An economic evaluation of fetal RHD typing in week 11 instead of week 27 of pregnancy (usual care), using RQ-PCR

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1. Summary

a. Background

Fetal RhD typing is currently conducted in the second trimester of pregnancy in the Netherlands, to target preventive treatment towards D-negative women with D-positive fetuses only, rather than all D-negative women. D-negative women with D-positive fetuses may develop antibodies against the fetus' red blood cells (immunization), which can cause hemolytic disease of the fetus and newborn (HDFN). This economic evaluation assesses the effect of fetal RhD typing in the first trimester, targeting all subsequent screenings and treatment. Knowing the fetus' RhD status earlier would remove the need for an antibody screen at week 27 for women with D-negative fetuses, as well as treatment against immunization in the case of sensitizing events in the second trimester, thus reducing costs. Consequences on health and immunizations (and associated treatment costs) need to be evaluated.

b. Methods

A cost-utility analysis was conducted to answer the research question: a decision tree model was used to define the current screening program (fetal typing at 27 weeks) and its alternative (typing at 11 weeks). The population considered is pregnant women in the Netherlands, who all participate in the national PSIE screening program. The model estimates outcomes as expected values per pregnancy. Outcomes were measured in terms of expected lifetime quality-adjusted life years (QALYs) of the child, chance of not being immunized in a single pregnancy and expected cost per pregnancy (2022 euros).
Information about probabilities, health outcomes and costs were collected from Sanquin (responsible for screening nationwide), Leiden University Medical Center, the Dutch costing manual and literature. A one-way sensitivity analysis and a probabilistic sensitivity analysis were used to address parameter uncertainty.

c. Results

With the alternative screening program, €2.3 would be saved on average per pregnancy, €15.8 on average per RhD negative pregnancy and €389 000 per year in the country. QALYs and immunizations only change slightly: per year, less than one QALY is lost, and less than one additional immunization occurs (with an estimate of 170 000 pregnancies yearly and nationwide). This makes the alternative screening program cost-effective for all Dutch threshold values.

d. Conclusion

Typing a fetus' RhD status in week 11 instead of week 27 of pregnancy is deemed cost-effective in the Dutch context. Further, more detailed evaluation (i.e., with a more detailed method regarding measurement of treatment costs and checking for heterogenous effects) is recommended to address the model's limitations and increase robustness of results. An observational study could evaluate the accuracy of fetal PCR testing in the first trimester.

2. Introduction

a. Topic and rationale

The prenatal screening for infectious diseases and erythrocyte immunizations (PSIE) is a national screening program active in the Netherlands. It aims to screen pregnant women for potential diseases transmissible to the fetus, as well as the presence of harmful antibodies in the blood. Compliance to this program is between 99% and 100% in the country yearly (van der Ploeg et.al., 2022). The antibody most likely to be dangerous to the fetus (in terms of prevalence and severity combined) is that against Rhesus D, or RhD, which is a protein present on D-positive individuals' red blood cells (Zwiers, 2019). A mother who is D-negative could develop such antibodies if her fetus is RhD positive, which is why she is screened for these antibodies (as well as others) in the first trimester and in week 27 of pregnancy, as part of the PSIE program. The fetus' RhD status is also determined in week 27.
Immunization is prevented with the use of anti-D prophylaxis, which is made from blood donations (Koelewijn et.al., 2008b). This is given to the mother before and after birth, as well as in the occurrence of sensitizing events (i.e. after invasive procedures or abdominal trauma) (Slootweg et.al., 2022). During these events, prophylaxis is given to all D-negative women until the fetus' RhD status is known. This study evaluates the cost-effectiveness of typing the fetus earlier in pregnancy, and thus also targeting antibody screens only towards D-negative women with D-positive fetuses.

b. Relevance

One of the goals of targeting anti-D administration earlier in pregnancy is to avoid unnecessary administrations. Since production of anti-D relies on blood donations, there is an incentive to use it sparingly and only if needed, i.e., only to RhD negative women carrying an RhD positive fetus. Ethical concerns were also raised about over-treating mothers, if that can be avoided (Kent et. al., 2014). Additionally, if the fetal RhD status is known earlier, the week 27 screen will no longer be needed for D-negative mothers with D-negative fetuses, thus saving unnecessary costs. This study is therefore socially relevant: it will guide Sanquin on further research by evaluating the cost-effectiveness of this care pathway, and contribute to the decision-making process. It is also important to evaluate the health effects of this change, to make sure that there is not an increase in immunizations: a mother's antibodies can attack the fetus' red blood cells and lead to anemia, which needs to be treated at birth. Severe anemia can lead to permanent brain damage to the newborn: 4% of surviving babies born with a severe case develop neurological disabilities (i.e. cerebral palsy). Additionally, 9% of severe cases lead to neonatal death (Lindenburg et.al., 2012). There could be slightly more immunizations with earlier typing, since the fetus can be falsely typed as negative and thus, no longer be treated against sensitizing events in the second trimester (when they would have been if the status was unknown until the 27th week).
In past literature, the effect of targeted versus non-targeted anti-D prophylaxis (using real-time quantitative PCR, or RQ-PCR testing) was studied. Targeting was found to reduce costs and blood waste while not leading to too many additional immunizations, due to the high accuracy of RQ-PCR tests. However, there is a lack of papers comparing early versus later targeting of anti-D. Neovius et.al. (2016) evaluated targeting anti-D after a 1st trimester fetal DNA test, however this was only compared to non-targeted routine anti-D prophylaxis (RAADP) (and no RAADP) instead of later targeting. In countries such as the UK and Australia, it is already proven that this test can accurately predict fetal RhD status from week 11 of pregnancy onwards (Chitty et.al., 2014; Gordon et.al., 2017), and screening procedures already require fetal typing from week 11 (NHS Blood and transplant, n.d.; National Blood Authority Australia, 2021). However, first-trimester PCR testing has not been previously carried out or tested in the

Netherlands. This paper will therefore add to the current body of literature, by evaluating first-trimester targeting in a new context.

c. Research question

The aim of this research is to evaluate the cost-utility of fetal RhD genotyping at week 11 instead of week 27. This treatment is suspected to be cost-effective based on prior research, since it reduces unnecessary use of anti-D by targeting it earlier in pregnancy (starting from week 16 instead of week 30). It will also remove the need for the week 27 antibody screen for women with D-negative fetuses.

The population studied is all pregnant women in the Netherlands, since the PSIE program intends to screen all women (and does so with a 99-100% compliance rate). The suggested intervention is to type fetal RhD status in week 11 of pregnancy using real time quantitative PCR testing (RQ-PCR) and targeting treatments and screens from week 16 onward. Its comparator is the current care pathway: typing fetal RhD in week 27 instead, and targeting treatments and screens from week 30. The outcomes used will be: (1) lifetime costs, (2) number of immunizations and (3) QALYs for newborns, estimated from a lifetime perspective. This is chosen because it measures both number of life years and quality of life. Additionally, consequences of immunization can last over a fetus' entire life: not only the mother's first sensitized fetus, but also her future fetuses. Considering these details, the following research question is evaluated:

What is the cost-utility of non-invasive fetal RhD typing in week 11 of pregnancy for pregnant women in the Netherlands, instead of typing in week 27 (usual care)?

d. Structure

First, a theoretical background will be drawn, clarifying important concepts (scientific and economic). The current care pathway for pregnancies in the Netherlands will be described. Previous economic evaluations on the topic of anti-D prophylaxis and fetal RhD typing will also be summarized. Second, the methodology is described: the model's framework is defined, inputs are presented and methods for analysis are explained. Section 5 presents model results, and section 6 provides a discussion evaluating results and limitations of the model, as well as providing suggestions for further research.

3. Theoretical background

a. Scientific concepts and definitions

Important terms will be clarified to fully understand the treatments and their given health effects.

During pregnancy, mothers are tested for different antigens present in their blood. This includes determining their ABO blood group for A and B antigens and IEAs (irregular erythrocyte antibodies), such as Rhesus D (RhD). If a mother does not have a certain antigen, for example if she is RhD negative, and her fetus has the antigen (i.e. is RhD positive), she may develop antibodies against her fetus' antigens. This happens during fetal-maternal hemorrhage, which is when the mother and fetus' bloods mix, and often happens during birth or events such as invasive procedures (i.e. abortions) or abdominal trauma, called sensitizing events (Slootweg et.al., 2022).

If the mother's immune system develops antibodies, she is immunized. This can have negative consequences for the fetus, who can develop anemia. This can be treated with intrauterine transfusions (IUTs) (Zwiers, 2019). After birth, the newborn can also suffer from jaundice, which can be treated with phototherapy or exchange transfusions to prevent future harm.

The disease described is called hemolytic disease of the fetus and newborn, or HDFN (Zwiers, 2019), and can cause brain damage resulting in developmental problems, cerebral palsy, deafness, or other problems, if untreated (Lindenburg et.al., 2012). It can also lead to perinatal death.

A fetus can be treated using transfusions (exchange transfusions, intrauterine transfusions) and phototherapy at birth, which has decreased the morbidity of HDFN.

RhD will be the focus of this paper as it is the only blood group system for which primary prevention to prevent alloimmunization has been developed: this is anti-D prophylaxis, a blood product injected pre- and postnatally to prevent the formation of antibodies (de Haas et.al., 2016). RhD also the most important cause of severe HDFN in the fetus. Other antibodies such as anti-K (Kell) are more harmful, but also rarer: 76% of immunizations are due to anti-D antibodies, while only 16% are due to anti-K (Zwiers, 2019). Anti-K immunoprophylaxis however has never been developed. Approximately 14.5% of the Dutch population is RhD-negative (van der Ploeg et.al., 2022). When a mother is immunized, the antibody titer will be determined: this shows how much antibodies are present in her blood. During the first pregnancy, the titer is usually lower, meaning the fetus will likely be healthy. However, in subsequent pregnancies the titer may increase, leading to more severe cases of HDFN or even neonatal death (Zwiers, 2019).

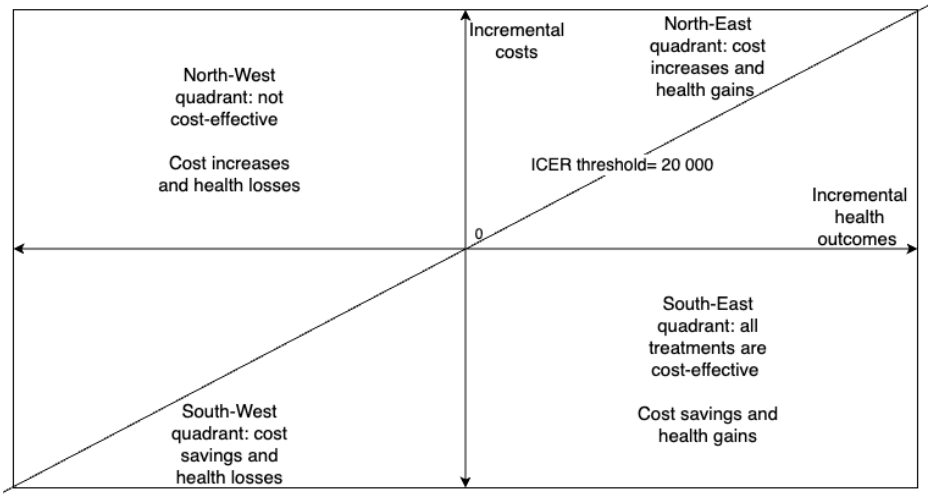
b. Economic evaluations and health technology assessment (HTA)

Economic evaluations, including cost-effectiveness and cost-utility studies, are used for healthcare decision-making at a country level in many nations such as the Netherlands, Sweden, France, the United Kingdom and Canada (Drummond, 2015). The goal of such an evaluation is to compare two alternatives for treatment (i.e. two drugs, devices or programs) in a systematic way, to inform a decision such as nation-wide reimbursement. Often, this involves comparing a new treatment to the current standard of care. For each alternative in the evaluation, costs and outcomes are both measured and valued. This helps to answer questions about the "new" treatment, i.e. the one being introduced to the country:

a) What is the additional cost, or how many cost savings are made?
b) By how much does it improve or worsen health outcomes?

Health outcomes can be measured in different ways, depending on the preference of the country's HTA body. In the Netherlands, the preferred measure is Quality-Adjusted Life Years (QALYs) (Versteegh et.al., 2016), which is a measure of life years discounted based on the individual's health state. One year in perfect health takes the value of one, while a year where the person has died takes the value of 0: different health states can yield results in-between these extremes, or below zero if a state worse than death is considered. QALYs are an estimate of a person's health utility over their lifetime, measured based on average preferences of the population (Drummond, 2015). Measuring health outcomes in terms of QALYs makes a study comparable to other cost-utility analyses, regardless of disease area, since it is a standard way of reporting health and longevity. Decision-makers can then see which new treatments should be reimbursed, across all disease areas, to maximize the population's utility when taking the budget into account. Considering these advantages, a cost-utility analysis will be conducted to answer the research question. The health outcome can also be measured with different clinical values, specific to the studied disease. This is a cost-effectiveness analysis, and can be more beneficial to certain stakeholders such as health professionals.
All outcomes of an economic evaluation are synthesized in one value called the incremental cost-effectiveness ratio, or ICER: this divides the difference in costs between both alternatives with the difference in outcomes. The ICER can then be compared to a predetermined threshold to draw conclusions on whether the standard-of-care treatment should be replaced by the new treatment. In the Netherlands, the ICER threshold ranges from 20,000 to 80,000, depending on the disease severity (a more severe disease yields a higher threshold). This means that the country is willing to pay up to this much to gain a single QALY, or that they are willing to give up one QALY to save this much (in Euros). This can be represented in a cost-effectiveness plane:

Figure 1. Cost-effectiveness plane, with a 20 000 ICER threshold.



Incremental costs/QALYs are measured by deducting the comparator's costs/QALYs to the treatment considered. Any treatment that falls below the threshold line is considered cost-effective, while treatments above the line are not. Decision-makers can then use the study as evidence to make a choice. Therefore, all treatments in the South-East quadrant are cost-effective regardless of the ICER's value, while all in the North-West quadrant are cost-ineffective. In the North-East quadrant, the ICER needs to be smaller than the threshold value, since that threshold represents the maximum willingness to pay to gain one QALY (WTP). In the South-West quadrant, the threshold is interpreted in a slightly different way: it is the minimum amount a country is willing to accept, in exchange for the loss of one QALY (WTA). Therefore, the ICER needs to be higher than this threshold for the treatment to be cost-effective.

To conduct a successful cost-effectiveness study, several guidelines are considered: valid results can only be found if appropriate methods are used. Drummond et. al. (2015) identifies five elements that determine the validity of an economic evaluation's results. First, the research question should be clear. This is done by defining which treatment will be evaluated and under which circumstances it is considered (patients, time horizon, etc.). Secondly, the comparator(s) should be relevant, usually by being (a) proven next best alternative(s). Third, the studied treatment should be deemed effective by prior medical research. The final two elements should be considered when measuring costs and effects: all relevant cost drivers/health outcomes for the perspective should be accounted for, and their measurements should be sufficiently accurate and come from reliable sources.

