that physicians will offer a genetic test.[43] Sensitivity analyses were performed to take into account the variability of published results.

Costs relate to the publicly funded health care system in Quebec. Only direct costs were estimated. The simulation analyses included services provided for the monitoring of Rh negative women as outpatients and services provided during hospitalizations of the mother and her baby, as already defined in the province of Quebec[27] and as described in Canadian guidelines.[4]

The sequence of services provided in each scenario is summarized in Figure 2.

Baseline values on the management of alloimmunization were retrieved from Canadian guidelines.[4] When these values were not available, data from peer-reviewed studies [3,11,22] and the opinions of experts in obstetrics and laboratory medicine were used. Extensive sensitivity analyses were performed. Unit prices for services consumed were calculated from the 2010 to 2011 fiscal year administrative data of the Quebec public health care system. The lowest prices from the list of drugs covered by Quebec public health care insurance (*Régie d'assurance maladie du Québec* [RAMQ]), were used to estimate the cost of medication, to which were added 6% for wholesalers and the pharmacist fee paid by RAMQ. All-Patient-Diagnosis-Related-Groups (APR-DRG) data were used to calculate the average cost of hospitalization, to which we added the physician fees paid

by RAMQ. The Ministry of Health data bank (*Système d'information financière et opérationnelle* [SIFO])[44] was used to calculate activity centre unit prices for ambulatory care services. These prices were increased to reflect the contribution of support activity centres to clinical services, using the direct method.[40]

Simulations were performed using the SCHNAPS platform (Synchronous Population and Agent-based Simulator) and run on the CLUMEQ network of supercomputers.[23,24] Each simulation was repeated 1000 times with newly generated virtual populations in order to produce a distribution of estimates. As the follow-up was less than one year, no discounting was performed.

The decision tree and the parameters were validated by consensus of four experts in obstetrics and medical biology (J.G., E.B., V.M., M.V.). Interpretation of the results was also submitted to the expert committee. Each stage of the simulation was validated to ensure that data generated by the simulator matched expected data (proportion of fetal and father's Rh types, number of pregnancies per woman, number of alloimmunized women, number of cases of HDF, and costs).[3,4,11,20,22,28,44,45] When a discrepancy between calculated and expected data of more than an arbitrary threshold of 5% was found, the underlying erroneous parameter was sought, identified, and corrected.

Sensitivity analyses were performed on the SCHNAPS platforms' sensitivity analyses module, with the variables expected to have the most influence on the outcomes (Table 2).

RESULTS

When the development of HDF and neonatal survival at 28 days were considered as clinical outcomes, two options emerged as the most cost-effective: routine prophylaxis and immunological Rh typing of the father in the first pregnancy (Table 3). However, confidence intervals overlapped between these options.

In the second pregnancy, when the outcome of number of babies without HDF was considered, the immunological Rh typing of the father emerged as the most cost-effective option (Table 4). When neonatal survival at 28 days was the clinical outcome considered, two options emerged as the most cost-effective: routine prophylaxis and immunological Rh typing of the father. Here also the confidence intervals overlapped between these options.

The combination of first and second pregnancies showed that routine prophylaxis and immunological Rh typing of the father are the more cost-effective options. In all cases (first or second pregnancy or the combination), the fetal genotyping option did not appear to be cost-effective.

Sensitivity analyses using the ranges of variables presented in Table 2 showed that when the cost of fetal genotyping is $140 or less (estimated through linear regression), fetal genotyping became the most cost-effective option in the first or second pregnancy, and also when considering both pregnancies in combination.

DISCUSSION

Our results suggest that the four proposed strategies for prevention and treatment of Rh(D) alloimmunization are similar in terms of effectiveness. This was expected as all the options include giving anti-D IgG prophylaxis to women who need it. Moreover, the specificity and sensitivity of both fetal genotyping and immunological Rh typing of the father are high, which means that women who need prophylaxis are generally properly identified. In addition, all women who refuse testing (30%) either for fetal genotyping or immunological Rh typing of the father receive prophylaxis at 28 weeks.

We also found that the options of routine prophylaxis and immunological Rh typing of the father are the least expensive in the first and second pregnancies. The costs of both options are similar. In terms of cost-effectiveness, however, two options are superior: routine prophylaxis and immunological Rh typing of the father. However, we recognize that combining these options is unlikely to be widely accepted by the medical community.

