Fetal and neonatal alloimmune thrombocytopenia: the proof of the pudding is in the eating

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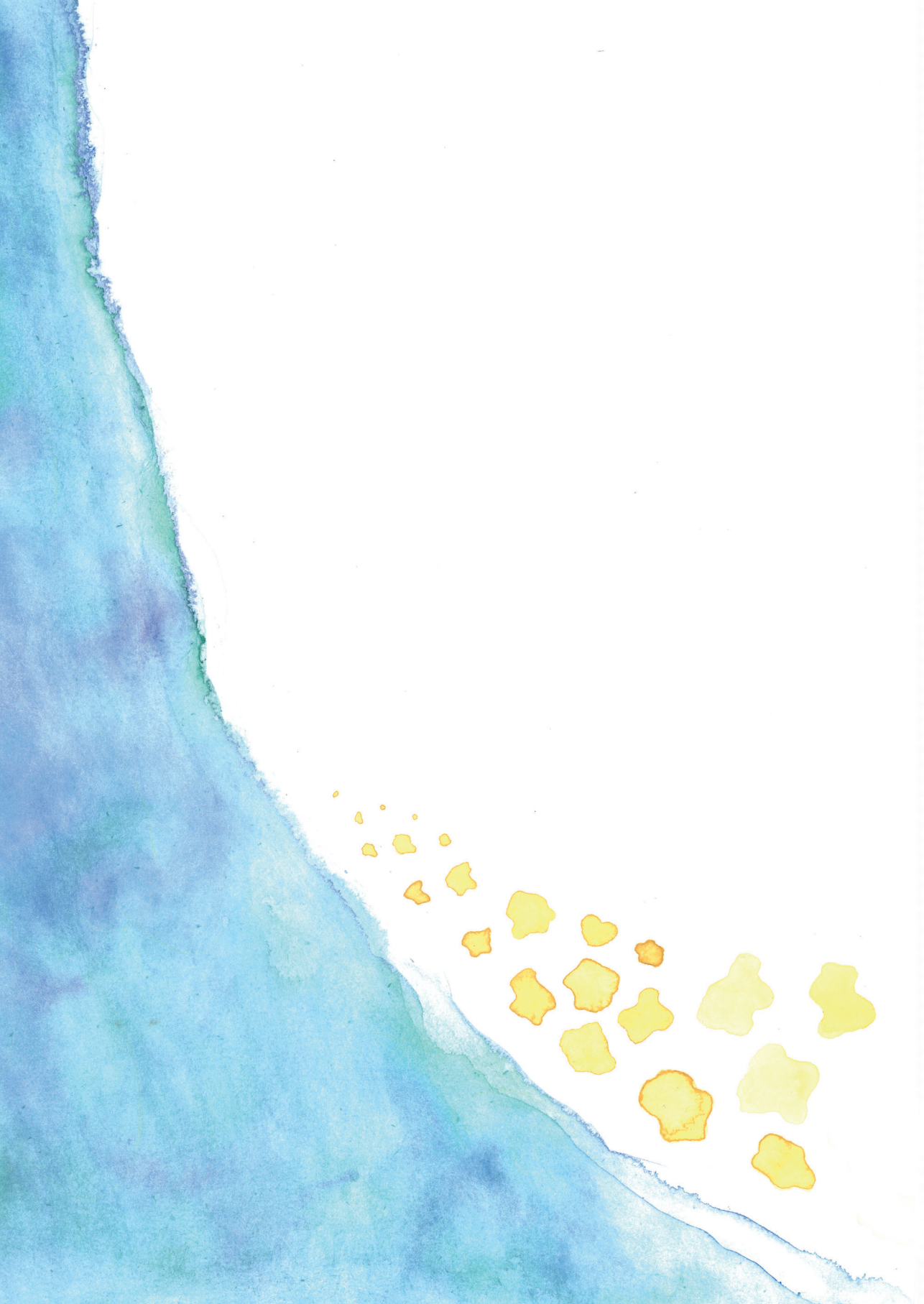
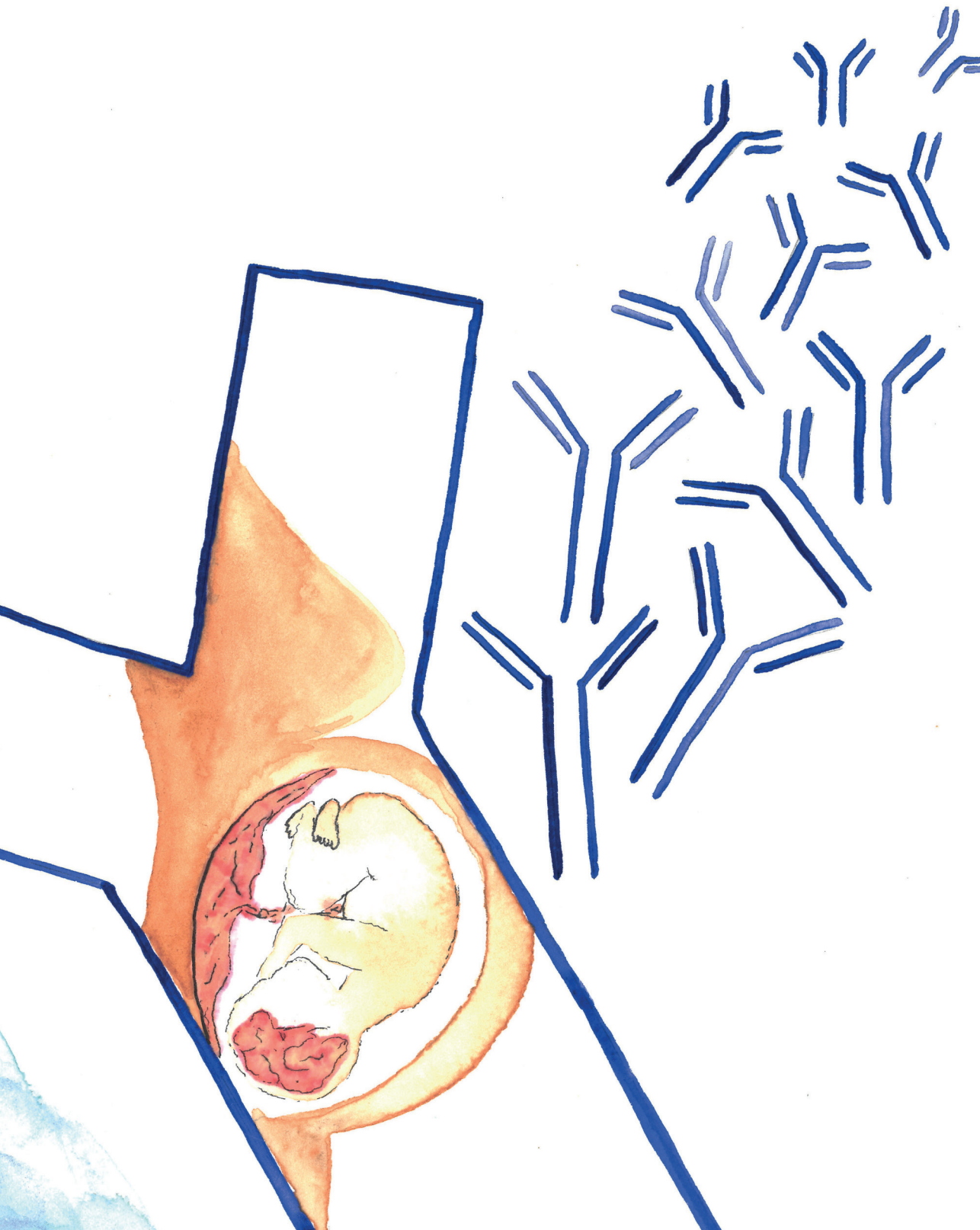