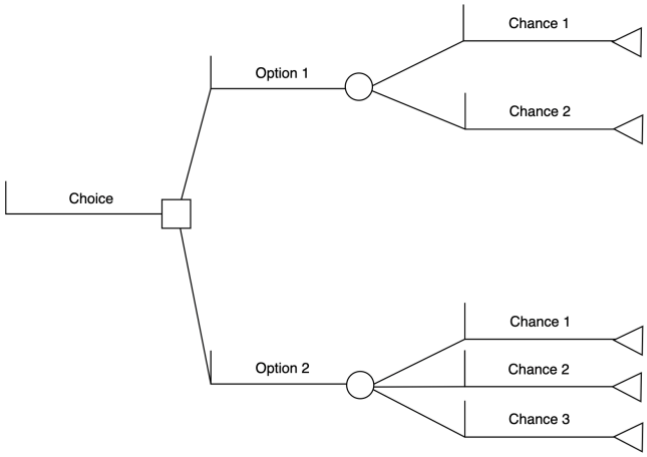
Two reporting guidelines were used in this analysis. Such guidelines are designed to ensure completeness and increase validity. CHEERS, the consolidated health economic evaluation reporting standards (Husereau et.al., 2022) will ensure that all important steps of an economic analysis are covered. This involves, among others: defining methods, reporting and evaluating uncertainty and discussing limitations. The second guideline, TECH-VER (Büyükkaramikli et.al., 2019), provides a list of tests to ensure the correctness of the model (its inputs, design and calculations). The study conducted is a cost-utility analysis, meaning that the health effect of both clinical pathways are measured in terms of utility: this is done with QALYs. Other outcomes in this study are costs (in 2022 euros) and number of immunizations, which is a clinical outcome. This is detailed in section 4c.iii. Results will then be summarized in two values: the incremental cost-effectiveness ratios (ICERs). These are ratios of the change in cost (new pathway - old pathway) and the change in outcomes (one measured in QALYs and the other with the number of immunizations).

Dutch guidelines for economic evaluations in healthcare (Versteegh et. al., 2016) also request studies to be completed using the societal perspective: this means that all costs of the disease need to be accounted for, even those incurred outside of the healthcare sector. This mainly includes informal care, i.e. when relatives need to care for a sick individual, and productivity losses of the individual due to the illness. To calculate the latter, guidelines advise the friction cost method: this will estimate productivity losses by calculating the individual's salary during the friction period, using his salary before illness. The friction period is defined as the period that one was absent due to illness, until they either re-join the workplace or are replaced.

c. Decision analytic modeling

A model was used to answer the research question: it conceptualizes the ways in which lifetime costs, immunizations and QALYs differ per treatment and estimate these outcomes. A decision tree model was chosen as it is simple and geared towards evaluating short term scenarios (i.e. screening procedures) (Drummond, 2015).
In a decision tree, the first branch split is the decision node: one branch follows the treatment, while the other follows its comparator. This is represented with a square (see figure 2). After that, different events will occur depending on chance: for example, the result of a screen can be positive or negative. These are shown by chance nodes, represented by circles, and each branch "split" has a probability attached to it. This is a conditional probability: the likelihood of an event, given that all the previous events occurred. Health outcomes are attributed at the end of the tree, represented by a triangle: to calculate the probability of one outcome, i.e. the path probability, all conditional probabilities along that path need to be multiplied. To calculate the expected health outcome of a treatment, QALYs assigned to each path are weighted with their respective path probability. The same is done to find a treatment's expected costs.

Figure 2. Example of a decision tree



A model's input parameters are only estimates of real-life costs, probabilities and health outcomes, therefore uncertainty around these parameters needs to be addressed when conducting a cost-effectiveness analysis. Dutch guidelines for economic evaluation in healthcare (Zorginstituut Nederland, 2016) recommend a probabilistic sensitivity analysis (PSA). This involves estimating a distribution for each input value, and randomly drawing numbers for each input from these distributions. Multiple simulations should be made in this way, and each time, incremental costs and QALYs should be noted. Around 1000 Monte Carlo simulations are recommended (Drummond, 2016). These simulations are then displayed on a cost-effectiveness plane. From there, the likelihood of the ICER being favorable is estimated, taking into account parameter uncertainty. PSA helps to show the full range of decision uncertainty, since all parameters can vary at once, and so give a more robust result than the deterministic analysis (where parameters are taken at face value).
Another analysis that can be conducted is the one-way sensitivity analysis. This is when inputs are changed one by one, by setting them to a plausible minimum, then a maximum. Parameters that affect the ICER the most when varied can then be represented on a tornado diagram: this identifies key parameters that the model is most sensitive to.

d. Findings from previous cost-effectiveness studies

In a systematic review, Gajic-Veljanoski et. al. (2021) summarized prior studies that evaluate the cost-effectiveness of targeted RAADP through fetal genotyping, compared to usual care. In these studies, usual care was non-targeted (universal) anti-D (i.e. treating all RhD-negative women with routine anti-D prophylaxis). Most papers used the healthcare perspective. Most often, effects were measured in terms of number of immunizations and/or healthy babies. Results were not consistent on whether targeted or universal RAADP was more cost-effective, due to a difference in healthcare contexts and ways to measure health outcomes.

One study in the UK (Saramago et. al., 2018) measured outcomes in QALYs by using a prior study's estimates of quality of life, for individuals with major or minor developmental issues caused by severe HDFN. This paper concluded that targeting anti-D administration in the second trimester led to a loss of QALYs due to additional immunizations, since fetuses with false negative test results were no longer administered anti-D. However, it was deemed cost-

effective, because prenatal tests are still highly accurate and targeting anti-D means that less blood material is wasted.

Gajic-Veljanoski et. al. (2022) also conducted a cost-utility analysis (measuring outcomes in QALYs), for the same treatment and comparator in Canada. Results were not entirely in-line with Saramago et. al.'s findings: in pregnancies that were not previously compromised by immunization, targeting led to both higher costs and more immunizations. However, it is mentioned that targeting could be cost-effective, if the price of fetal typing were lower. This observation is tied to the Canadian context.

Another study used evidence from a clinical trial to determine the cost-effectiveness of targeting RAADP, using a French population (Darlington et. al., 2018). Targeting was deemed cost-effective, but conclusions were different from the UK study: outcomes were measured as the number of avoided unnecessary injections of anti-D, which improved with the use of fetal Rh typing. However, costs were deemed higher when targeting anti-D, due to the introduction of fetal screening-related costs. Similarly, an Australian study (Gordon et.al., 2017) looked at the cost-effectiveness of targeting prophylaxis in weeks 28 and 34 of pregnancy, as well as after birth, compared with non-targeted treatment. This led to better performance when measured as the percentage of women receiving appropriate treatment, but slightly higher costs due to fetal typing.

In Sweden, a study measured cost-effectiveness of the same treatment and comparator (Neovius et.al., 2016), in terms of immunizations avoided: similar to the French and Australian studies, targeting anti-D led to higher costs. It also led to more immunizations however, deeming the study cost-ineffective. Therefore, the priority goal (low immunization rate versus giving appropriate treatment) strongly determines the outcome of the study.

In the Netherlands, the decision was made to use an RQ-PCR in week 27 to subsequently target anti-D administration in week 30, due to evidence that test accuracy was high and blood waste was reduced (De Haas et.al., 2016; van der Schoot et.al., 2017). Using RQ-PCR also removed the need for cord serology (CS), previously used to type the newborn's blood and target postnatal anti-D. CS is now only used in the case of inconclusive PCR results, or if the mother will give birth to twins (since each twin's RhD status cannot be differentiated). Other countries also currently target RAADP in the third trimester, such as Denmark, Norway and Finland (Legler, 2020).

The studies mentioned above used different methods for evaluation, most often modeling (either with a decision tree or a Markov model). The Swedish evaluation used a cohort study, and the French one used a prospective two-armed trial.

e. Netherlands- clinical pathway and methods

This study is adapted to the Dutch situation, as each country's standard of care and methods differ: this means different results should be expected in each context. Country-specific differences include the method used to determine the fetus' RhD status: in the Netherlands, an RQ-PCR test is used with a certain algorithm to determine positive, negative and inconclusive results. Changes in this algorithm can affect the sensitivity and specificity of the test (measures of the test's accuracy, in terms of detecting positive results correctly and not falsely detecting results as positive when they should be negative). In various countries' studies, result accuracy has ranged from 98.87% to 99.93% in the second and third trimester, and down to 97.75% in

the first trimester (van der Schoot et.al., 2017). Dutch estimates are provided in the methodology.

The PSIE program (Prenatale Screening Infectieziekten en Erytrocytenimmunisatie), which is active in the Netherlands, screens all pregnant women to monitor presence of red blood cell (RBC) antibodies and blood-related diseases such as HIV and Syphilis (RIVM, 2021a). Blood samples are generally processed by one of 80 laboratories in the Netherlands. If RBC antibodies are detected, material is sent to Sanquin Diagnostic Services or -if a pregnancy is in care in the three northern provinces- the laboratory of the University of Groningen (the BIBORIVM, 2018). Rates for processing blood samples and investigating types and titers of antibodies are therefore standardized nationwide. Compliance to the PSIE program ranges from 99 to 100% yearly (van der Ploeg et.al., 2022).

If antibodies are detected in a blood sample, a standardized procedure is also followed. This involves matching the blood sample to different reagents to determine the type of antibodies present. If the antibody found is clinically relevant (i.e. poses a threat to the fetus), the father's blood is tested to determine whether the fetus has a chance of having the antigen (since the fetus inherits their red blood cell antigens from the father). If there is a chance of this, the fetal status is determined, and if needed an ADCC assay and titer evaluations are performed. The ADCC assay determines antibodies' ability to destruct red blood cells (RIVM, n.d.), while the titer is a measure of the quantity of antibodies present in the blood (Vandenbussche & Klumper, 2009). Both have an impact on HDFN severity. This is represented in Appendix 3. Information on this procedure was collected internally at Sanquin, with Heleen Woortmeijer.

4. Methodology

a. Framing

i. Perspective

The healthcare perspective was chosen for this study, despite the Dutch guidelines favoring the societal perspective. This is due to lack of information about costs incurred outside of healthcare (i.e. productivity costs or informal care), and time constraints for the Master thesis. Additionally, only the timing of the RQ-PCR is changed between both clinical pathways compared: spillovers into other sectors are not expected to change significantly, especially since test accuracy does not change after week 10 of pregnancy (Darlington et. al., 2018). Despite this, a sensitivity analysis was conducted in which non-healthcare costs, mainly informal care, are included. Assumptions were made about these costs: these are explained in section 4f.i.

ii. Time horizon

A lifetime horizon was chosen, as it defines the total effect of differences between pathways on the newborn's life. Consequences of HDFN, such as developmental issues, can indeed affect individuals over a lifetime.

iii. Population

The population is all pregnant women in the Netherlands, as the PSIE program intends to screen all pregnant women in the country.
In 2021, approximately 176 400 women were screened with PSIE. Costs and outcomes will be presented both as an expected value per woman, and as a yearly total according to the yearly average of 170 000 newborns.

iv. Intervention

The suggested intervention is to use RQ-PCR to type fetal RhD status in week 11 of pregnancy. Its comparator is the current care pathway: using this test to type fetal RhD in week 27.
Just like the comparator, the intervention still involves typing the woman's blood during or before week 12, therefore the blood for fetal and mother testing can be collected at the same time. Anti-D prophylaxis will still be administered at week 30 and after birth if the mother has a D-positive fetus, and the week 27 antibody screen is still needed for D-negative women with D-positive fetuses. The antibody screen is no longer conducted if both mother and fetus are D-negative. Women who develop antibodies during pregnancy are still monitored using the same protocol.

v. Comparator

A relevant comparator was chosen: here it is standard care, as it is considered as the most cost-effective clinical pathway to this day. As mentioned in section 3, many countries are moving towards targeting anti-D using an RQ-PCR in the second trimester, rather than giving anti-D to all D-negative women.

vi. Outcome

The outcomes used were: (1) lifetime costs, (2) number of immunizations and (3) QALYs for newborns, estimated from a lifetime perspective. QALYs are chosen because they measure both survival chances and probability of health issues at birth. The number of immunizations was also measured: alloimmunization of a mother affects future pregnancies even more than the current, due to an increase in antibody presence over time (i.e., all future children of the

immunized mother will be impacted). This results in two ICERs: one for either costs per immunization avoided or cost savings per additional immunization, and one for either costs per QALY gained or cost savings per QALY lost.

A mother is considered immunized when an antibody test, either before the start of pregnancy or during the week 12 or 27 antibody tests, detects anti-D antibodies. Alternatively she can develop antibodies between week 27 and birth. Three QALY estimates will be formulated for:

1. Healthy newborns, i.e. those with no long-term consequences of, or not affected by, HDFN;
2. Unhealthy newborns, i.e. those who face long-term consequences of severe HDFN;
3. Dead newborns, i.e. those who do not survive HDFN neonatally.

These health states were chosen based on the LOTUS study (Lindenburg et.al., 2012) conducted in the Netherlands, where children born with severe HDFN were followed-up. A large proportion of children born with HDFN had no long-term health consequences, which was taken into consideration by separating the health states by long-term health status rather than likelihood of (severe) HDFN.

b. Decision tree model

The model used was a decision tree, which is appropriate to evaluate screening procedures. It is presented in figures 3-5. The decision tree model is available on the Erasmus University Rotterdam SharePoint, by scanning the QR code or copying the link in appendix 9.