Overall, our results show that the fetal genetic testing option is not a cost-effective option unless its cost is considerably lower than at present. In many countries, Rh genotyping remains costly and is performed by only a few laboratories.[2] The test is not currently automated in Canada, which contributes to its high cost, but in Germany the cost of the test after automation was estimated at €26.[57] As automation of Rh genotyping should be implemented in the next few years throughout the world, it is reasonable to predict that

the cost of the test will soon be less than $140, at which point it would be cost-effective. Until then, our results support the economic logic of the current guidelines[4,7,8] that propose routine anti-D IgG prophylaxis and eventually immunological Rh typing of the father, in order to reduce the incidence of fetomaternal Rh(D) alloimmunization.[4]

As with any economic evaluation, the most important limitation of our study is the uncertain external validity of the results, because the costs cited apply to a single jurisdiction. The characteristics of different populations will likely result in different findings. However, we believe that our extensive sensitivity analyses help to mitigate this limitation. The second important limitation is associated with the methodological approach based on simulations. Simplifications of real life are difficult to avoid. However, we attempted to limit the biases due to this simplification. For example, the anticipated compliance of physicians and patients was quantified, and sensitivity analyses were performed on variables deemed likely to affect the results. Finally, the perspective of the study was limited to the public health care system. A pregnancy bears important costs for women and their families. There are also important indirect costs, and these should be considered in future studies.

CONCLUSION

Until automation of Rh(D) fetal genotyping is implemented and the cost of screening falls below $140, immunological Rh typing of the father and routine anti-D IgG prophylaxis are the most cost-effective options. Because routine immunological Rh typing of the father would probably not be adopted by the majority of Canadian

clinicians, routine prophylaxis remains the preferred option, as recommended by the Canadian guidelines for the prevention of maternal-fetal Rh alloimmunization.

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Table 1. Scenarios

Scenario 1	Systematic prophylaxis : the routine use of anti-D immunoglobulin at 28 weeks' gestation
Scenario 2	Fetal Rh(D) genotyping by PCR of fetal free circulating DNA in maternal blood
Scenario 3	Immunological determination of the father's Rh type
Scenario 4	Mixed screening: immunological determination of the father's Rh type, followed if positive by fetal Rh(D) genotyping

Table 2. Input variables for the analyses

Variable		Baseline values	Values used in sensitivity analyses	References
Nulliparous pregnancy	At 12 weeks' gestation fetus Rh+	0.167%	0.107% to 2.8%	28
	Probability of alloimmunization without prophylaxis (at 28 weeks) fetus Rh+	2.08%	1.33% to 2.8%	28
	Probability of alloimmunization after prophylaxis (at 28 weeks)	0.33%	0% to 1.167%	4

Variable		Baseline values	Values used in sensitivity analyses	References
	fetus Rh+			
Subsequent pregnancy	Probability of alloimmunization after prophylaxis (at 28 weeks) in non-alloimmunized women fetus Rh+	0.33%	0% to 1.167%	4
	Probability of alloimmunization for non-alloimmunized women and postpartum prophylaxis fetus Rh+	2.92%	2.67% to 3.17%	4
	Probability of alloimmunization for non-alloimmunized women and no prophylaxis fetus Rh+	23.33%	20% to 26.67%	4

Variable	Baseline values		Values used in sensitivity analyses		References
Unknown father	2.6%		7% (mothers stating being single)		39
Genotyping	specificity	sensitivity	specificity	sensitivity	
	97%	100%	97%–100%	100%	11,30
Father Rh (immunological)	97.9%	100%	83% to 97.9%	50.3% to 100%	46
Indirect Coombs test positive	84%	95%	84%	90% to 100%	46,47,
Compliance of patients with genotyping	70.0%		60% to 98%		42
Compliance of physician with recommendations	73%		60% to 98%		11
Compliance of patients with postpartum prophylaxis	84%		81% to 87%		48

Variable		Baseline values	Values used in sensitivity analyses	References
Outcomes in alloimmunized women	Prenatal death Neonatal death Prematurity	9.1‰ 4.95‰ 8.1%	8.4‰ to 11.2‰ 3.96‰ to 6.27‰ --	49,50
HDF	Prenatal death Neonatal death Prematurity	1.4% 0.6% 57%	(0.7 to 2.1%) (0.3 to 0.9%) 40 to 70%	Expert opinion 51,52
Prematurity	death	11%	(5% to 18%)	53
Moderate and severe HDF without treatment	Prenatal death Neonatal death Prematurity	32.2% 13.8% 57%	-- -- 40% to 70%	54
Cost of fetal genotyping		$471	$70 to 470	55,56
Prophylaxis (anti-D immunoglobulin)		$81	$71 to 91	Quebec Ministry of health
HDF treatment	11–21 days NICU 7 days pediatric unit	$47 228	$22 656 to 47 228	44,46