PART SIX

Cost effectiveness



CHAPTER 9

Cost-utility analysis of screening of pregnant women for fetal neonatal alloimmune thrombocytopenia

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Manuscript in preparation

ABSTRACT

BACKGROUND

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) results from maternal platelet-directed antibodies which can cause severe intracranial haemorrhage (ICH) in fetuses and new-borns. Screening for human platelet antigen-1a (HPA-1a) directed antibodies during pregnancy could allow for timely intervention with antenatal treatment and prevent the occurrence of severe ICH. As the incidence of severe ICH due to FNAIT is low, assessing the cost-effectiveness of adding screening for anti-HPA-1a to the prenatal screening program is relevant for decision making.

METHODS

A decision analysis model was developed to assess lifetime costs and effects of antenatal anti-HPA-1a screening with subsequent diagnostic and treatment interventions compared to the current situation without screening in the Netherlands. Model parameters were based on literature and expert opinions. One-way-sensitivity analysis and probabilistic sensitivity analysis were performed.

RESULTS

Adding of screening for HPA-1a to the current antenatal screening program of the Netherlands will lead to an additional cost of 4.7 million euro per year, and a gain of 226 Quality-Adjusted Life Years (QALY) per year, indicating an incremental cost-effectiveness ratio (ICER) of €20,782 per QALY gained. One-way-sensitivity showed that the uncertainty around the incidence of ICH, lifetime costs of disabled children and the probability of having antibody quantitation > 3.0 IU/ml at 20 weeks had the highest effect on the ICER.

CONCLUSION

Antenatal HPA-1a screening might be cost-effective. To obtain more knowledge and thereby reduce the uncertainty on risk stratification and the efficacy of intravenous immune globulin treatment in immunised pregnancies identified by screening, a pilot screening program is warranted.

INTRODUCTION

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is a rare severe disease that may cause intracranial haemorrhage (ICH) and organ bleeding in fetuses and neonates. FNAIT results from maternal IgG antibodies directed against paternally inherited antigens on the fetal platelets. In the white population, the majority of FNAIT cases are caused by antibodies directed against human platelet antigen 1a (HPA-1a).[1] Implementation of population-based screening for FNAIT, in analogy to red blood cell antibody screening for secondary prevention of severe haemolytic disease of the fetus and neonate, is debated for decades.[2-4] It is argued that by screening, HPA-1a alloimmunised pregnancies can be identified and that timely antenatal intervention could prevent the occurrence of severe haemorrhage, and its life-long neurological sequelae.[2-8]

Over the last decades, cost-effectiveness studies on HPA-screening were performed in Canada,[5] France,[6] United Kingdom,[7] and Norway.[8] Gafni *et al.*[5] performed a hypothetical calculation assuming that prophylaxis would prevent all FNAIT related morbidity, however primary prophylaxis is not available yet. Another study[6] focused on the diagnostic costs of screening in new-borns to screening in primiparous women. However, antenatal treatment was only available in subsequent pregnancies in this screening design, whereas later became apparent that 63% of the ICH are diagnosed in first-born children.[9] Due to these limitations both studies were not further considered.[5, 6] In 1998, Williamson *et al.*[10] showed that screening of all pregnant women may indeed prevent severe bleeding and proposed to select high-risk pregnancies based on maternal HLA DRB3*01:01 status and antibody levels. The authors also proposed screening mid-pregnancy since women in their first ongoing pregnancy may produce clinically relevant HPA-1a antibodies, whereas antibody levels of multigravida women may decline during pregnancy to non-relevant quantities.[10] Based on these insights Turner *et al.*[7] performed a screening study and calculated the diagnostics test costs for antenatal screening, however their calculations were based on a study with a relatively limited sample size. Finally, Killie *et al.*[8] performed a cost-effectiveness study based on a large screening study including 100,448 pregnant women[11] with the assumption that near-term caesarean section would prevent the development of ICH.

We propose to treat HPA-1a alloimmunised women identified by a screening program with high risk of severe neonatal outcome with antenatal intravenous immunoglobins (IVIg) during pregnancy. We aimed to assess the cost-effectiveness of an antenatal screening program to timely detect HPA-1a antibodies during pregnancy in the Netherlands compared to the current situation without screening.

METHODS

We compared the lifetime costs and effects of antenatal anti-HPA-1a screening to the situation without screening in the Netherlands by developing a decision-analysis model. This model was built in Microsoft Excel (Microsoft Corporation, Redmond, WA). Because the proposed screening program aims to impact both the life expectancy and quality of life of children with FNAIT, outcome was expressed in Quality-Adjusted Life Years (QALYs). The incremental cost-effectiveness ratio (ICER) was expressed in terms of incremental cost per QALY. We assessed the costs and consequences of platelet antibody screening from a societal perspective, i.e., all costs and consequences were included, regardless of who incurs the costs and who obtains the effects. Costs have been discounted at a constant rate of 4% and effects at a constant rate of 1.5% according to the Dutch guidelines.[12] The price level of 2022 was used. Calculations were based on a population of 171,713 pregnant women.[13] Since the consequences of ICH can result in lifelong handicaps,[14] we applied lifetime horizon of the child.

PROBABILITIES

Situation without antenatal HPA-1a screening

The situation without antenatal anti-HPA-1a screening is summarised in Figure 1A (decision tree is shown in Supplemental Figure 1). In absence of anti-HPA-1a screening, FNAIT is often not recognised and therefore highly underdiagnosed.[15] In the base case, the probability of ICH due to undiagnosed FNAIT (5.5 cases/year in the Netherlands) was based on data from a screening study in The Netherlands (HIP study [HPA screening in pregnancy study], de Vos, Winkelhorst *et al*., manuscript in preparation) and the results of previous antenatal screening studies summarised in a systematic review.[16]

In the situation without screening, FNAIT is predominantly diagnosed postnatally. The probability of giving birth to a child diagnosed with FNAIT postnatally (9.3 cases/year in the Netherlands[17]) was based on a study of the national reference laboratory and clinical expertise centre in The Netherlands (2002-2019).[17] In most cases, FNAIT is suspected upon the detection of neonatal bleeding symptoms in combination with low platelet counts or if low platelet counts are detected as a finding by chance upon platelet count done for other reasons. Probabilities on the postnatal outcome (e.g. platelet count) of newly diagnosed FNAIT cases were retrieved from the FNAIT Registry 2020, an international database consisting of 408 FNAIT cases.[18]