Figure 3. Decision between treatment and comparator

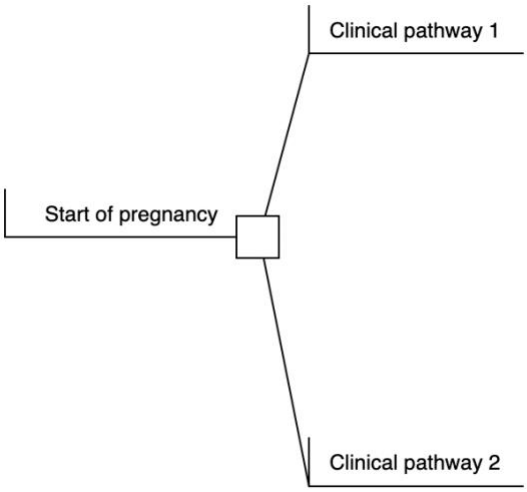


Figure 4. Pathway 1, current protocol in the Netherlands (comparator)

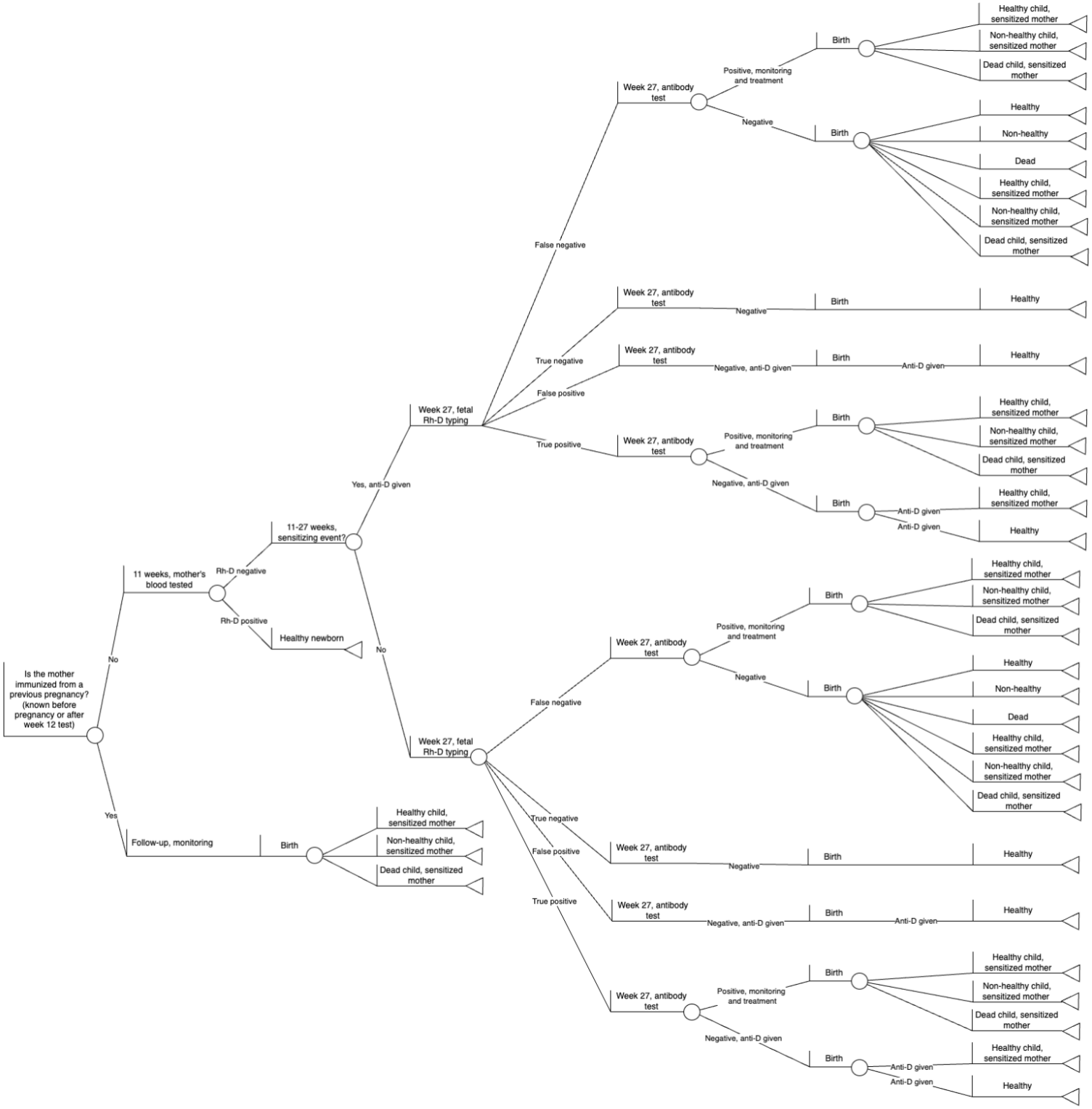
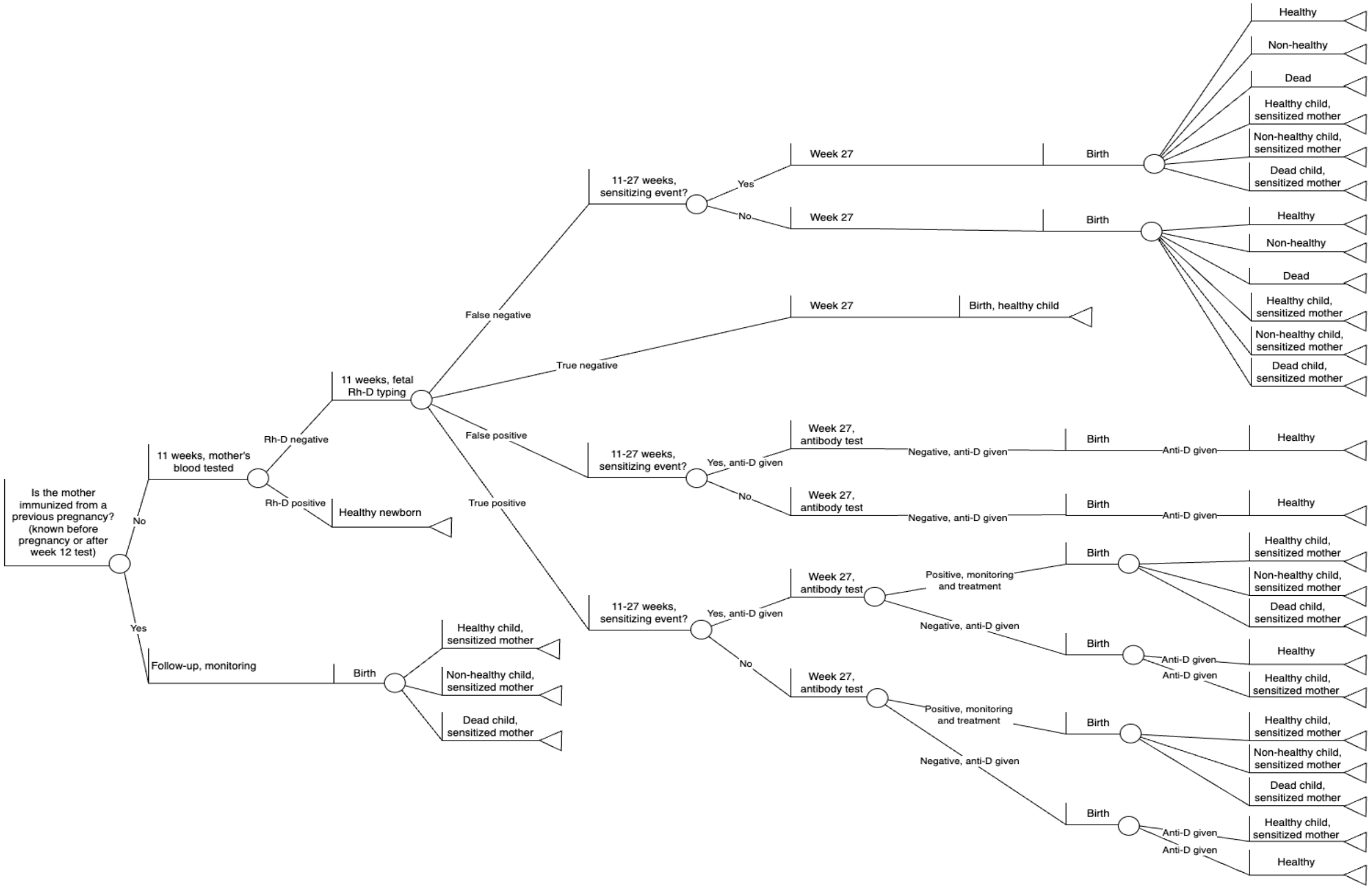


Figure 5. Pathway 2, evaluated protocol in the Netherlands (treatment)



Differences between care pathways are as follows:

1. In pathway 1, the fetus' RhD status is only determined during the week 27 screen. This means that in the case of a sensitizing event before week 27, anti-D prophylaxis is administered for all RhD negative women. In pathway 2, since the fetus' status is known by week 16, sensitizing events occurring after week 16 can already be targeted to D-negative women with RhD positive fetuses only, thus incurring less costs.
2. Since anti-D needed before week 27 is newly being targeted, RhD positive fetuses that falsely test as negative (false negative PCR results) will no longer be administered anti-D prophylaxis during sensitizing events (before week 27). This might increase the chance of immunization.
3. In pathway 1, because the fetal RhD status is not known by the time of the week 27 screen, antibodies are screened for all RhD negative women (and women with other relevant blood group statuses, such as Rhc-negative). Meanwhile, this is not necessary in pathway 2, if the status of the D-negative mother's fetus is known to be D-negative as well. In this situation the mother cannot develop antibodies, since the fetus does not possess RhD antigens. This saves costs on the week 27 screen.
4. For the same reason, costs of antibody determination and follow-up (in the case of a positive antibody test) will no longer be incurred for D-negative women with D-negative fetuses in week 27 (if no other antibodies were found in first trimester that pose a threat to the fetus).
5. Finally, since antibody tests are no longer conducted for RhD-negative fetuses in pathway 2 (at week 27), there is a chance that they may be immunized by antigens other than RhD during sensitizing events and no longer be detected and treated. Although this probability is small, it should not be neglected as it affects the number of immunized newborns.

c. Data collection

Data was mainly collected from Sanquin, TNO and the LUMC, in collaboration with Renske van 't Oever, Heleen Woortmeijer and Masja de Haas. Assumptions about the data were also made in consultation with Elske van den Akker-van Marle, to ensure their plausibility. Collection methods and input choices are presented below, and Appendix 7 provides a summary of final inputs for the decision tree.

i. Event probabilities

All event probabilities are summarized in table 1 as well as appendices 1 and 2, where each probability is attributed to a branch in the decision tree.

First, the percentage of RhD negative pregnant women in the Netherlands was estimated using the 2020 PSIE monitor (van der Ploeg et.al., 2022). This was 14.5% in 2020, the most recent available year, and the monitor's report notes that this remained stable over time. The chance that a woman has an RhD negative status depends on her ethnicity: estimates are of 15% for Caucasian women, 8% for women with ancestors from African countries and 1% for Asian women (Sanquin). Therefore, a change in the population composition would affect the prevalence of D-negative status in pregnancies.

Second, the percentage of women that are sensitized at the start of the pregnancy (i.e., from a previous pregnancy), was estimated. Records from Sanquin, presenting results of the week 12 screen, were used. It is assumed that if a woman tests positive for RhD antibodies this early in

pregnancy, it is not because of that current pregnancy. Records were found between 2018 and 2021: these included adjustments made after accounting for BIBO's results. The number of women with RhD antibodies was counted for each year, then divided by the total number of screened women in that year. An average was taken as a final value. The number of screened women per year was taken from PSIE monitors of 2018-2020 (and the preliminary 2021 monitor) (van der Ploeg et.al., 2022).

The chance for a woman that is not yet immunized in week 12, to have antibodies in week 27, was also calculated with Sanquin records. These displayed results of the week 27 screen for all women: the number of new antibodies (i.e. not detected before week 27) was calculated for each year from 2018 to 2021. To find the probability conditional on previous events in the trees, this was divided by the number of D-negative women found in each year. It is assumed that the chance of finding new antibodies in week 27 is the same regardless of whether a woman underwent a sensitizing event or not (Slootweg et.al., 2022).

The likelihood that a woman will undergo a sensitizing event (including invasive procedures, abdominal trauma, abortions, etc.) was estimated using records provided by TNO from 2019, 2020 and 2021. These include the number of sensitizing events in each week, and note whether this is a woman's first, second or third event. In pathway 1, the treatment of events after week 27 with prophylaxis is targeted towards women with D-positive fetuses only. Since the fetus' status is known by week 16 in pathway 2, events occurring between weeks 16 and 27 can now be targeted as well. Therefore, only the likelihood of having an event in this period is calculated. In each year, the number of women with one or more events is divided by the total number of D-negative women. The average of these three years was taken.

Percentages of false positives/negative and true positive/negative results of the PCR test for fetal RhD typing were needed. Sanquin records between 2016 and 2022 counted the number of positive, negative and inconclusive results for each year, as well as the requests for new samples (if the blood sample could not be evaluated). For each year, percentages of positive and negative results were calculated, in which inconclusive results were treated as positive, since further treatments would still need to be conducted. An average of all years was taken.
Values for false positive and false negative rates were taken from de Haas et. al. (2016).
In that paper, two PCR result algorithms were evaluated: in the main one, which is a simpler algorithm, more fetuses were deemed as RhD positive rather than inconclusive: this reduced the number of inconclusive results. However, as advised by Masja de Haas, the alternative algorithm's sensitivity and specificity were used since it is currently applied (in 2023): it considers more results as inconclusive, and thus yields less false positive results. A false positive rate of 0.57% was therefore taken, and a false negative rate of 0.03%. True positive and true negative rates were then calculated from the Sanquin's record of results, by taking these error rates into account. Confidence intervals were also taken from de Haas et. al. (2016). The number of requests for a new sample were used later, when estimating costs.

Table 1. Summary of conditional probabilities used in the model

Input	Value	Source
Percentage of already immunized women (before or during week 12)	0.04%	Sanquin databases
Percentage of women with RhD negative status	14.5%	van der Ploeg et.al., 2022

Fetal antibody determination- true positive results	61.62%	Haas et. al. (2016); Sanquin data
Fetal antibody determination- false positive results	0.57%	Haas et. al. (2016); Sanquin data
Fetal antibody determination- false negative results	0.03%	Haas et. al. (2016); Sanquin data
Fetal antibody determination- true negative results	37.87%	Haas et. al. (2016); Sanquin data
RhD negative women- chance of RhD antibodies detected in week 27 screen	0.09%	Sanquin databases
Likelihood of having 1 or more sensitizing event during weeks 16-27	2.60%	TNO databases

ii. Costs

Cost estimates were made using methods described in this section. Appendix 7 provides a summary of final inputs for the decision tree.

1. Tests and screens, antibody determination, follow-up

As mentioned in previous sections, all blood tests, antibody investigations and follow-up tests are centralized at Sanquin, and so rates for these services were collected directly from there. These values are summarized in table 2.

Table 2. Tests and screens, antibody determination and follow-up costs

Input	Value (2022 €)	Source
Cost of blood typing- mother	31.61	Collected with Sanquin
Cost of fetal PCR for RhD typing	52.13	Collected with Sanquin
Cost of antibody determination, negative/inconclusive result	56.7	Collected with Sanquin
Cost of antibody determination, positive due to anti-D prophylaxis	213.81	Collected with Sanquin
Cost of antibody determination, 1 antibody present	435.05	Collected with Sanquin
Cost of antibody determination, more than 1 antibody present	623.53	Collected with Sanquin
Cost of ADCC	213.8	Collected with Sanquin
Cost of antibody follow-up	132.82	Collected with Sanquin

Cord blood testing (test + order rate)	17.13	Collected with Sanquin

Costs incurred in case of a positive antibody result depend on the reason for this positive result: it could be due to one antibody being present or more than one, making determination more difficult (and therefore more expensive). Antibody tests may also be positive because it detects anti-D prophylaxis that was administered to the mother previously (i.e. during a past pregnancy). The result of an investigation can also be negative or inconclusive: if it is inconclusive, anti-D is still administered and the test still regarded as positive. To estimate the determination cost of a single pregnancy with a positive antibody result, an average per woman was estimated (total determination costs in a year were divided by the number of D-negative women). This was done using Sanquin databases that recorded the number of determinations resulting in inconclusive results, positive results due to prophylaxis and antibody findings. Women were identified with an ID number, which helped in calculating the number of antibodies found per pregnancy.
Determination costs were split in two categories based on fetal RhD status, which was recorded in the 2020 and 2021 databases. If the fetus is D-positive, the mother will be screened in week 27 regardless of pathway (treatment or comparator): antibody determination costs are identical in both, and so were not included in the model. However, if the fetus is D-negative, the week 27 screen only occurs in pathway 1. Determination costs for D-negative mothers with D-negative fetuses are therefore included in the model (for pathway 1).