Variable		Baseline values	Values used in sensitivity analyses	References
Prematurity treatment	14–21 days NICU 7 days pediatric unit	$47 228	$26 408 to 47 228	44,46

Table 3. Cost-effectiveness simulation analysis: first pregnancy results

Scenarios	Total costs, $ / 10 000 pregnancies	No. of babies without HDF / 10 000 pregnancies	No. of surviving babies /10 000 pregnancies	Costs/ number of babies without HDF, $	Costs / number of surviving babies, $
Systematic prophylaxis	101 848 991 ± 76 463	9975 ± 0.31	9811 ± 0.83	10 211 ± 8	10 381 ± 8
Immunological Rh typing of the father	101 911 011 ± 75 829	9975 ± 0.31	9812 ± 0.84	10 217 ± 8	10 387 ± 8
Mixed typing	102 864 181 ± 73 786	9975 ± 0.31	9811 ± 0.85	10 313 ± 7	10 485 ± 8
Fetal genotyping	103 310 771 ± 75 911	9975 ± 0.32	9811 ± 0.85	10 357 ± 8	10 530 ± 8

± denotes the 95% confidence interval

Table 4. Cost-effectiveness simulation analysis: second pregnancy results

Scenarios	Total costs, $ / 10 000 pregnancies	No. of babies without HDF / 10 000 pregnancies	No. of surviving babies /10 000 pregnancies	Costs/ number of babies without HDF, $	Costs / number of surviving babies, $
Immunological Rh typing of the father	106 362 892 ± 124 345	9912± 6	9808 ± 6	10 731 ±11	10 845 ± 11
Systematic prophylaxis	106 687 882 ± 124 991	9912 ± 6	9807 ± 6	10 764 ±11	10 879 ± 11
Mixed typing	106 837 257 ± 118 826	9914 ± 6	9808 ± 6	10 777 ± 11	10 894 ± 11
Fetal genotyping	107 193 950 ± 124 504	9914 ± 6	9808 ± 6	10 812 ± 11	10 929±11