A minority of the FNAIT cases is diagnosed during pregnancy after the detection of ICH in the fetus on ultrasound (1 case/year in The Netherlands[17]). When there is no fetal death related to ICH, IVIg treatment is started directly after FNAIT is diagnosed, or the child is delivered by caesarean section. In this model we assumed that all these antenatally diagnosed cases

were treated with antenatal IVIg treatment. Outcome of children with ICH was estimated on a case series of 21 children with FNAIT related ICH: 52% died, 33% were alive and had neurodevelopmental impairment (classified as disabled) and 14% were alive without neurodevelopmental impairment (classified as not disabled).[14]

Lastly, there is a group of women with follow-up pregnancies after a previous child was diagnosed with FNAIT (estimated on 4.2 cases/year in The Netherlands).[17] If fetal-maternal incompatibility is proven in the follow-up pregnancy, these women are offered IVIg treatment to reduce the risk of bleeding. Based on a recent study published by our group we assumed no disability in the group of children treated with IVIg in subsequent pregnancies.[19] Probabilities of the situation without screening are listed in Supplemental Table 1.

Antenatal screening

The situation with HPA-1a screening is visualised in Figure 1B (decision tree in Supplemental Figure 2). In the situation with HPA-1a screening, all pregnant women will be typed for HPA-1 early in pregnancy. If the mother is HPA-1a negative, maternal HLA typing is performed. This is done because women negative for HLA DRB3*01:01 rarely develop high levels of anti-HPA-1a.[20] HPA-1a negative women positive for HLA DRB3*01:01 are offered antibody screening at the 20th and 27th week in pregnancy. If anti-HPA-1a is detected, fetal typing is performed because multigravida pregnant women may carry an HPA-1a negative fetus not being at risk for FNAIT. HPA-1a immunised and incompatible pregnancies are subsequently classified as either high-risk or low-risk pregnancies using antibody quantitation according to the cut off values determined based on the Norwegian screening study.[21] If antibody quantitation is > 3 IU/ml, the pregnancy is considered high-risk, and the mother is treated by weekly administration of IVIg (dosage; 0.5 gram/kg/week) from the moment that the antibody is > 3 IU/ml.

The proportion of HPA-1a negativity was (2.4%) was based on the results of the HIP study (de Vos, Winkelhorst *et al*., manuscript in preparation). The probability of being HLA DRB3*01:01 positive (33%) was based on data of two cohorts of healthy blood donors.[22, 23] Data on the course of antibody quantitation and probabilities of having antibody quantitation > 3 IU/ml at 20th week and/or 27th week were based on the Norwegian screening study (additional data needed for the calculations of these probabilities were kindly provided by Jens Kjeldsen-Kragh and Mette Kjær).[21] Probabilities of the situation with HPA screening are shown in Supplemental Table 2.