ADCC and antibody follow-up costs depend on the antigen that was found, and when in pregnancy it is detected. For RhD antibodies, an average of 5 follow-up tests per woman was taken. In available databases (2020/21), only one D-negative woman with a D-negative fetus had a clinically relevant antibody needing follow-up, other than RhD. Because of the low prevalence, this cost was not included.

Another cost incurred to determine the RhD status of a fetus is for cord serology (CS). As mentioned in section 3, CS is only used in the case of an inconclusive PCR result, to determine the newborn's Rh status. However, both pathways use CS in the same circumstances. The chance of inconclusive results will not change if the PCR test is conducted in week 11 according to experts, therefore the same costs will be incurred in both pathways, thus canceling each other out and not affecting the ICER. They are thus not included in the model.

2. Prenatal treatment costs

Anti-D prophylaxis is purchased centrally by the RIVM-DVP. According to Draaiboek PSIE (RIVM, 2021b), this is either under the brand RheDQuin or Rhophylac. RheDQuin was discontinued as of 2021 (RIVM, 2021a), therefore the price of Rhophylac was used (Zorginstituut Nederland, n.d.). This costed €70.09, for a pre-filled syringe containing 1000 IU anti-D. This dosage is used both at week 30 and after birth (if the fetus tests D-positive). Sometimes a higher dose is required at birth, if the mother has a higher volume of hemorrhage (Slootweg, 2022): this is only the case in 1.4% of deliveries (Lubusky, 2012). Since this should not change when typing the fetus earlier, one dose at birth was still assumed in the model. For sensitizing events, the dose depends on the amount of blood exchange between mother and fetus. However, the same cost is assumed since the syringe is single-use, and so a smaller dose results in the same costs.
Some women have more than one sensitizing event (up to three), therefore an average number of events per woman (that have at least 1 event) was calculated using the TNO data. This leads to an average of 1.02 events and a cost of €72.62, per woman with at least one event.

Women who become immunized during the pregnancy are monitored in different ways, depending on the ADCC/titer results. For this model, three different care procedures were identified based on risk level (low, moderate and high), and an average was estimated based on likelihood of each of these risk levels.
The low-risk cases are monitored by a gynecologist in a general hospital with an average of 9 consultations and 1 ultrasound. Moderate cases are monitored biweekly in general hospitals, with 1 ultrasound per visit. Severe cases are all referred to the LUMC (academic hospital), where they are monitored weekly with an ultrasound, specialist consult and an MDO (multidisciplinary specialist consult). Since most severe cases start as moderate ones, the cost of 6 general hospital visits (incurred over 12 weeks of monitoring in the moderate-risk category) is added to the severe risk case's estimation. Twelve weeks is an estimate of the time between detection of a moderate-risk pregnancy (that eventually becomes severe), and the moment when it becomes severe. A weighted average of mild, moderate and severe cases was calculated in appendix 6: number of women followed-up at LUMC were provided (2018-2021), and the rest of all immunized women per year was split evenly between mild and moderate. Estimates were provided by Renske van 'T Oever (using data from the LUMC), as well as the number of weeks between referral and birth. Costs for specialist and outpatient visits (both in general and academic hospitals) were taken from the costing manual (Hakkaart-van Roijen, 2015), and the rest was collected at the LUMC.

3. HDFN treatment costs

Treatment of HDFN depends on the severity of the situation, therefore three severity categories were used: mild, moderate and severe. Since data on treatment costs were only available for the LUMC, it is assumed that treatment is sufficiently similar in hospitals nationwide. Depending on whether a pregnancy is the first immunized one or a subsequent pregnancy, the chances for each HDFN severity level varies: therefore, two cost estimates were made (see appendix 7). Severity percentages were taken from a cohort study on RhD negative women (Zwiers, 2019).
Mild HDFN was assumed to be treated neonatally with phototherapy during five days at the hospital, according to LUMC colleagues. For moderate HDFN, the cost for phototherapy, exchange transfusions and top-up transfusions was estimated. For severe HDFN, costs for IUT (intrauterine transfusions) carried out during pregnancy were estimated, as well as neonatal care costs (phototherapy, exchange transfusions and top-up transfusions). Resource use for each severity level depended on the percentage of pregnancies where each treatment was needed, and a measure of average quantity used (i.e. number of top-up transfusions or phototherapy days). These values, as well as unit costs, were estimated with LUMC data and experts and are summarized in table 3. One limitation was that costs of phototherapy could not be found, and so an estimate of 100€ per day of phototherapy was used, on top of the standard cost per day in the NICU (at LUMC). In reality, costs incurred in the NICU vary depending on treatment, and phototherapy costs depend on factors such as the number of lights used on each newborn.

Table 3. Treatment costs for hemolytic disease of the fetus and newborn (HDFN)

Expected costs per woman (2022 €)	Severe HDFN	Moderate HDFN	Mild HDFN
IUT	4 339.35	0	0
Exchange transfusion	159.87	111.71	0

Top-up transfusion	250.88	136.99	0
NICU use	7 098.70	8 873.37	8 873.37
Phototherapy (based on NICU days)	400	500	500
Total	1 2409	9 734	9 373

Treatment costs also include costs incurred later in life because of long-term consequences of HDFN. An average per child was calculated for the "unhealthy" outcomes in the tree.
As per section 4c.iii, three conditions were detected in unhealthy newborns: cerebral palsy, neurodevelopmental problems and bilateral deafness.

To estimate medical costs related to cerebral palsy (CP), two different studies were consulted. The first one is a Dutch study that measures annual costs for children with CP (Hoving et.al., 2008). The second one is a Danish study estimating total lifetime medical costs of individuals with CP (Kruse et.al., 2009). The advantage of using Hoving et.al. 's results is that their study was also set in the Netherlands, and so is more relevant to this study's context. However, it only estimates cost per year for children: it is likely that these will not remain uniform as they move into adulthood. The Danish study is therefore preferred: it accounts for heterogeneous costs over a lifetime. However, the healthcare context is different and costs were discounted with a 5% rate, which is higher than the Dutch rate. Therefore, the Dutch study was used in a sensitivity analysis. Danish costs were translated with the real exchange rate of 2009 (purchasing power parity (OECD, 2022) and indexed to 2022. Medical costs were assumed as equal for both CP and neurodevelopmental delay (ND), as will be explained in section iii.

To estimate costs of bilateral deafness, a general estimate was used: the national expenditure for hearing-related problems was 985 300 000€ in 2019 (RIVM, 2022). This was divided by the number of people with a diagnosis in this disease area (Vanhommerig et.al., 2022) for a yearly cost estimate. This value was multiplied by the Dutch life expectancy (see 4c.iii), indexed to 2022 and discounted.

Table 4. Downstream costs for newborns unhealthy due to hemolytic disease of the fetus and newborn

Input	Value (2022 €)	Source
Annual medical costs- CP*, children (Dutch study)	1 573	Hoving et.al., 2008
Lifetime medical costs CP (Danish study)- average of men/women's estimate	65 706.5	Kruse et.al., 2009
2019 costs related to hearing problems, Netherlands	985 300 000	RIVM, 2022
2019 individuals with hearing problems, Netherlands	806 500 people	Vanhommerig et.al., 2022
Value of 1 informal care hour, Netherlands	15.15	Hakkaart-van Roijen

		et.al., 2015
Average informal care hours needed per week- CP	31.2 hours	Mitchell et.al., 2015

Note: *CP= Cerebral palsy

iii. Health outcomes

Two different health outcomes were measured. The first, immunization, is a binary value taking the value of 1 if the mother is immunized, and 0 otherwise. This is either because she had antibodies at the start of pregnancy, due to a past pregnancy or blood transfusion, or because she develops antibodies as a result of fetal-maternal hemorrhage during the current pregnancy (i.e. the period evaluated in the decision tree). In most cases this is already represented in intermediate branches of the trees. However, if a woman does not present antibodies in week 12 or 27 screens, there is still a chance that she may become immunized after the second screen and until delivery. Estimates were given by Masja de Haas for the chances of immunization in three scenarios, presented in table 5. Finally, an important difference in pathway 2 is that in the false negative branches, women with sensitizing events between weeks 16 and 27 are no longer treated with prophylaxis. Renske van 't Oever and Masja de Haas derived chances of immunization from sensitizing events with and without treatment from Saramago et. al. (2018), by adapting these UK estimates to the Dutch context.

Table 5. Chances of immunization during pregnancy, for a D-negative mother with a D-positive fetus

If the mother is given anti-D prophylaxis prenatally and postnatally	0.3%
If the mother is only given anti-D prophylaxis postnatally	0.6%
If the mother is given no anti-D prophylaxis	12%
If a sensitizing event has occurred with anti-D prophylaxis	0.3%
If a sensitizing event has occurred with no anti-D prophylaxis	0.6%

Literature was consulted to estimate the likelihood of different health outcomes for the newborn. As mentioned in section 4a, the outcomes of healthy, non-healthy and dead were chosen because only a fraction of newborns affected by HDFN will face long-term health consequences that could lead to a lower quality of life. QALYs for all children with HDFN would therefore be extremely variable, depending on the disease's effects into childhood and adulthood. The likelihood of developing HDFN was first evaluated, to then determine the proportion of non-healthy newborns.
According to Zwiers (2019), the likelihood of severe HDFN if a mother presents antibodies during the week 27 screen is of 3% during the first pregnancy, while this increases to 31% if the mother is already immunized from a previous pregnancy. Severe HDFN is defined as a case of HDFN which either results in death or requires an intrauterine transfusion (Koelewijn et.al., 2008a). Less severe cases of HDFN were not considered when measuring QALYs, as they do not have long-term consequences for the newborn.

The chance of having different long-term health consequences in case of severe HDFN were estimated using the LOTUS study, conducted in the Netherlands on children born between

1988 and 2008 and treated with IUT at birth (Lindenburg et.al., 2012). 451 newborns were found, of which 44 died either in utero or neonatally. 291 of these children were followed-up, and it was found that 11 had either cerebral palsy or severe developmental delay, while 3 had bilateral deafness. Therefore, 4.8% of children with severe HDFN are placed in the "unhealthy" category of the model. Using values from Zwiers and the LOTUS study, percentages were calculated for each branch of the tree. The values are summarized in table 6.

Disaggregated results are presented as the chance of immunization during one pregnancy (i.e., a value between 0 and 1). Since a lower percentage is more desirable, the ICER will be calculated as 1 - the chance of immunization, or the chance of no immunization. This will also be used to present results of the sensitivity analysis on a cost-effectiveness plane, for clarity of interpretation of the quadrants.

Table 6. Likelihood of severe HDFN in immunized mothers; chance of long-term health consequences for newborns with severe HDFN

Input	Value	Source
Severe HDFN chance in first immunized pregnancy	3%	Zwiers, 2019
Severe HDFN chance in second immunized pregnancy	31%	Zwiers, 2019
Chance of healthy newborn in case of severe HDFN	85.9%	Lindenburg et.al., 2011
Chance of cerebral palsy/neuro-developmental delay in case of severe HDFN	3.41%	Lindenburg et.al., 2011
Chance of bilateral deafness in case of severe HDFN	0.93%	Lindenburg et.al., 2011
Chance of death in case of severe HDFN	9.76%	Lindenburg et.al., 2011

Finally, QALYs were attributed to each health outcome. For the death outcome, QALYs are 0 by definition. For the other two heath states, non-healthy and healthy , life expectancy and yearly utilities were estimated from the literature.

Healthy newborns were given the population-wide life expectancy in the Netherlands (CBS, 2022) (see table 7). An average was taken between the men's and women's life expectancy. To value the quality of life of an average Dutch individual, values were taken from Janssen et.al. (2019). In this paper, non-institutionalized citizens were asked to fill in the EQ-5D-3L questionnaire. This questionnaire evaluates an individual's health in five categories: mobility, self-care, usual activities, pain/discomfort and anxiety/depression (EuroQol group, 2022). Each category's severity can be ranked on three levels. Questionnaire results were then indexed using two different value sets: both attributed values to the answers of each category, through a regression of population preferences. This results in a single utility value between 0 and 1 for a given health state (defined by answers to the questionnaire).
For the first value set, the European population was asked to rate different health states using a visual analog scale (VAS), ranging from 0 to 10. For the second, the Dutch population was given a time trade-off (TTO): they had to select preferences between a full life in a certain (imperfect) health state defined by the questionnaire, and a life in perfect health shorter by a given number of years. TTO and VAS methods each have their biases (Drummond, 2015),

which often result in different utilities. Indeed, both methods yielded slightly different utilities (0,892 and 0,91), therefore their average was taken as final input.

Unhealthy newborns consist of newborns with CP, ND and deafness. For the utility of living with CP, a study evaluating a lifestyle program for Dutch teenagers with CP was consulted (Slaman et.al., 2015). In this study, utilities were derived from participants' answers to the Short-Form-36 questionnaire, translated into 0-1 values using the University of Sheffield algorithm. Before the lifestyle intervention, this utility was estimated at 0.7921. This was assumed as the average utility of individuals with CP over their lifetime. Two estimates for life expectancy were found (Blair et.al., 2019): 33.2 years for those with a disability score higher than 9 and 59.3 for other cases. Disability scores range from 1 to 12, and reflect the number and severity of impairments (motor and/or cognitive) that an individual has. 59.3 was used for a more conservative result: since we expect more mothers to be sensitized in pathway 2, costs were not underestimated. The life expectancy of 33.2 years was used in a sensitivity analysis.

Neurodevelopmental delay is an umbrella term, defined in the LOTUS study as having a certain (low) score on the intelligence scale for children (Lindenburg et.al., 2012). Because of this, no study evaluated utility for this condition in general. Therefore, the same utility and life expectancy as for CP were assumed, since this condition falls within the umbrella of ND.

The utility of bilateral deafness was estimated from a study concerning prelingual deafness in the Netherlands (Klop et.al., 2009), before and after the implementation of Cochlear implants. Since these implants are currently reimbursed by basic Dutch insurance packages (Health Council of the Netherlands, 2001; Zilveren Kruis, 2022), it is assumed that most or all deaf individuals have access to them. Therefore, the utility after implementation was taken: 0.8. A limitation is that it was measured directly by patients with a VAS: direct, unindexed valuation using this tool is not considered accurate, and does not meet ideal standards defined by Dutch guidelines.

Estimates were also made for the chance of death and morbidity caused by other antibodies for newborns of RhD negative mothers. This is important for the comparison, since some will no longer be screened at week 27 in pathway 2. The chance of other, clinically relevant antibodies was estimated using Sanquin records (2018–2021). On average, 0.13% of D-negative screened women present non-RhD, clinically relevant antibodies. In Sanquin's 2021 database, 12 of such cases were from D-negative women with D-positive children, while 3 were from those with D-negative children. These values were of 10 and 6 in 2020, showing a much higher chance of developing other relevant antibodies if the RhD statuses of mother and child are not compatible. In the decision tree, D-negative women with D-positive children who are not sensitized with anti-D still therefore have a chance of giving birth to an unhealthy or dead newborn.