± denotes the 95% confidence interval

Figure 1. Decision trees

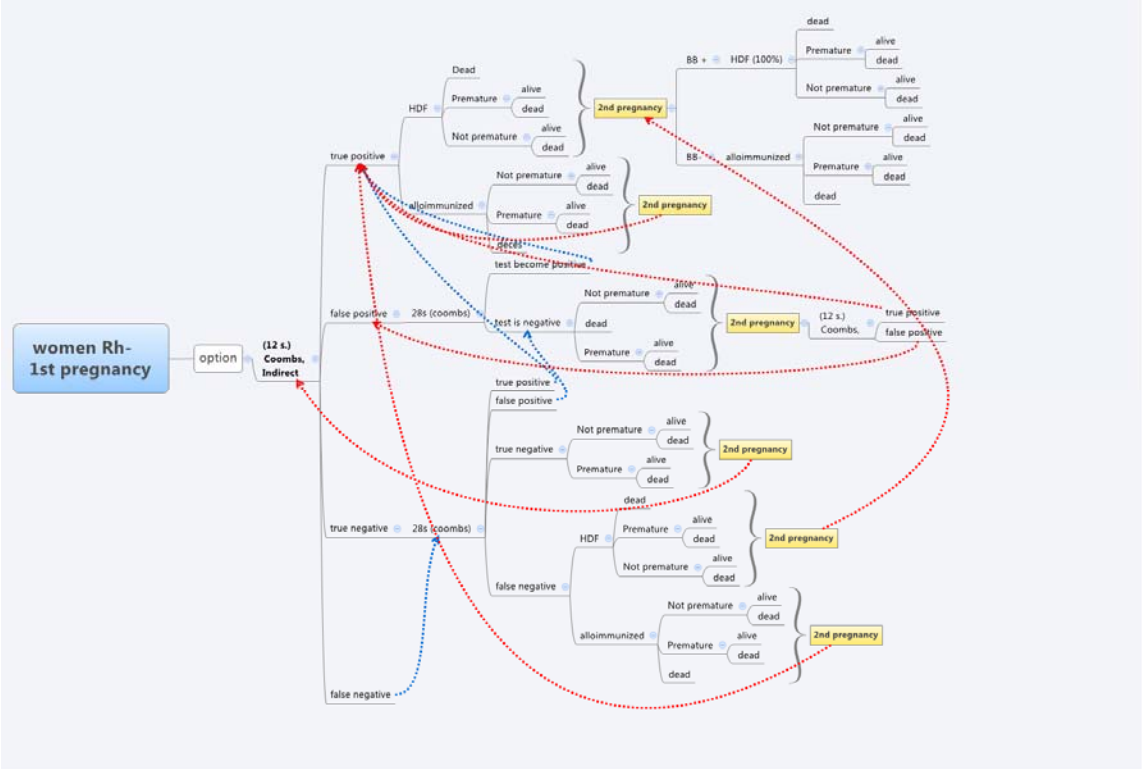
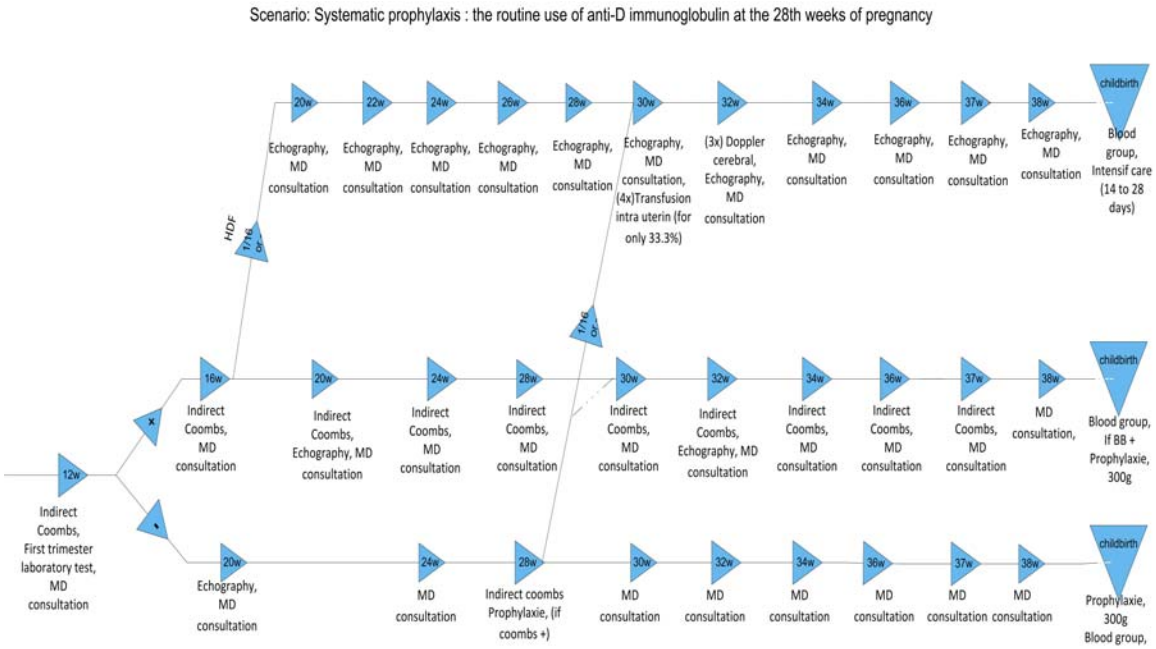
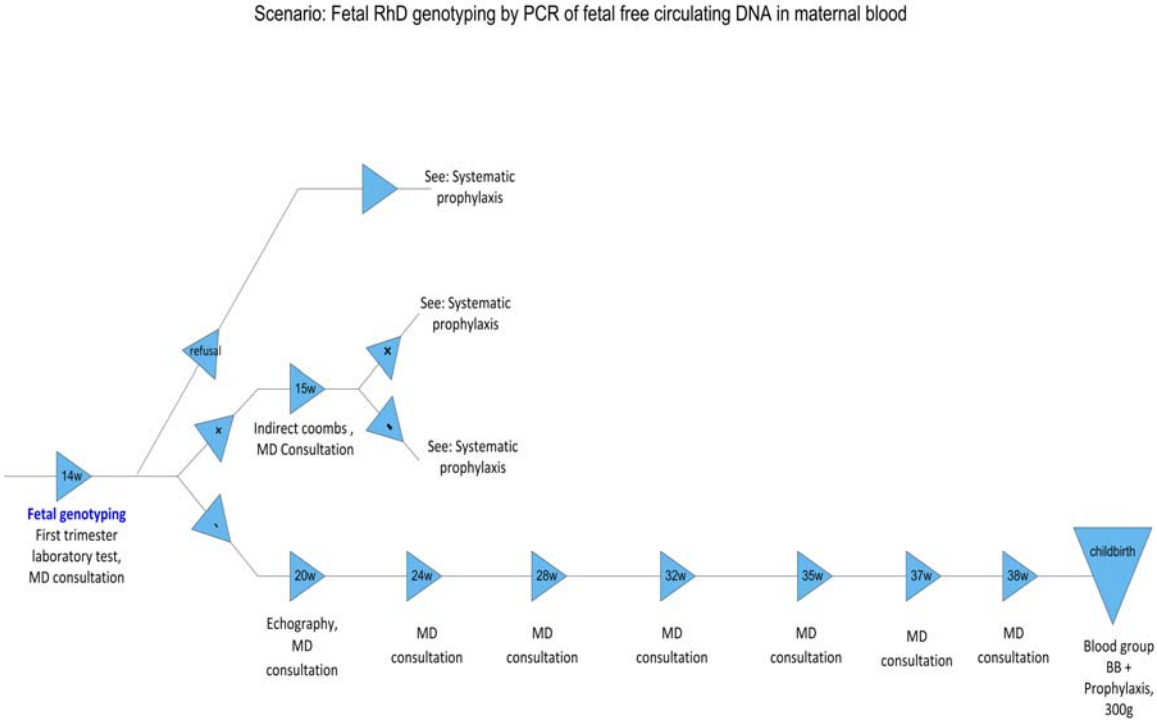
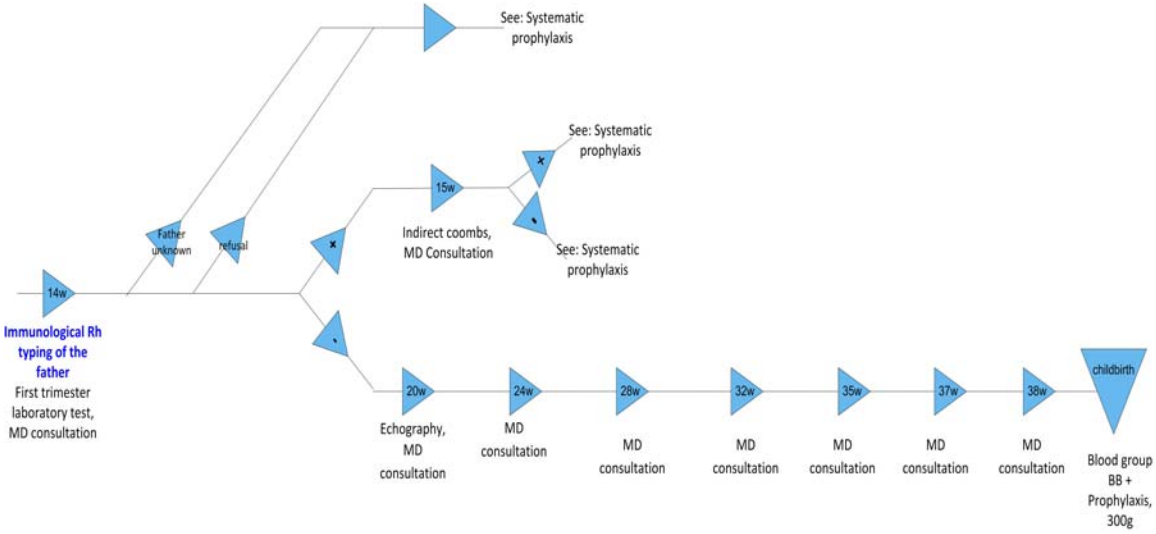


Figure 2. Sequence of services consumed in each scenario





Scenario: Immunological determination of the father's Rh factor



Scenario: Mixed screening: immunological determination of the father Rh, followed, if the result is positive, by fetal RhD genotyping