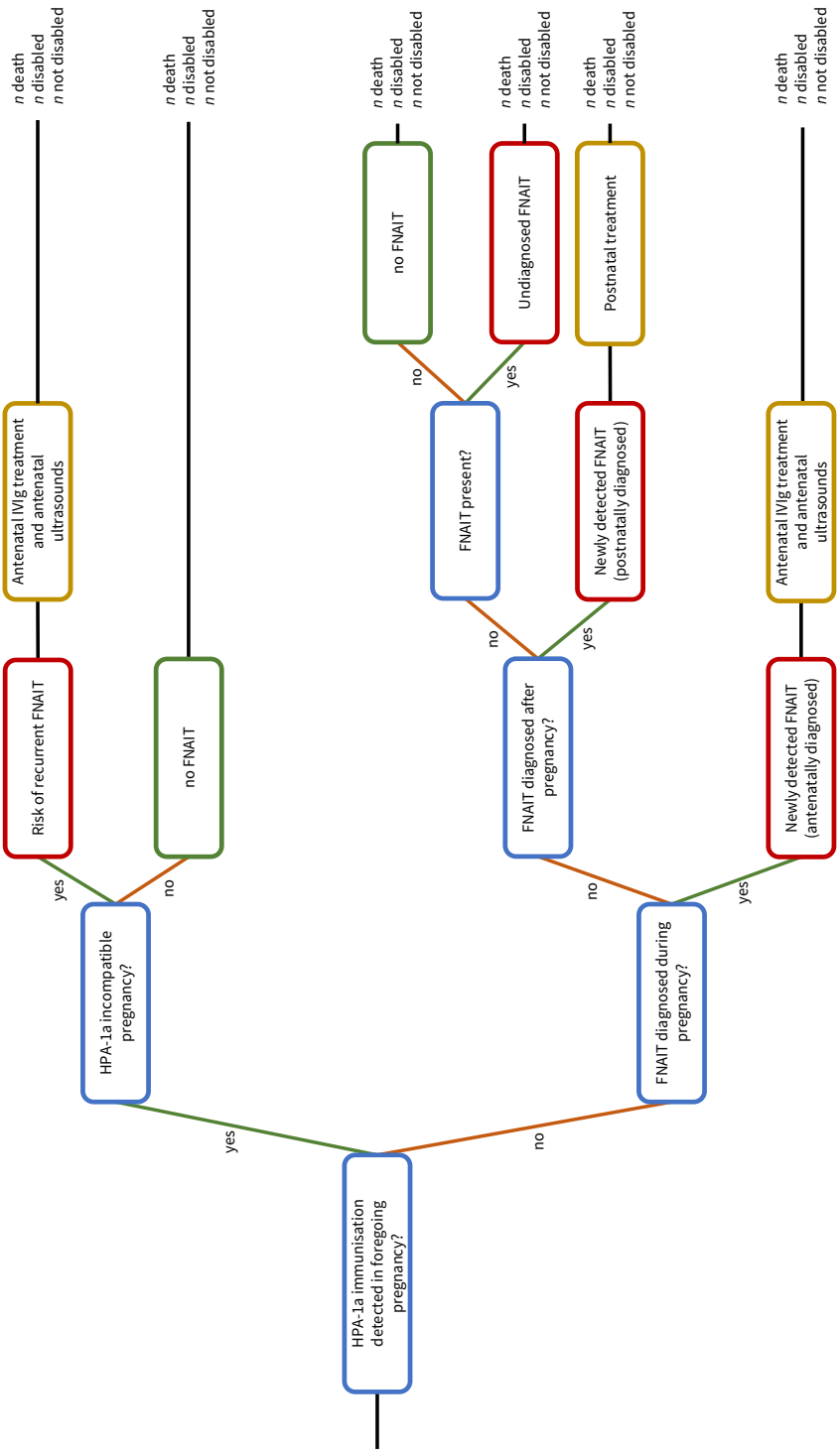

FIGURE 1A. Diagram of situation without screening

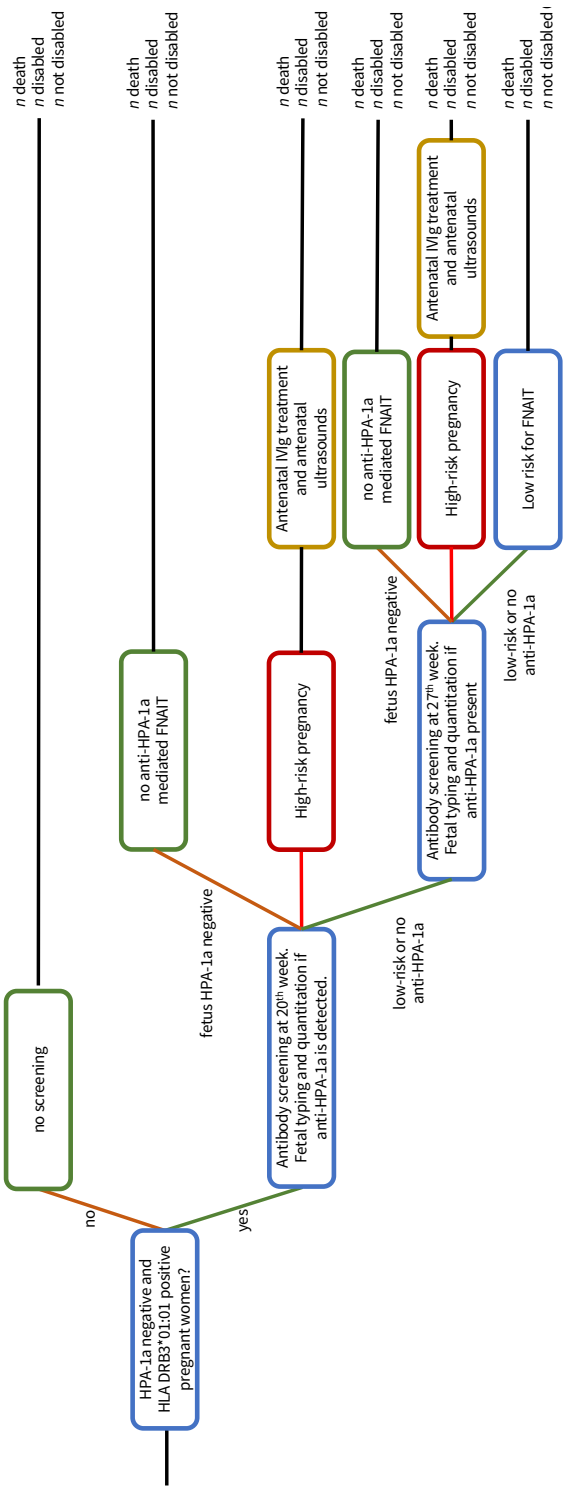

FIGURE 1B. Diagram of situation with HPA-1a screening.

Abbreviations: HPA, human platelet antigen; FNAIT, fetal and neonatal alloimmune thrombocytopenia; IVIg, intravenous immune globulin.

COSTS

Diagnostics test costs

Costs of diagnostic tests are shown in Supplemental Table 3. In the no-screening situation, FNAIT is diagnosed with maternal, paternal and neonatal (molecular) comprehensive HPA 1, 2, 3, 5 and 15-typing, HPA and HLA antibody identification and cross-matching paternal platelets with maternal serum (€1953). Costs of testing in the situation without screening were based on the prices of the nationwide reference laboratory.[24, 25] In case of antenatal screening for FNAIT, typing and antibody screening will be focused on HPA-1a, the sample throughput will increase which lowers the costs per sample. Costs for diagnostic tests in a screening setting were calculated by diagnostic experts on platelet antibody screening from Sanquin (Masja de Haas and Leendert Porcelijn). Costs used for the screening setting in the base case were €15 for maternal HPA-1 typing (including costs for drawing of the blood sample, sample logistics and report generation), €40 for maternal HLA typing, €75 for HPA antibody screening and €150 for antibody quantitation.

Treatment costs

Treatment costs are presented in Supplemental Table 4. Antenatal treatment costs consist of both administration costs and medication costs for weekly administration of IVIg (€223 per vial of 2.5 g[26]). Every first IVIg dosage during pregnancy is given in the hospital on day-care basis (€304[27]), subsequent dosages are administered by home care nurses (€200 per administration [personal communication Sanquin home service]). Additionally, costs for healthcare resource use were calculated including outpatient clinic visits[27] with costs of advanced fetal ultrasounds (€851[28]) at week at 21, 27, 31 and 35 weeks gestational age. These costs were calculated as additional costs compared to healthcare costs in the situation without screening. Travel costs and productivity costs of pregnant women were also taken into account.

Postnatal treatment costs depend on postnatal platelet counts, which were categorised in three groups. Neonates with platelet count > 100 × 10^9/L are regarded not at risk for bleeding and discharged, no additional costs were calculated for this group. Neonates with a platelet count 25-100 × 10^9/L will be admitted for clinical surveillance to the maternity ward (3 days, €449 per day[29]) including daily measurements of platelet counts. In addition, cranial ultrasound (€100[29]) will be performed to screen for ICH. Neonates with platelet count < 25 × 10^9/L will be admitted to the neonatology ward (high care, €1830 per day[29]) and receive one HPA-matched platelet transfusion (€365 [personal communication]). In addition, brain imaging and platelet count measurements will take place. Health care related and travel costs that might be attributable to the father were not included in this analysis. No productivity costs were applied since postnatal treatment falls within the period of maternity leave.

Lifetime costs per health state

Additional lifetime costs related to FNAIT per health state are shown in Supplemental Table 4. Additional lifetime costs for the outcomes: healthy, not disabled or death were set at €0. Literature on the lifetime costs for FNAIT related disability is lacking, therefore we used reports on lifetime costs of cerebral palsy (CP). We used data from a study from Denmark[30] that reported on the lifetime costs for healthcare, productivity costs and societal costs for children with CP (€802,868 excluding informal costs). Productivity costs were subtracted from the lifetime costs using the friction cost approach.[27] According to this approach disabled children do not account for productivity costs since they never entered and therefore will never leave the labour market. Costs for informal caregiving (€341,000) were based on a study reporting on the mean hours of informal care per week for severe neurologic conditions[31] and the Dutch manual for healthcare costs.[27]

EFFECTS

In Supplemental Table 5 utility values, reflecting the quality of life within a particular health state, are shown. No data was available on health-related qualify of life related to FNAIT. One study systematically assessed the long-term outcome of children with FNAIT related ICH and reported that 70% had cerebral palsy, 40% had severe visual impairment and 40% was diagnosed with epilepsy.[14] Therefore, literature on the utility scores of children diagnosed with CP[32], visual impairment[33, 34] and epilepsy[35] was used. Based on the available literature, the utility score of FNAIT related disability was estimated at 0.55. A utility score of 0 was assigned to the 'death' as health state. For the healthy and not disabled health state the Dutch population norm score was used (0.910).[36] Life expectancy of disabled children was assumed to be 50 years[37] and 81.7 years for children not disabled.[38]

ASSUMPTIONS

Although the efficacy of IVIg treatment in immunised pregnancies identified via antenatal screening was never proven in a randomised controlled trial, in the base case we assumed no failure of antenatal treatment. Moreover, we assumed all cases with FNAIT-related ICH develop antibodies at 27th weeks or earlier, and that all cases with ICH had antibody quantitation > 3 IU/ml at one of the moments of screening.