Table 7. Life expectancy and health utilities

Input	Value	Source
Dutch life expectancy, men	79.7 years	CBS, 2022
Dutch life expectancy, women	83.1 years	CBS, 2022
Life expectancy CP*, disability score>=9	33.2 years	Blair et.al., 2019

Life expectancy CP, disability score<9**	59.3 years	Blair et.al., 2019
Average utility of Dutch population, European VAS valuation	0.89	Janssen et.al., 2019
Average utility of Dutch population, Dutch TTO valuation	0.91	Janssen et.al., 2019
Average utility, bilateral deafness	0.8	Klop et.al., 2007
Average utility, CP and severe neurological delay	0.79	Slaman et.al., 2015

Notes: *CP= Cerebral palsy; **disability score range from 1 (low disability) to 12 (high disability) based on the number and severity of impairments

To find lifetime QALYs, life expectancies were multiplied with their respective utility value. They were then discounted yearly (see section iv).

Table 8. Lifetime QALYs per health state

Value	Value
QALYs for healthy newborns	73.34
QALYs for unhealthy newborns- CP*/neurodevelopmental delay	46.97
QALYs for unhealthy newborns- bilateral deafness	65.12
Weighted average- QALYs for unhealthy newborns	50.86
QALYs for death state	0

**Cerebral palsy*

iv. Price indices and discount factors

Discount factors used were 4% for costs and 1.5% for outcomes, as according to the Dutch guidelines for economic evaluations (Zorginstituut Nederland, 2016). These were mainly used to discount QALYs, downstream healthcare costs and informal care costs for healthy and unhealthy newborns.

Price indices were used to find the present value of costs retrieved from past years. StatLine CBS data is recommended by Dutch guidelines. From 2015 to 2022, consumer price indices (CPIs) were broken down per spending category (14 in total): values for the health category were taken (CBS StatLine, 2023a). These were in terms of percentage change in CPI, compared to the previous year. For years before 2015, the CPI was not broken down per category: the country-wide values were taken instead (CBS StatLine, 2023b), and were varied in the probabilistic sensitivity analysis due to their lower accuracy. To index a value, it was multiplied by (1 + CPI percentage change) for each year until 2022. All CPI values used are reported in Appendix 4.

d. Probabilistic sensitivity analysis

After estimating results with a deterministic analysis (i.e., by taking all parameters at face value), a PSA was conducted using 1000 simulations, as per section 3c. To conduct this, input distributions were first formulated. The following distributions were used:

1. Beta distributions, in the case of probability inputs. This limits the distribution to values between 0 and 1.
2. Gamma distributions, in the case of cost inputs. This limits the distribution to positive values only.
3. Dirichlet distributions, for probability inputs with three or more chance outcomes: this considers the fact that all probabilities should add up to 1.

A uniform distribution was also estimated in the case of annual cerebral palsy medical costs taken from Hoving et.al (2008), as the paper states a range of uncertainty for their output, and the reported value is equal to the higher bound of the range. Normal distributions were taken for annual CPI changes between years 2010 and 2015: for these years, sector-specific CPI changes were not available, and so values for the healthcare sector are unknown. Changes in CPI can be positive or negative, which a normal distribution allows.
When probabilities were calculated using population numbers, i.e. for proportions of women with positive antibody tests, distribution parameters alpha and beta were calculated using these populations.

If values were taken from Sanquin or literature, i.e. for all cost inputs, alpha and beta were estimated with standard formulas according to their distribution (beta or gamma). Standard errors were estimated as a percentage, ranging from 1% to 50% of the input value, depending on its complexity. For example, the cost of prophylaxis was taken from a fee list and is applied country-wide. This is not expected to vary, so 1% of the value was taken as the standard deviation. Meanwhile, lifetime medical costs of cerebral palsy and bilateral deafness depend on many sub-factors (i.e. severity of disease, individual needs and cost of resources), therefore the standard error was taken as 50% of the estimate. Other percentages used were 5% for most percentages and costs, and 20% for annual CPI changes based on all sectors.
Some inputs were not varied during the PSA, such as the discount rates used, number of women screened per year (an average is already taken between years 2018-2021) and prevalence of RhD negative status in the population (which is stable according to the PSIE monitor).

Once distributions were drawn for all relevant values, a macro was formulated on Excel to conduct all 1000 simulations. Each simulation draws a random set of values within the distributions and reports the expected costs and outcomes for both treatment and comparator. Results are presented on a cost-effectiveness plane, and likelihood of cost-effectiveness is represented on a cost-effectiveness acceptability curve. The average ICER was also calculated and used for conclusions.

e. One-way sensitivity analysis

A one-way sensitivity analysis was conducted to identify the parameters that affect the ICER the most. The same distributions as the PSA were used, however another macro was constructed to vary the parameters one by one instead of all at once. For each parameter, two outputs were drawn: one with the lower bound of the value distribution, and one with its upper bound. These bounds were determined as the 2.5th and 97.5th percentiles of the attributed distribution. The range of ICER was then calculated as the difference between both outputs.

To represent these results, inputs were sorted based on how much they can vary the ICER. The 15 parameters that vary the ICER the most were then displayed on a tornado diagram, showing the minimum and maximum ICERs found.

f. Other sensitivity analyses

Three other sensitivity analyses were conducted, where assumptions about value inputs were changed. For each of these sensitivity analyses, a macro was constructed where this assumption was changed, and both deterministic and probabilistic outputs were drawn.

i. Societal perspective

In this analysis, non-medical costs of HDFN were also included in calculations. According to Drummond (2015), non-medical costs can include:

1) Productivity losses, if the individual misses work for a significant amount of time or if their productivity is limited due to a disease.
2) Jurisdiction costs if the disease is associated with an increased chance of criminal activity.
3) Costs of informal care, if the individual's close ones need to care for them (affecting their own productivity and well-being).

According to Dutch guidelines, productivity losses should be estimated using the friction cost method (FCM): this values each hour of work lost to the disease with the average hourly earnings of an individual during a friction period of 12 weeks. Since this study evaluates a disease that starts at birth, the FCM will not identify any productivity losses: salary before the disease is non-existent. HDFN-related morbidities are also not associated with increased criminal behavior.

Societal costs are therefore assumed to include only informal care costs. For newborns with cerebral palsy and other severe neurodevelopmental issues, informal care hours were estimated using Mitchell et. al. (2015), a study conducted on informal caregivers of individuals with different neurological conditions (with a mean age of 43) in Canada, between 2003 and 2010. For cerebral palsy, an average of 31.2 hours of informal care per week was found. This was adjusted to the life expectancy of individuals with cerebral palsy to find informal care hours in a lifetime, then multiplied with the value of an hour of informal care, according to the Dutch costing manual (Hakkaart-van Roijen, 2015). This estimate was also taken for individuals with severe developmental delay, since, as explained in section 4c.ii, this is an umbrella term that includes cerebral palsy.
For bilateral deafness, no informal care costs were assumed: since informal care is most likely concentrated in childhood (i.e., parents learning sign language and adapting to the child's disability), valuing these care hours is difficult, and it is hard to differentiate care related to deafness from regular parent care. Values were also not found in literature.

ii. Using a different LE estimate- cerebral palsy

As per section 4c.iii, two different estimates were available for life expectancy with CP. In this analysis, the lower life expectancy (i.e. for more severe cases with a disability score of 9 or more) was used.

iii. Using different estimates for cerebral palsy medical costs

In the main analysis, lifetime medical costs of cerebral palsy were estimated using a Danish study (Kruse et.al., 2009). This was preferred to Hoving et.al. (2008)'s numbers, since it follows costs over a lifetime instead of only in children; and costs are expected to differ

between adults and children with this disability. However, the study of Hoving et. al. study was conducted in the Netherlands, and so costs are more country-specific. Dutch discount rates can also be applied, since the estimate is yearly instead of aggregated for a lifetime. An estimate of lifetime costs was made using this alternative source and included instead of the estimates of Kruse et.al.

g. Tech-Ver model verification

After completion, the model was verified using the Tech-Ver checklist (Büyükkaramikli et.al., 2019). This checklist consists of systematic steps to take on a health economic model to verify that it is implemented correctly. Steps involve checking model inputs, intermediate and final calculations as well as uncertainty analyses. Black box tests were conducted in the model, which consists of changing parameters and making sure that the outputs react in an expected manner. When an error was identified, white-box tests were conducted to locate the root cause of the error. Examples of when such tests detected an error are detailed in appendix 5. Following such a checklist ensures that the model functions correctly and does not contain any unintended mistakes.

5. Results

Results of the deterministic analysis are presented in tables 9 and 10. Pathway 2 leads to 2,3€ less spent per pregnancy. The chance of immunization increases by 3.4×10^{-9} percent, and the expected QALYs of the newborn decreases by 4.9×10^{-10}. Assuming 170 000 pregnancies per year in the Netherlands, almost 390 000€ will be saved yearly with less than 1 QALY lost and less than 1 additional immunization.

a. Deterministic results

Table 9. Results of deterministic analysis

	Pathway 1 (comparator): Fetal RhD typing at week 27 of pregnancy	Pathway 2 (treatment): Fetal RhD typing at week 11 of pregnancy	Increment
Expected cost per pregnancy (2022 €)	72.63	70.34	-2.29
Expected lifetime QALYs of fetus per pregnancy (discounted)	42.98	42.98	-4.9×10^{-10}
Chance of immunization (%)	7.9×10^{-4}	7.9×10^{-4}	3.4×10^{-9}
ICER-QALYs*			**4 604 367 453**
ICER- Immunization**			**673 486 374**

*Savings per QALY lost (€); **Savings per additional immunization (€)

Table 10. Results of deterministic analysis, yearly estimates (170 000 pregnancies)

	Pathway 1 (comparator): Fetal RhD typing at week 27 of pregnancy	Pathway 2 (treatment): Fetal RhD typing at week 11 of pregnancy	Increment
Expected cost per year (2022 €)	12 346 690	11 958 188	-388 503
Expected lifetime QALYs of fetuses per year (discounted)	7 307 129	7 307 129	-8.4×10^{-5}
Immunizations per year (%)	134.68	134.68	5.8×10^{-4}

b. PSA results

Results of the probabilistic sensitivity analysis are presented in two cost-effectiveness planes, one for the QALY outcome and one for the chance of immunization (figures 6/7). The X-axis

in figure 7 shows the chance of not being immunized during a pregnancy. Averages for all simulations are presented in table 11. Finally, the chance of pathway 2 being cost-effective for different ICER thresholds is presented on a cost-effectiveness acceptability curve (figure 8).

Table 11. PSA results, average of 1000 simulations

	Pathway 1 (comparator): Fetal RhD typing at week 27 of pregnancy	Pathway 2 (treatment): Fetal RhD typing at week 11 of pregnancy	Increment
Expected cost per pregnancy (2022 €)	75.67	73.39	-2.29
Expected lifetime QALYs of fetus per pregnancy (discounted)	43.06	4.06	-4.8×10^{-10}
Chance of immunization (%)	7.9×10^{-4}	7.9×10^{-4}	3.4×10^{-9}
ICER-QALYs* (95% CI)			**4 736 259 919 (930M - 164 607M)**
ICER- Immunization** (95% CI)			**669 393 742 (154M - 12 289M)**
Yearly cost savings (2022 €)			**388 458**

*Savings per QALY lost (€); **Savings per additional immunization (€)