ANALYSES

Base case analysis

A base case analysis was performed by using the values for the model parameters described above. We reported costs, QALYs, FNAIT related death and FNAIT related disability for the situation without screening and the situation with antenatal HPA-1a screening. To calculate the incremental cost effectiveness ratio (ICER), difference in mean costs between the situation with and without antenatal screening are divided by the difference in mean QALYs.

Sensitivity analyses

One-way sensitivity analysis (OWSA) and probabilistic sensitivity analysis (PSA) were performed to address the uncertainty of the model parameters and to quantify the impact on the costs and QALYs. To perform these analyses beta, gamma and Dirichlet distributions were used around the parameters: the beta distribution was applied to all parameters values that needed to stay within the 0-1 range, thus for the probabilities and utilities. A gamma distribution applies to parameters that are not allowed to drop below 0. This distribution has therefore been used for all costs, as well as the expression of an amount such as the length of stay in the hospital or the annual number of pregnant women. A Dirichlet distribution was chosen when a parameter consisted of more than two proportional parameters that had to add up to one every time. Ranges of these distributions were based on expert opinion (Thijs de Vos and Masja de Haas). For the beta and gamma distribution either a standard error has been assumed or values for alpha and beta were estimated in line with the assumed minimum and maximum value of the parameter. Assumptions about the standard error (SE) were made in collaboration with the experts, taking a percentage of the deterministic value depending on how much variation was considered likely. The more variation assumed, the higher the assumed SE. For the costs related to the disabled health state e.g., an SE of 50% was assumed because these costs are expected to show a lot of variation, given that lifetime costs depend greatly on the severity of the NDI.

OWSA included all probabilities except the parameters with Dirichlet distribution. The 15 parameters with the largest effect on the ICER were presented in a Tornado diagram. PSA was performed by random draws from the probability distribution for 1,000 simulations. Subsequently, costs and QALYs were calculated for each simulation. Results for this analysis were displayed in a cost-effectiveness (CE) plane and cost effectiveness acceptability curve (CEAC).

Scenario analysis 1 - Quality control after birth

In the first years after the introduction of HPA-1a screening quality control will be performed to verify if clinically relevant FNAIT cases will be left untreated. In this scenario analysis, platelet counts will be performed in all neonates of HPA-1a negative women to assess extra costs of this quality control.

Scenario analysis 2 – Improvement of risk stratification

In the base case analysis women are considered to have a high-risk pregnancy if antibody quantitation is > 3 IU/ml. Currently assays to identify pregnancies at high-risk with a higher sensitivity are being developed. To assess the cost reduction when these assays become available, we performed a scenario analysis in which we set the threshold at 10 IU/ml. At present, it is thought that increasing this threshold would lead to missing cases with ICH, but the number of ICH missed by increasing this threshold is currently unknown.

Scenario analysis 3 – Reduced sensitivity of risk stratification

In general, cases with ICH in prospective screening studies had high antibody levels.[10, 11, 39, 40] However, antibody quantitation is doubted as single predictor for disease severity because in retrospective studies cases were identified with ICH and low antibody levels.[41] To address this uncertainty, we performed a scenario analysis in which yearly one out of 194 pregnancies classified as low risk at 27 weeks gestational age, ended with the delivery of a child with ICH.

RESULTS

BASE-CASE ANALYSIS

Results of the base case analysis with an annual number of 171,713 pregnant women is shown in Table 1. Incorporating these annual expected numbers and the effect assumptions an expected yearly number of 2.5 children with FNAIT related disability and 3.8 cases of FNAIT related death was obtained for the Netherlands.

In the situation with antenatal screening, we expect to identify 64.7 high-risk pregnancies at 20th week of pregnancy and 10.7 high-risk pregnancies at 27th week of pregnancy. Due to the earlier HPA-antibody detection and antenatal treatment, we expect to prevent all FNAIT related disability and death: a gain of 226 QALYs was expected (discounted). Total costs increment of HPA-1a screening expected was €4,688,100. Dividing the difference in costs by the 226 QALYs gained resulted in a cost-utility ratio of €20,782 per QALY gained.

TABLE 1. Disaggregated results and increments compared to no screening situation for a cohort of 171.713 (€ 2022)

Category	No screening	HPA-1a screening	Increment
Annual number of dead children caused by FNAIT	3.83	0.00	- 3.83
Annual number of disabled children caused by FNAIT	2.48	0.00	- 2.48
Total QALYs attained (discounted)	7,208,369	7,208,595	+ 226
Diagnostic test costs	€26,200	€3,042,100	+ €3,015,900
Antenatal treatment costs	€252,400	€4,630,200	+ €4,377,800
Postnatal treatment costs	€66,800	€201,600	+ €134,800
Lifetime costs	€2,840,400	€0	- €2,840,400
Total costs	€3,185,800	€7,873,900	+ €4,688,100

Abbreviations: HPA, human platelet antigen; FNAIT, fetal and neonatal alloimmune thrombocytopenia, QALY, Quality-life adjusted years

SENSITIVITY ANALYSIS

Results of the OWSA are presented in Figure 2, in this analysis we changed the base case parameters to their minimum and maximum values (see Supplemental Tables 1 – 5). The uncertainty around the incidence of ICH in the group of unidentified FNAIT, lifetime costs of disabled children and the probability of having antibody quantitation > 3.0 IU/ml at 20 weeks of gestation had the highest impact on the ICER.

In addition, a probabilistic sensitivity analysis was performed, (Figure 3 and Figure 4), at a willingness to pay threshold of €20,000 per QALY the probability of the screening strategy being cost-effective compared to a situation without screening was 26%. At a willingness-to-pay threshold of €80,000 this percentage was 96%.

SCENARIO ANALYSES

Performing platelet count in all HPA-1a negative mothers as a quality control (scenario analysis 1) would lead to yearly additional costs of €26,387 and no additional effects. If diagnostic assays become available improving the selection of high-risk pregnancies equivalent to treating pregnancies only with antibody quantitation > 10 IU/ml, this would lead to considerable reduction in costs (scenario analysis 2). Costs increment will be €2,930,164 instead of €4,688,103. It is however currently uncertain to what extent this might lead to missing cases at risk for ICH. If yearly one case with ICH would be missed (scenario analysis 3), a gain of 192 QALYs was expected resulting in a cost-utility ratio of €26,559 per QALY gained.

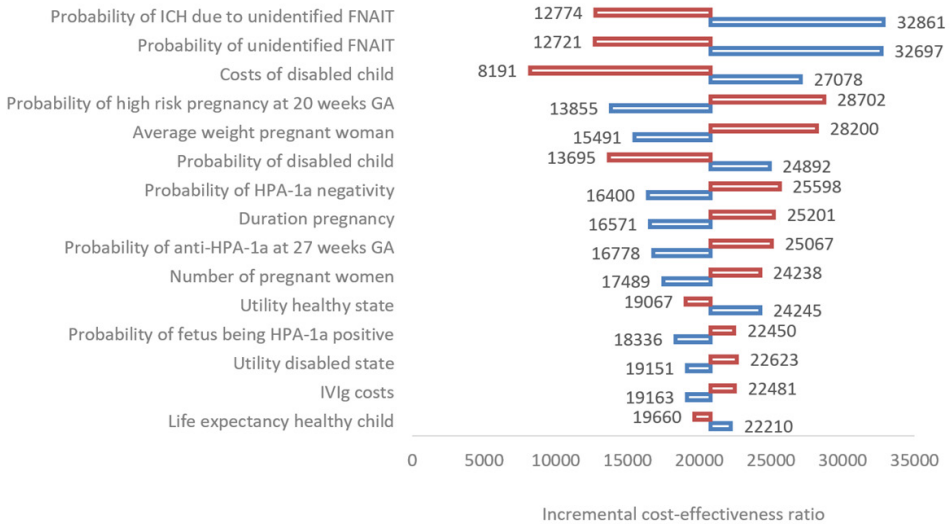

FIGURE 2. One way sensitivity analysis

Univariate sensitivity analysis: cost-effectiveness ratio (cost per QALY) for minimum (red bars) and maximum values (blue bars) of the input parameters. Base case ICER €20,782 per QALY (price level 2022).

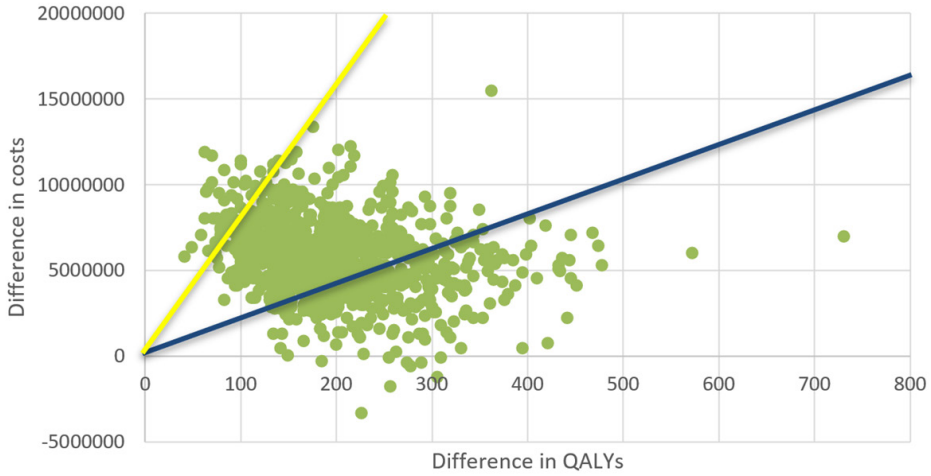

FIGURE 3. Probabilistic sensitivity analysis cost effectiveness plane

Cost effectiveness based on 1000 probabilistic simulations. The blue line represents the €20,000 per QALY threshold and the yellow line represents the €80,000 per QALY threshold.

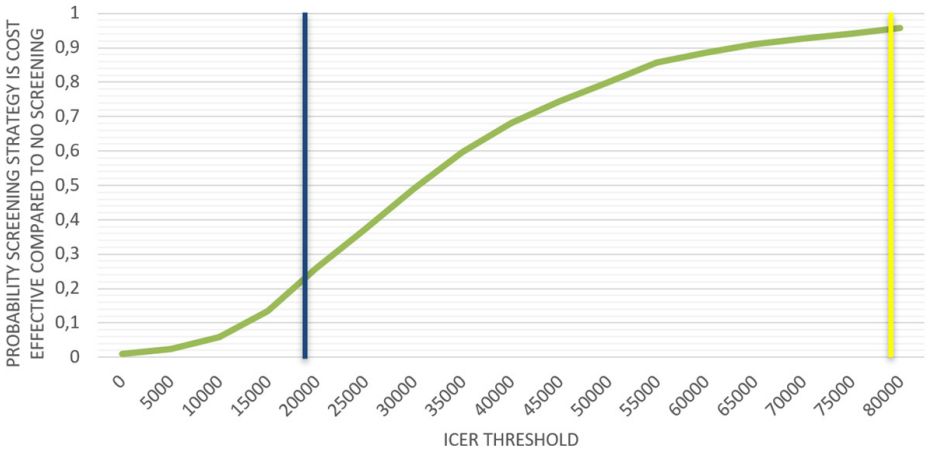

FIGURE 4. Probabilistic sensitivity analysis: cost effectiveness acceptability curve

Cost effectiveness based on 1000 probabilistic simulations. The blue line represents the €20,000 per QALY threshold and the yellow line represents the €80,000 per QALY threshold.

DISCUSSION

Based on our model we calculated that addition of HPA-antibody screening to the current antenatal screening program of the Netherlands will lead to additional cost of 4.7 million euro per year, and a gain of 226 QALY per year. Thus, the incremental cost-effectiveness ratio was €20,782 per QALY gained. This estimate was based on literature data and expert opinions. The one-way sensitivity analysis showed that the uncertainty around the incidence of ICH in the group of unidentified FNAIT, lifetime costs of disabled children and the probability of having antibody quantitation > 3.0 IU/ml at 20 weeks of gestation had the highest effect on the ICER.

Turner *et al.*[7] calculated $71,067 per QALY gained. This higher amount can be possibly explained by the fact that this study included only costs for diagnostic testing without taking the costs for treatment into account. Therefore, no effect on the reduction of life-time treatment costs was included, resulting in a higher cost-effectiveness ratio. Killie *et al*.[8] calculated that all screening strategies were cost-saving, based on the results of the largest screening study on FNAIT thus far.[11] In their screening, a near term caesarean section was considered to prevent adverse outcome in FNAIT. If this approach indeed would reduce FNAIT-related severe bleeding has however been questioned.[42] In the Norwegian study, it was estimated that screening of 100,000 women would lead to 210-230 gained QALYs (discounted rate). This was higher compared to the rate in our study (132 QALYs per 100,000 pregnant women). This difference can be explained by using a different probability of disability and death within the immunised population.