Figure 6. Cost-effectiveness plane, QALYs

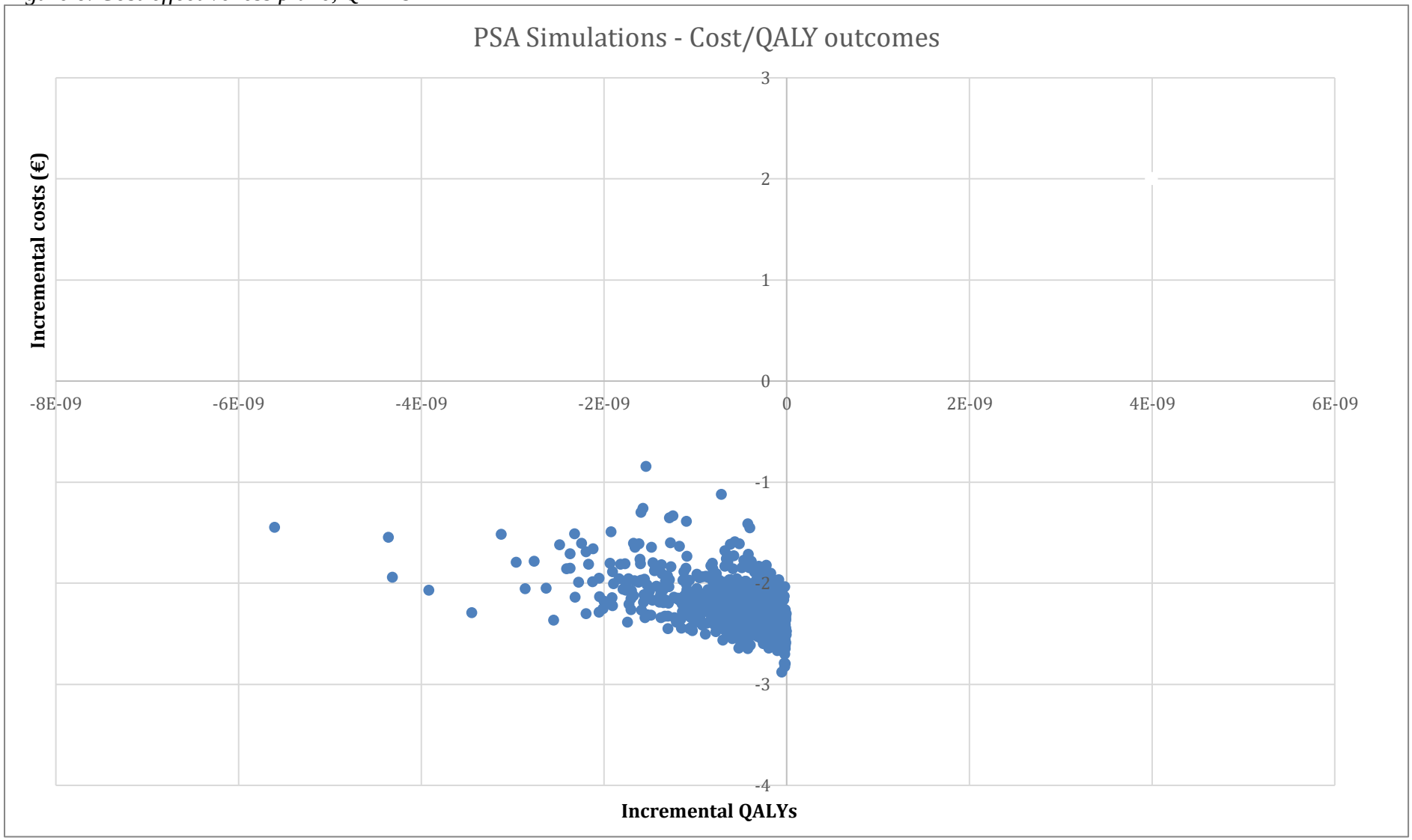


Figure 7. Cost-effectiveness plane, number of immunizations avoided

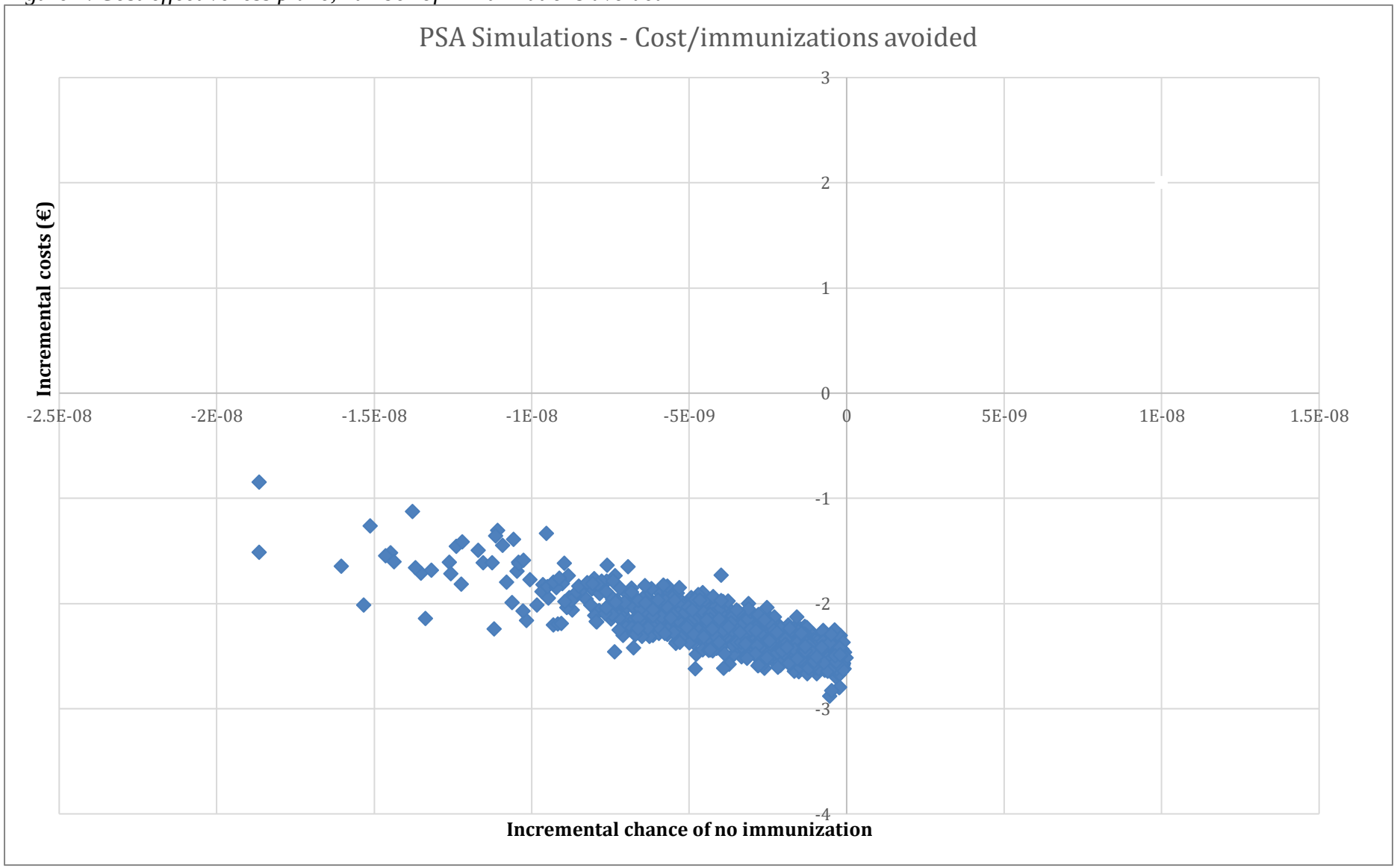
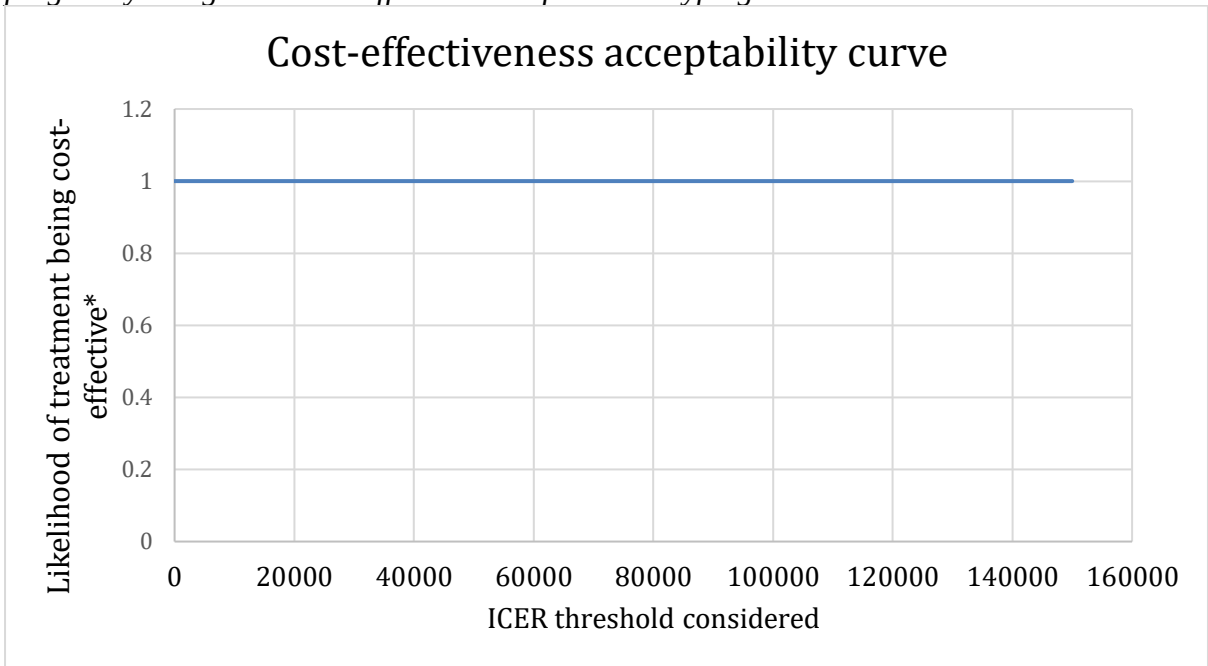


Figure 8. Cost-effectiveness acceptability curve: likelihood of fetal RhD typing in week 11 of pregnancy being more cost-effective than fetal RhD typing in week 27



*Treatment: Fetal RhD typing in week 11 of pregnancy, compared to fetal RhD typing in week 27 of pregnancy.

c. Sensitivity analyses

Results of the one-way sensitivity analysis are presented in two tornado diagrams, one for each health outcome (figure 9/10). The other three sensitivity analyses are summarized in table 12. The ICERs presented refer to their respective PSAs.

Table 12. Other sensitivity analyses- results (from PSAs)

	ICER-QALYs*	ICER-Imm.**
Societal perspective- adding informal care costs	4 756 582 009	666 283 410
CP life expectancy- using a lower estimate	4 159 889 813	667 510 451
CP medical costs- using Hoving et.al. (2008)	4 453 375 071	665 899 430
Main PSA results- comparison	**4 736 259 919**	**669 393 742**

*Savings per QALY lost (€); **Savings per additional immunization (€)

Figure 9. Tornado diagram, 15 most sensitive parameters (QALY ICER)

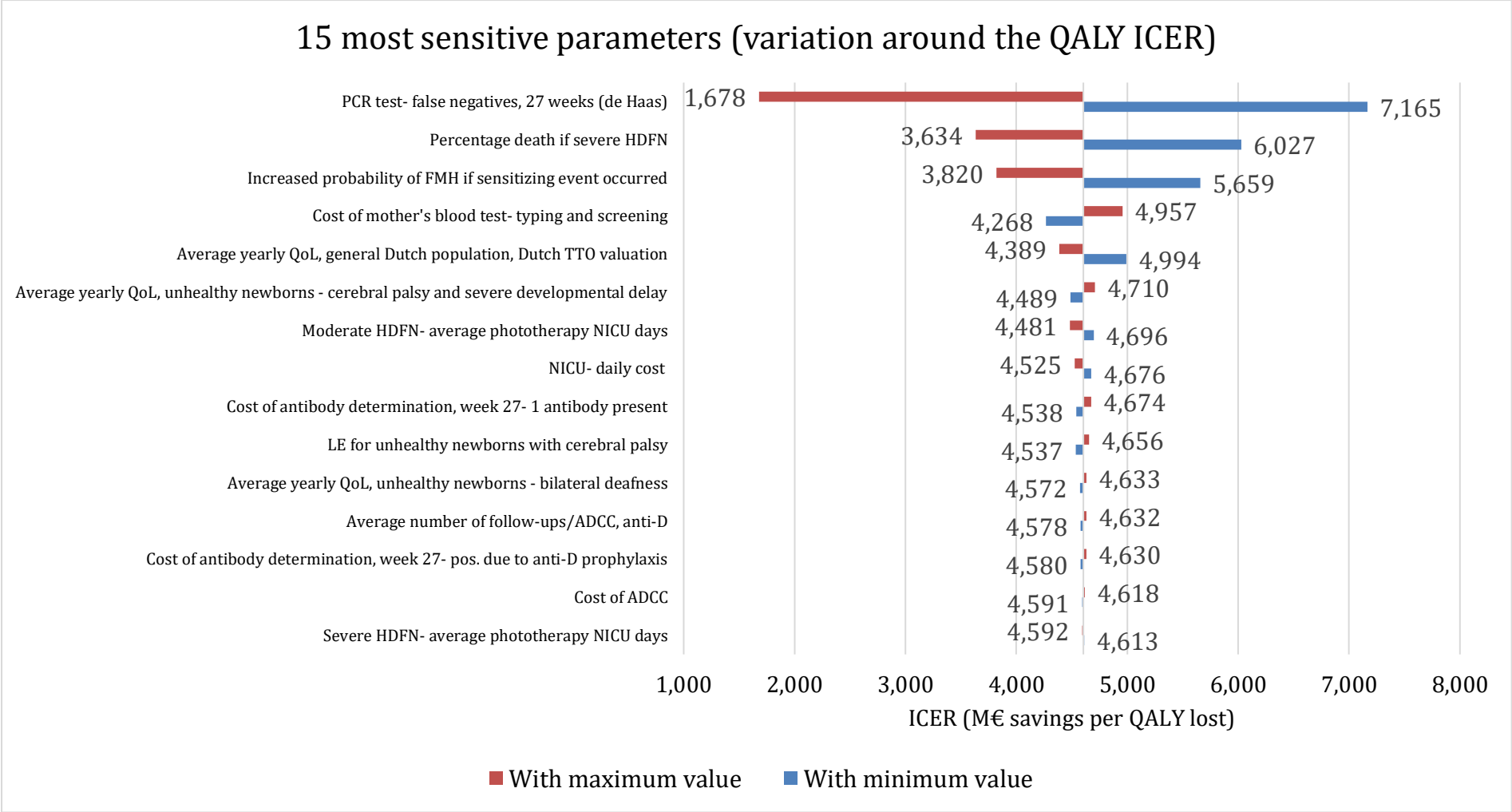
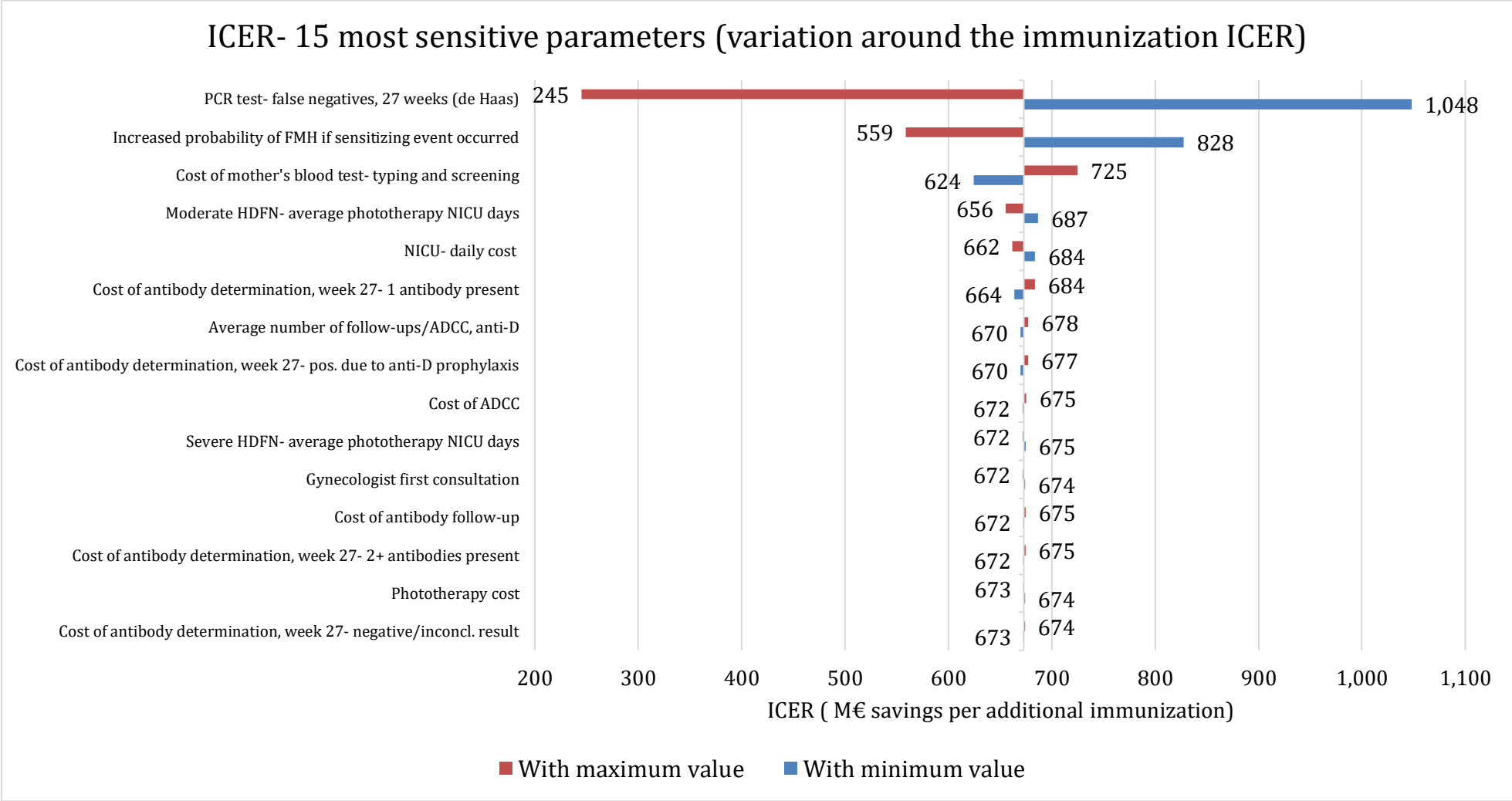


Figure 10. Tornado diagram, 15 most sensitive parameters (immunization ICER)



6. Discussion

a. Results

According to the model, typing the RhD status of a fetus in week 11 is cost-effective compared to typing in week 27, at all ICER thresholds in the Netherlands (€20 000 to €80 000 per QALY gained). Since the treatment (pathway 2) is cheaper than the comparator (pathway 1), the ICER threshold represents how much needs to be saved to give up one QALY (i.e. the WTA), and so the ICER should be higher than the threshold to be treated as cost-effective. This would indicate that cost savings are high enough to warrant the loss in QALYs.
Since QALYs remain almost the same between treatments, the savings per QALY lost are very high and all thresholds deem pathway 2 more cost-effective.