In line with the conclusions of Killie *et al*., cost-effectiveness ratio found in our study is possibly acceptable for European countries.[43] In addition, further cost reductions in future seems feasible. At present, maternal blood group typing (ABO, RhD, Rhc) is repeated in every pregnancy. When these test results including HPA-1 and HLA typing are stored in a central database, this information can be used for subsequent pregnancies also. This prevents unnecessarily retesting, and thus significantly reduce diagnostic test costs. In addition, when prophylaxis may become available in future, immunisation can be prevented and may further reduce the number of immunised and possibly high-risk pregnancies requiring (expensive) IVIg treatment.[44]

Our study has several limitations. Most importantly, our study assumed that IVIg treatment could prevent all FNAIT related ICH and that all immunisations leading to ICH will be detected in this screening strategy. It is not known whether IVIg also reduces the risk of bleeding in *first* HPA-1a immunised pregnancies. The impact of these assumptions can be explored in a scenario analysis in which the effectiveness of IVIg treatment in pregnancies identified by antenatal screening is assumed to be lower. The only way to finally obtain more

knowledge on this subject is to introduce population-based screening in a study setup with a control group. Given the low incidence of ICH, it would be preferable to conduct a national pilot screening. In addition to information about the effectiveness of IVIg treatment, this could also provide information about risk stratification within HPA-1a immunised pregnant women. Possibly, Fc core fucosylation of anti-HPA-1a[45] or the presence of certain subtypes of antibodies interfering with endothelial cell functioning[46] are antibody characteristics which could be used to improve risk stratification in FNAIT. It could be justifiable to start a pilot screening with an antibody threshold of 10 IU/ml instead of 3 IU/ml for discrimination of high-risk pregnancies with the start of IVIg. The threshold of 3 IU/ml was designed to detect cases with severe thrombocytopenia (platelet count < 50×10^9/L).[21] However, severe thrombocytopenia does not always lead to ICH. Most cases with ICH in prospective studies have antibody thresholds above 10 IU/ml.[10, 11, 39, 40] It could be that cases with ICH will be missed by using this threshold, however screening is not necessarily intended to find all cases, but to find as many as possible in a cost-effective way. In addition, improvements can be made with the knowledge gained in such a pilot program. Another limitation of our study is that knowledge about the long-term costs is limited, while our OWSA showed that the uncertainty around this value had the biggest impact on the ICER, this uncertainty should be addressed in future research.

Acknowledging the limitations of our study about the effect of IVIg treatment in first affected pregnancies and the uncertainty in estimating life-time costs of disabled children we think that HPA-1a screening in pregnancy has the potential to be cost-effective. For a screening program it is of the utmost importance to allow risk stratification within the group of HPA-1a immunised pregnant women, to restrict IVIg therapy to women with a high-risk of having a child with intracranial haemorrhage.

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SUPPLEMENTAL MATERIAL

SUPPLEMENTAL TABLE 1. Probabilities situation without HPA-1a screening

Parameter	Probability	Distribution Beta (SE) or Dirichlet (n1, n2, n3,..)	Source
General			
Termination of pregnancy / fetal loss during pregnancy	0.033	Beta (0.002)†	Process Monitor PSIE [13]
Probabilities of pregnancies of women who were diagnosed with HPA-1a immunization in previous pregnancy			
Pregnant woman diagnosed with FNAIT in foregoing pregnancy	2.459×10^{-5}	Beta (4.918×10^{-6}) §	Nationwide FNAIT database [17]
Fetus HPA-1a positive if FNAIT was diagnosed in foregoing pregnancy	0.844	Beta (0.042) †	Calculated based on data from the HIP study [4]
False-negativity rate fetal HPA-1a typing	0.030	Beta (0.003) ‡	Assumed equal to fetal RHD typing. [47]
Fetal loss due to failure of antenatal treatment	0.000	Dirichlet (1,1700,1400,1000)	Expert opinion
PC > 100×10^9/L after antenatal treatment	0.415	Dirichlet (1,1700,1400,1000)	FNAIT registry 2020[18]
PC 25-100×10^9/L after antenatal treatment	0.341	Dirichlet (1,1700,1400,1000)	
PC < 25×10^9/L after antenatal treatment	0.244	Dirichlet (1,1700,1400,1000)	
Dead if PC > 100×10^9/L	0.000	Dirichlet (1,10,999989)	Expert opinion
Disabled if PC > 100×10^9/L	0.000	Dirichlet (1,10,999989)	
Not disabled if PC > 100×10^9/L	1.000	Dirichlet (1,10,999989)	
Dead if PC 25-100×10^9/L	0.000	Dirichlet (1,10,99989)	
Disabled if PC 25-100×10^9/L	0.000	Dirichlet (1,10,99989)	
Not disabled if 25-100×10^9/L	1.000	Dirichlet (1,10,99989)	
Dead if PC < 25×10^9/L	0.000	Dirichlet (1,5,94)	
Disabled if PC < 25×10^9/L	0.000	Dirichlet (1,5,94)	
Not disabled if PC < 25×10^9/L	1.000	Dirichlet (1,5,94)	
Probabilities if FNAIT is diagnosed in current pregnancy			
FNAIT detected during current pregnancy	6.022×10^{-6}	Beta (9.218×10^{-6})	Dutch nationwide FNAIT database [17]
Termination of pregnancy/IUFD due to FNAIT	0.800	Beta (0.160)‖	
Fetal loss due to failure of antenatal treatment	0.000	Dirichlet (2,1,1,100)	Expert opinion
PC > 100×10^9/L after antenatal treatment	0.000	Dirichlet (2,1,1,100)	
PC 25-100×10^9/L after antenatal treatment	0.000	Dirichlet (2,1,1,100)	
PC < 25×10^9/L after antenatal treatment	1.000	Dirichlet (2,1,1,100)	
Dead if PC < 25×10^9/L after antenatal treatment	0.000	Dirichlet (1,10,90)	
Disabled if PC < 25×10^9/L after antenatal treatment	0.100	Dirichlet (1,10,90)	
Not disabled if PC < 25×10^9/L after antenatal treatment	0.900	Dirichlet (1,10,90)	
Probabilities if FNAIT is diagnosed postnatally			
FNAIT detected after birth	5.601×10^{-5}	Beta (5.601×10^{-6}) ‡	Dutch nationwide FNAIT database [17]
PC > 100×10^9/L	0.000	Dirichlet (1,300,940)	
PC 25-100×10^9/L	0.242	Dirichlet (1,300,940)	
PC < 25×10^9/L	0.758	Dirichlet (1,300,940)	
Dead if PC 25-100×10^9/L	0.000	Dirichlet (1,10,99989)	Expert opinion
Disabled if PC 25-100×10^9/L	0.000	Dirichlet (1,10,99989)	
Not disabled if 25-100×10^9/L	1.000	Dirichlet (1,10,99989)	

SUPPLEMENTAL TABLE 1. Continued

Parameter	Probability	Distribution Beta (SE) or Dirichlet (n1, n2, n3,..)	Source
Death if PC < 25 × 10^9/L after postnatal diagnosis	0.021	Dirichlet (20,84,836)	Winkelhorst *et al.*[14] Tiller *et al.*[9]
Disabled if PC < 25 × 10^9/L after postnatal diagnosis	0.089	Dirichlet (20,84,836)	
Not disabled if PC < 25 × 10^9/L after postnatal diagnosis	0.889	Dirichlet (20,84,836)	
Probabilities concerning unidentified FNAIT			
Unidentified FNAIT	3.613 × 10^{-4}	Beta (7.227 × 10^{-5})||	HIP study[4] Kamphuis *et al.*[16]
ICH due to unidentified FNAIT	0.092	Beta (0.018)||	
Dead due to ICH	0.524	Dirichlet (11,7,3)	Winkelhorst *et al.*[14] Tiller *et al.*[9]
Disabled due to ICH	0.333	Dirichlet (11,7,3)	
Not disabled despite ICH	0.143	Dirichlet (11,7,3)	

† SE of 5%. ‡ SE of 10%. § SE of 15%. || SE of 20%. # SE of 50%.
Abbreviations: HPA, human platelet antigen; FNAIT, fetal and neonatal alloimmune thrombocytopenia; PC, Platelet count.