It is important to note that there is debate on the interpretation of the ICER threshold for treatments that fall in the South-West quadrant of the cost-effectiveness plane (figure 1). This national threshold was constructed with the North-East quadrant in mind, as most new interventions considered in economic evaluations are more costly and improve health: it therefore represents the WTP more than the WTA. However, there is a disparity between how much someone is willing to pay for a health gain, and how much they are willing to accept for a health loss (Grutters et.al., 2008): this is due to loss aversion and the endowment effect. These are both biases that make individuals value the decrease in utility from losing a certain amount (of health) as greater than the increase in utility from gaining that same amount. Due to this, one's WTA for a loss is often higher than their WTP for a gain. Therefore, some economic evaluations adapted the ICER threshold by adding a kink in the cost-effectiveness threshold at the origin, doubling the threshold value in the South-West quadrant (Klok & Postma, 2014). According to this principle, this would mean willingness to accept a loss of one QALY would be between €40 000 and €160 000, since the Dutch threshold for WTP for a QALY is between €20 000 and €80 000. On the other side of the debate on WTA thresholds, researchers argue that using different thresholds for WTP and WTA would lead to inefficient allocation of resources: this bias for the status quo can mean that an inefficient treatment is kept at the expense of another, more efficient one, just because removing the inefficient treatment would lead to a loss in current endowment. This study presents all thresholds regardless of WTA interpretation, and according to deterministic results, the treatment is cost-effective at the highest threshold of €160 000.

The PSA reveals that cost savings are slightly smaller when taking uncertainty into consideration (€388 458 per year instead of €388 503). The deterministic ICER is still within the PSA's 95% confidence interval as shown in table 9, so the difference is not significant. QALY losses and additional immunizations remain small and do not decrease the ICER enough to deem it cost-ineffective. For all simulations, the ICER falls in the South-West quadrant, below the threshold (see figures 1, 6 and 7). All simulations are still under the threshold line if it is increased up to 160 000. This makes the treatment cost-effective in 100% of cases, regardless of threshold and considerations for loss aversion, which is represented in figure 8.

When using the societal perspective, i.e. adding costs of informal care, health outcomes remain the same. Costs increase relatively equally in both the treatment and comparator, so cost savings per pregnancy remain identical. Using the shorter life expectancy estimate for CP leads to 1 cent less saved per pregnancy, while health outcomes only slightly decrease (yearly, a decrease of 9.0×10^{-5} QALYs instead of 8.4×10^{-5}). Using Hoving et.al. 's estimates to calculate lifetime medical costs of CP (instead of Kruse et.al. 's numbers) has the opposite effect of

adding informal care costs, since the estimate is lower (despite using the Dutch discount rate, which is 1% lower). This does not affect cost savings. Results of all three sensitivity analyses show that using estimates for lifetime costs (medical and non-medical) of different literature findings does not affect the ICER by a lot. This is likely due to the low percentage of children that develop neurodevelopmental delay from HDFN, and the low number of additional immunizations in pathway 2.

The univariate sensitivity analysis shows that cost-effectiveness results are the most sensitive to the rate of false negative PCR results, with a minimum and maximum of respectively 0.02% and 0.07% as stated in literature (de Haas, 2016). This places the QALY ICER between 7165M€ per QALY gained with the highest rate, and 1678M€ per QALY gained with the lowest, while the immunization rate ICER ranges between 245M and 1048M euros saved per additional immunization. In all cases, cost-effectiveness is still achieved. The reason for this high sensitivity of the rate of false negative PCR results is that if there are more false negative results, more mothers who need anti-D prophylaxis will no longer receive it during sensitizing events (between weeks 16 and 27). This could lead to more immunizations and subsequently more unhealthy newborns, increasing the QALY loss as well. The opposite holds if there are less false negative results. Overall, this highlights the importance of an accurate PCR algorithm to avoid health losses from a more targeted anti-D prophylaxis policy.

Other sensitive parameters include the likelihood of neonatal death (in case of severe HDFN) which would affect the QALY loss, chance of having a sensitizing event and cost of an antibody test. Although the cost of an antibody test was only varied with a 5% standard deviation (this price is centralized in all of the Netherlands), it is still largely sensitive because of the large decrease in tests needed in pathway 2 (compared to pathway 1).
With all parameter variations, the ICER remains above the 80 000€ saved per QALY lost (and thus 20 000€ saved per QALY lost) threshold.

b. Comparison to previous studies

Results of this study are in line with previous investigations into screening procedures and administration of anti-D: an increased targeting of screening and treatment procedures leads to a small decrease in QALYs and increase in immunizations, which are outweighed by high cost savings (due to a smaller number of antibody screens conducted at week 27). The French and Australian studies (Darlington et.al., 2018; Gordon et.al., 2017) do not contradict these results, since in their case increased costs were due to implementation of additional testing (which is not the case here; less testing is conducted). When compared to van der Schoot et.al. (2017), it is logical that the increase in immunization rate is not as high: this study's comparator already targets routine prophylaxis (administered in week 30 and after birth), so the difference is only due to sensitizing events no longer being treated in false negative outcomes, and less antibody tests being conducted (which may miss clinically relevant, non-RhD antibodies) Previously, targeted RAADP was compared to non-targeted RAADP, for all D-negative women.

c. Limitations and their consequences on the ICER

Four main limitations were identified in the methodology, and are discussed in this section.

1- Decision analytic modeling

Modeling in economic evaluations is a useful solution to evaluating treatments, however it cannot represent reality with certainty. Even if values are taken from real observations, the Dutch population has never been exposed to this new method of screening for fetal rhesus status and mother antibodies. Therefore, applying this new way of screening in the care system can always bring about unexpected consequences that cannot be foreseen by any model. This particular decision tree has other limitations: it only observes one pregnancy at a time, and some inputs are determined by the outputs, especially the chance of immunization before week 12. This chance of being immunized from a previous pregnancy is based on historical data and may change over time: when a change made to the PSIE program affects the chance of immunization, effects may not be seen in the short term. However, once women reach their second or third pregnancy, the chance of HDFN may increase, until reaching a new equilibrium. Although according to this model the chance of immunization does not change much from one pathway to another, effects on costs (i.e. needing to monitor more pregnancies, treat more HDFN cases and informal care) may be observed.

2- Costs for treatment of HDFN, monitoring of immunized mothers

Inputs such as the average days of phototherapy needed, costs of a day in the NICU and average number of IUTs per woman are towards the top of the list of most sensitive parameters, according to the OWSA. Costs of treating HDFN neonatally are also some of the most uncertain, as mentioned in the methodology section. This is due to lack of observational data from the LUMC: resource use was estimated instead of monitored in the hospital, due to the scope of this thesis. Additionally, costs such as that of one NICU day are fixed despite the fact that phototherapy is one treatment among many others possible in the NICU.

If costs of treating HDFN are higher than expected, this may lower cost savings, resulting in a lower ICER. The OWSA does not point to any cost-ineffective outcomes when varying these parameters one by one, however it is uncertain whether the treatment would remain cost-effective if all the parameters are set to their maximum. Even with a favorable PSA, costs could still be much higher than expected by uncertainty ranges and result in a cost-ineffective conclusion.

Costs for monitoring D-immunized mothers were also difficult to collect, and mostly based on estimates. Some women are treated outside of the LUMC (in other hospitals and by midwives), and the exact protocol followed may differ in each establishment (for example, the number of follow-ups through the pregnancy). This could also decrease the ICER and expected cost savings.

3- Sensitivity of PCR test

The most sensitive parameter is the rate of false negatives. This percentage is based on the current algorithm used in PCR testing, which is now conducted during week 27. Although experts do not expect this to change if the test were done in the first trimester rather than the second, it may still be subject to a slight change, which could have an impact on the ICER. According to the OWSA and PSA, all values within the 95% confidence interval of false

negatives remain cost-effective, however the exact number of additional immunizations and QALYs lost could be better estimated if the false negative rate were measured at 11 weeks.

4- Population stratification

The population was defined as all pregnant women in the Netherlands, since they are all screened as part of the PSIE program. However, only HDFN caused by anti-D antibodies was investigated: this only potentially affects 14.5% of the population. Therefore, any changes in QALYs of newborns and additional immunizations are concentrated in this 14.5%, making the expected QALY/immunization rate changes very small in reported results. Cost changes in D-negative pregnancies are also diluted.

Additional to these main limitations, the opportunity cost of anti-D prophylaxis was not considered: producing it uses up donated blood, which is a scarce resource that is often needed in healthcare to save lives. This added value may not be reflected in the price of prophylaxis. However, a higher value would only lead to more savings in pathway 2, and an even higher ICER. Uncertainty around the QALY estimates is also large, however results are not sensitive to changes in these values, as seen in the sensitivity analyses.

d. Policy implications

Sanquin is investigating the possibility of changing the PSIE program, to type RhD status of fetuses earlier in the first trimester instead of the second. This would save costs of antibody typing where it is unnecessary and reduce waste of blood product, by further targeting administration of prophylaxis. This research can be used as a preliminary study to determine cost-effectiveness of the desired change, and a basis for further investigation. Due to the limitations of this research and time constraints of the Master thesis, more research is recommended before making any changes to the PSIE program. However, this study indicates a high chance of cost-effectiveness, giving a green light for the usefulness of further investigation.

e. Research recommendations

The recommendations outlined below aim to address limitations discussed in section 6c.

1- Decision analytic modeling

Uncertainty regarding modeling cannot be entirely eliminated, however it can be reduced through certain steps. First, the decision tree could be extended to include two pregnancies from the same woman instead of a single pregnancy, as the fertility rate is currently at 1,6 children per woman (CBS StatLine, 2022). In this way, if more immunizations occur in pathway 2, this will be reflected in the number of second pregnancies that need to be monitored and costs of treating HDFN. Second, parameters that were found as most sensitive (for the ICER) from the OWSA could be observed on the population through a cohort study, to increase precision in the estimates.

2- Costs for treatment of HDFN, monitoring of immunized mothers

More precise measures of these costs are needed to ensure that pathway 2 is indeed cheaper than pathway 1. Exact resource use, especially those occurring in the NICU, could be monitored at the LUMC through direct observation. This can include machinery use and number of lamps during phototherapy. Costs can also be estimated more precisely in this way,

using a bottom-up approach (i.e. estimating each component's use and price before aggregating them).
To estimate resource use when monitoring immunized mothers, other hospitals could be consulted on how often they monitor these women, as well as how many ultrasounds are conducted on average.

3- Sensitivity of PCR test

Even if sensitivity and specificity of the PCR test are not expected to change if it is conducted in the first trimester, these could be estimated once again in the context of a cohort study, for example. Monitoring the test accuracy would err on the side of caution and ensure that more QALYs are not lost/ more immunizations do not occur.

4- Population stratification

Future studies could focus only on D-negative mothers, so that the results focus on the target population for the change in screening guideline. This sub-population was also considered in most of the previous literature in other countries (Darlington et.al., 2018; Gordon et.al., 2017, etc.). Other studies only looked at effects on non-alloimmunized mothers (Gajic-Veljanoski et.al., 2022; Saramago et.al., 2018), since women already immunized will not be affected by a change in the screening process. Unequal effects on different sub-groups could then be examined.

7. Conclusion

Overall, this study shows that fetal RhD typing using an RQ-PCR test in week 11 of pregnancy, rather than in week 27, reduces expected costs per pregnancy. Due to high accuracy of PCR testing, earlier typing does not lead to significant QALY losses or additional immunizations either (much less than 1 expected QALY lost yearly in the Netherlands).

The only potential health loss occurs if a D-negative woman's fetus is falsely typed as D-negative, and she has a sensitizing event between weeks 16 and 27 during which she becomes immunized. This is very unlikely to happen since the false negative rate, chance of sensitizing events in weeks 16-27 and immunization chance during such events without anti-D treatment, all have low likelihoods.

The decrease in costs is mostly due to less antibody tests being carried out in week 27, now that RhD status of fetuses is already known by week 16 of the pregnancy. Additionally, sensitizing events in the second trimester are only treated with prophylaxis for D-negative mothers with RhD positive fetuses, reducing unnecessary use of blood products. This results in a cost-effective ICER, at all thresholds considered: savings per QALY lost are extremely high.

More research is needed for making a final decision; however, this study can be considered as preliminary research that confirms the high potential for cost-effectiveness.

8. Conflicts of interest

The author does not have any conflicts of interest. Masja de Haas does, as laboratory director of the immunohematology department, and responsible for the national screening program done at Sanquin.

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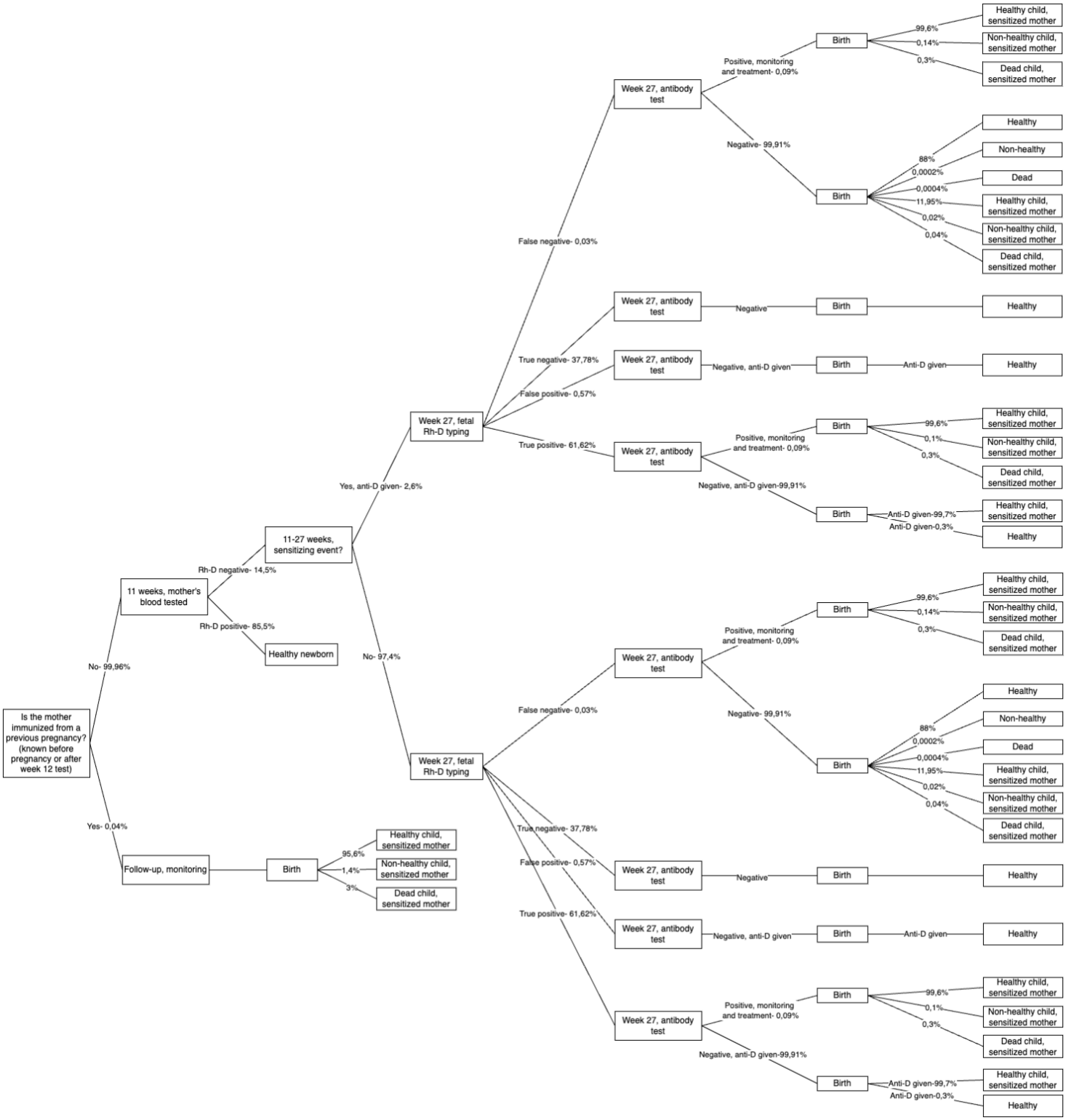
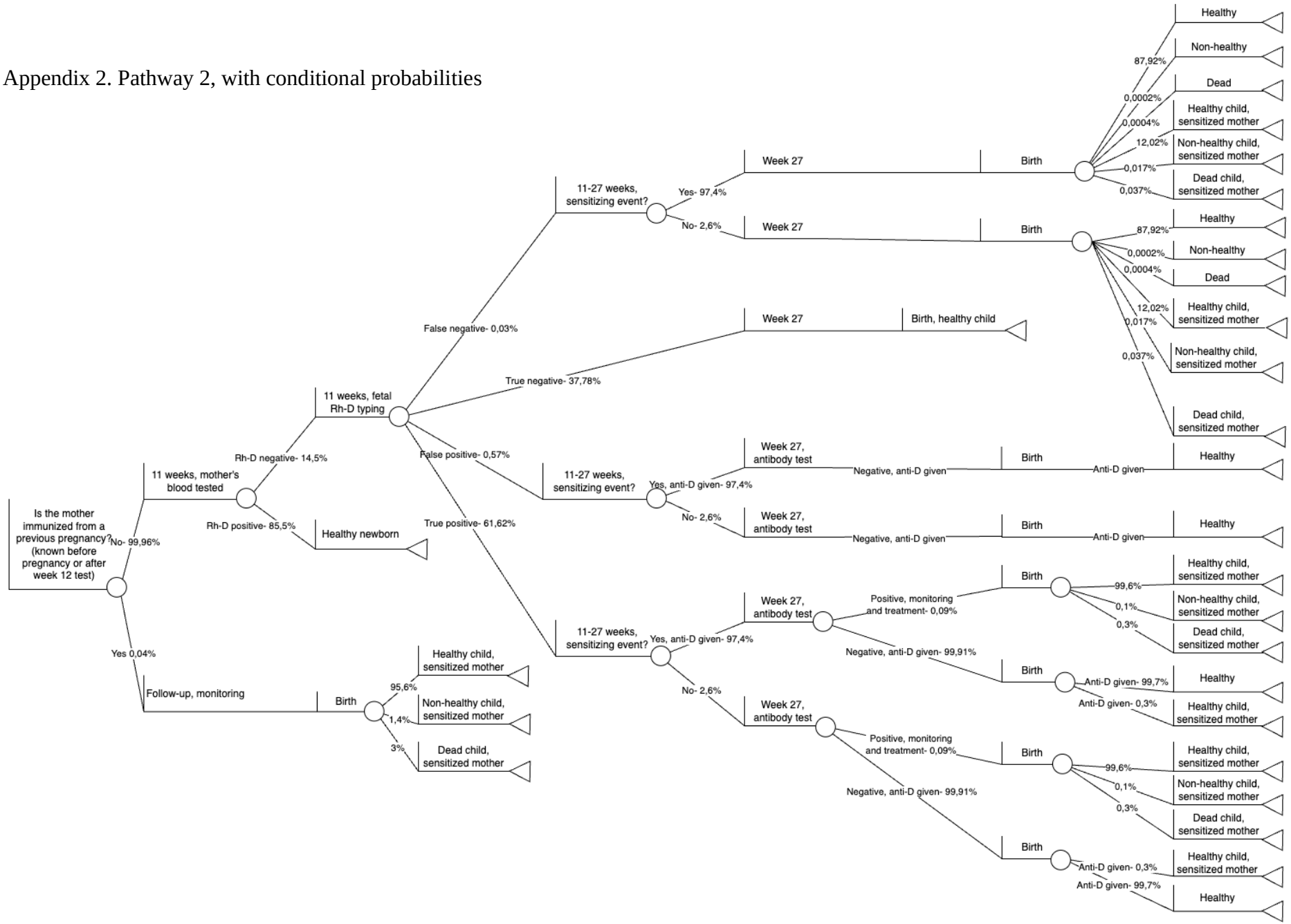
11. Appendices

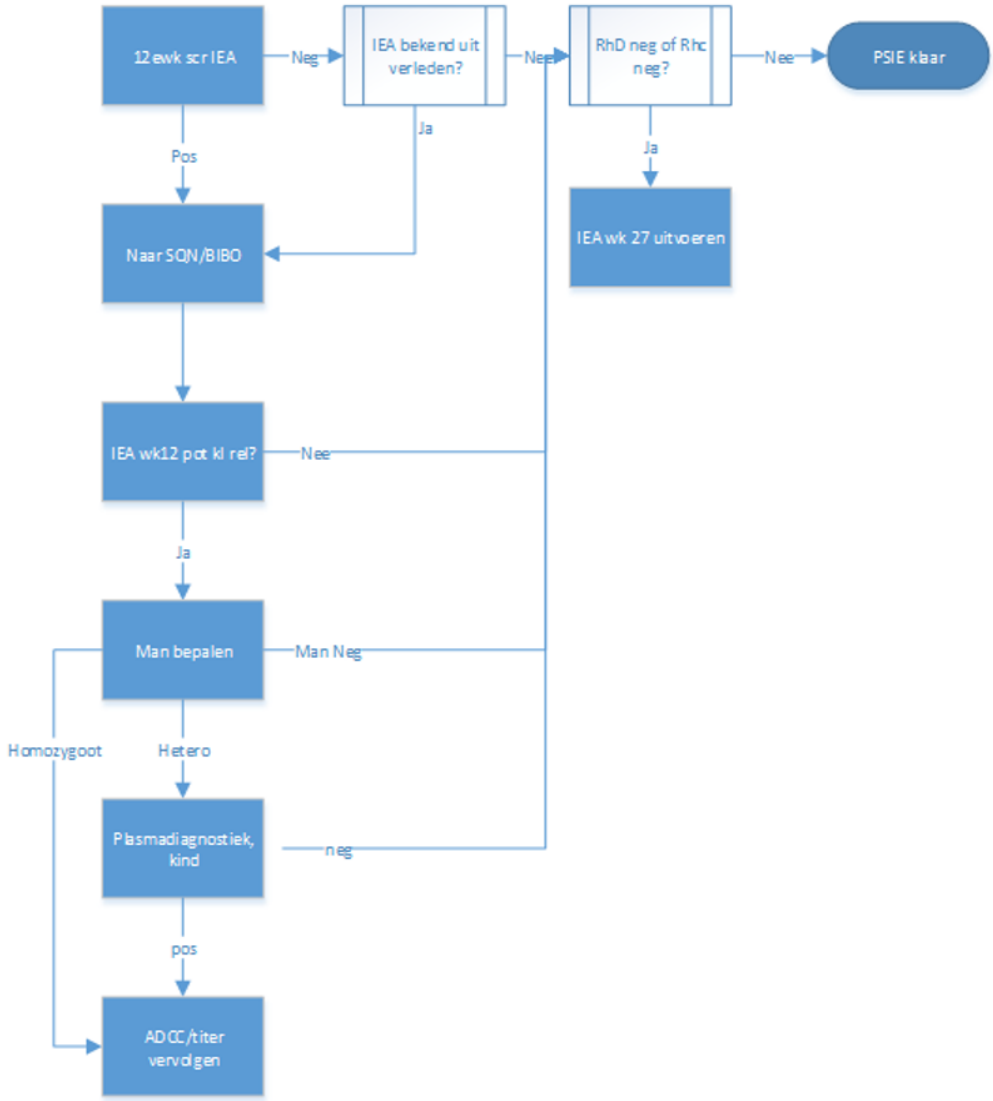
Appendix 1. Pathway 1, with conditional probabilities



Appendix 2. Pathway 2, with conditional probabilities



Appendix 3. Antibody screen protocol in the Netherlands



Source: Sanquin.

Appendix 4. Annual CPI changes used

Year / spending category	Value (% change compared to previous year)
2010, all categories	1.3
2011, all categories	2.3
2012, all categories	2.5
2013, all categories	2.5
2014, all categories	1.0
2015, all categories	0.6
2016, health category	-2.0
2017, health category	0.6
2018, health category	1.4
2019, health category	2.5
2020, health category	1.9
2021, health category	0.9
2022, health category	2.1

Source: CBS StatLine database.

Appendix 5. Model verification Tech-Ver, examples of errors found

Black box test	White box testing	Source found
All path probabilities in a tree should sum up to 1; they summed up to 99.96%	Probabilities were calculated manually, formulas to assign them to each branch were checked	One branch was assigned a 99.7% chance probability when it was the only outcome possible
Decreasing the standard deviation on the most sensitive parameter (according to the OWSA); the ICER variation did not decrease	The macro designed for univariate analysis was revised step-by-step by conducting these steps manually	Instead of varying one by one, parameters were set to a maximum for the rest of the macro's duration; parameters lower on the list were varied at the same time as all the ones above
Life expectancies were set to 0, but QALY outcomes did not become 0	Formulas on the sheet on QALY calculation were revised	Life expectancy parameters were not used for QALY calculation: the number of life years was hardcoded into the table as the number of rows, and was not able to change

Appendix 6: Follow-up of immunized mothers, estimate of severe, moderate and mild cases

Type of immunization	Calculation based on	Result
Severe; treated at the LUMC	Number of followed-up women at the LUMC each year, total number of women immunized by week 12	30%
Moderate; treated in a general hospital	50% of remaining cases	35%
Mild; treated by a midwife	50% of remaining cases	35%

Appendix 7. Summary of final model inputs

Cost inputs	**Value (in 2022 €)**
Typing of the mother's blood, week 12 and 27	31.6
Anti-D prophylaxis in case of sensitizing event (weighted average cost based on number of events between weeks 16 and 27)	72.62
PCR for fetal rhesus typing	52.13
Average cost of antibody determination (week 27), for D-negative women with D-negative fetuses (saved in pathway 2)	0.53
Average ADCC and follow-up costs if positive RhD antibody	1 733
Anti-D prophylaxis (incurred once during routine administration and once after birth, as well as if a sensitizing event happens between weeks 16 and 27)	70.09
Treating severe HDFN neonatally (immunized before pregnancy, average cost)	8 729
Treating severe HDFN neonatally (immunized from current pregnancy, average cost)	6 757
Monitoring of immunized mothers, average per pregnancy	16 254
Downstream medical costs, unhealthy newborns	67 297
Downstream informal care costs, unhealthy newborns	454 379
Decision tree chances	**Value**
Mother is immunized from a previous pregnancy	0.04%
Mother is RhD negative	14.5%
Fetal PCR test- true positive	61.62%
Fetal PCR test- true negative	37.78%

Fetal PCR test- false positive	0.57%
Fetal PCR test- false negative	0.03%
At least 1 sensitizing event between 11 and 27 weeks	2.6%
Week 27, new RhD antibodies detected (D-positive fetus)	0.09%
Extra immunization chance from sensitizing event if no anti-D given	0.3%
Sensitization chance if no anti-D is given	0.12%
Sensitization chance if anti-D is only given postnatally	0.06%
Sensitization chance if anti-D is given at 30 weeks and after birth	0.03%
D-negative women with D-positive children, chance of having non-RhD, clinically relevant antibodies	0.13%
Severe HDFN if the mother developed RhD antibodies	3.2%
Severe HDFN if the mother already had RhD antibodies	31.1%
Chance of long-term health consequences from severe HDFN	4.3%
Chance of death from severe HDFN	9.7%
Decision tree, lifetime utility outcomes (discounted)	**Value (QALYs)**
Healthy newborns	43.0
Unhealthy newborns	33.3
Neonatal death	0

Appendix 8. CHEERS checklist (source : Husureau et. al., 2022)

Section/topic	Item no.	Guidance for reporting	Reported in section
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	_Cover page_
Abstract			
Abstract	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	_1_
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	__2__
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	__4c__

Section/topic	Item no.	Guidance for reporting	Reported in section
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	_4.a.iii__
Setting and location	6	Provide relevant contextual information that may influence findings.	__3.e__
Comparators	7	Describe the interventions or strategies being compared and why chosen.	_4.a.v_
Perspective	8	State the perspective(s) adopted by the study and why chosen.	_4.a.i__
Time horizon	9	State the time horizon for the study and why appropriate.	_4.a.ii_
Discount rate	10	Report the discount rate(s) and reason chosen.	_4.c.iv_
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	_4.a.vi_
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	_4.c.iii_
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	_4.c.iii_
Measurement and valuation of resources and costs	14	Describe how costs were valued.	_4.c.ii_
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	_4.c.iv_
Rationale and description of model	16	If modeling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	_4.b__
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	__4.g__
Characterizing heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	__N/A__
Characterizing distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	__N/A__
Characterizing uncertainty	20	Describe methods to characterize any sources of uncertainty in the analysis.	_4.d/e/f_
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	__4.c__
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	4d/Appendix 7
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarize them in the most appropriate overall measure.	__5.a__

Section/topic	Item no.	Guidance for reporting	Reported in section
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	_5.b/c_
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	__N/A__
Discussion			
Study findings, limitations, generalizability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	__6__
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	___N/A__
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	__8__

Appendix 9: QR code and link to the decision tree Excel model (accessible with an Erasmus University Microsoft account)

RhD alloimmunization model.xlsm