SUPPLEMENTAL TABLE 2. Probabilities situation with HPA-1a screening

Parameter	Probability	Distribution Beta (SE) or Dirichlet (n1, n2, n3,..)	Reference
General			
Termination of pregnancy / fetal loss during pregnancy	0.033	Beta (0.002)†	Proces Monitor PSIE[13]
Maternal typing first trimester			
HPA-1a negative pregnant women	0.024	Beta (0.002)‡	HIP study[4]
Women HLA DRB3*01:01 positive	0.330	Beta (0.017)†	Cohort from DISIII[23] and Bloodtyper study.[22]
Maternal HPA-1a typing false negative	0.035	Beta (0.003)‡	Winkelhorst *et al.*[48]
Antibody screening at 20 weeks' GA			
Anti-HPA-1a detected	0.232	Beta (0.023)‡	HIP study[4]
Fetus HPA-1a positive if mother is HPA-1a immunised (and DBR3*01:01 positive)	0.896	Beta (0.045)†	HIP study[4]
False-negative fetal HPA-1a typing	0.030	Beta (0.003)‡	Assumed equal to fetal RHD typing.[47]
Antibody quantitation > 3 IU/ml at 20 weeks GA. (High risk pregnancy)	0.242	Beta (0.048) #	HIP study[4] and Killie *et al.*[21]
Antibody screening at 27 weeks' GA			
Antibodies present at 27 weeks GA but < 3.0 IU/ml at 20 weeks GA.	1.000	Beta (N/A) alpha=40, beta=1	Killie *et al.*[21]
Pregnancy at high risk for FNAIT when antibodies are detected at 27 weeks GA when considered low risk at 20 weeks GA	0.040	Beta (0.008) #	HIP study [4] and Killie *et al.*[21]

SUPPLEMENTAL TABLE 2. Continued

Parameter	Probability	Distribution Beta (SE) or Dirichlet (n1, n2, n3,..)	Reference
Dead after being considered at low risk for FNAIT (no antenatal treatment)	0.000	Dirichlet (1,10,99989)	Expert opinion and Killie *et al*.[21]
Disabled after being considered at low risk for FNAIT (no antenatal treatment)	0.000	Dirichlet (1,10,99989)	
Not disabled after being considered at low risk for FNAIT (no antenatal treatment	1.000	Dirichlet (1,10,99989)	
PC > 100 × 10^9/L after being considered at low risk for FNAIT (no antenatal treatment)	1.000	Dirichlet (9989,10,1)	
PC 25-100 × 10^9/L after being considered at low risk for FNAIT (no antenatal treatment)	0.000	Dirichlet (9989,10,1)	
PC < 25 × 10^9/L after being considered at low risk for FNAIT (no antenatal treatment)	0.000	Dirichlet (9989,10,1)	
Dead after no antibodies were detected (no antenatal treatment)	0.000	Dirichlet (1,10,999989)	
Disabled after no antibodies were detected (no antenatal treatment)	0.000	Dirichlet (1,10,999989)	
Not disabled after no antibodies were detected (no antenatal treatment)	1.000	Dirichlet (1,10,999989)	
PC > 100 × 10^9/L if no antibodies were detected (no antenatal treatment)	1.000	Dirichlet (99989,10,1)	
PC 25-100 × 10^9/L if no antibodies were detected (no antenatal treatment)	0.000	Dirichlet (99989,10,1)	
PC < 25 × 10^9/L if no antibodies were detected (no antenatal treatment)	0.000	Dirichlet (99989,10,1)	
Fetus HPA-1a positive in HPA-1a negative mother in case antibodies are detected at 27 weeks' GA if were absent at 20 weeks' GA	1.000	N/A	
Antibodies present at 27 weeks' GA if were absent at 20 weeks' GA	0.020	Beta (0.002) ‡	HIP study [4] and Killie *et al*.[21]
Pregnancy at high risk for FNAIT when antibodies are detected at 27 weeks' GA if absent at 20 weeks' GA	0.132	Beta (0.026) #	
Outcome after antenatal treatment			
Fetal loss due to failure of antenatal treatment	0.000	Dirichlet (1,1700,1400,1000)	Expert opinion
PC > 100 × 10^9/L after antenatal treatment	0.415	Dirichlet (1,1700,1400,1000)	FNAIT registry 2020
PC 25-100 × 10^9/L after antenatal treatment	0.341	Dirichlet (1,1700,1400,1000)	
PC < 25 × 10^9/L after antenatal treatment	0.244	Dirichlet (1,1700,1400,1000)	
Dead if PC > 100 × 10^9/L	0.000	Dirichlet (1,10,999989)	Expert opinion
Disabled if PC > 100 × 10^9/L	0.000	Dirichlet (1,10,999989)	
Not disabled if PC > 100 × 10^9/L	1.000	Dirichlet (1,10,999989)	
Dead if PC 25-100 × 10^9/L	0.000	Dirichlet (1,10,99989)	
Disabled if PC 25-100 × 10^9/L	0.000	Dirichlet (1,10,99989)	
Not disabled if 25-100 × 10^9/L	1.000	Dirichlet (1,10,99989)	
Dead if PC < 25 × 10^9/L	0.000	Dirichlet (1,5,94)	
Disabled if PC < 25 × 10^9/L	0.000	Dirichlet (1,5,94)	
Not disabled if PC < 25 × 10^9/L	1.000	Dirichlet (1,5,94)	

† SE of 5%. ‡ SE of 10%. § SE of 15%. || SE of 20%. # SE of 50%.

Abbreviations: HPA, human platelet antigen; FNAIT, fetal and neonatal alloimmune thrombocytopenia; PC, Platelet count; IU, international units; ml, millilitre.

SUPPLEMENTAL TABLE 3. Diagnostic test costs

Parameter name	Value	Distribution Gamma (SE)	Source
Situation without HPA-1a screening			
Fetal HPA-1 typing	€1345.23	N/A	Sanquin Diagnostic Services [24]
Test to detect FNAIT in fetus or neonate	€1953.66	N/A	Sanquin Diagnostic Services [25]
Platelet count	€22.39	Gamma (2.24) ‡	Dutch rate decision[49]
Order rate	€9.01	N/A	Dutch rate decision [49]
With HPA-1a screening			
Maternal HPA-1 typing	€15.00	Gamma (0.75) †	Sanquin Diagnostics Services (calculated by LP and MdH)
Fetal HPA-1 typing	€43.00	Gamma (2.15) †	
HLA DRB3*01:01 test	€40.00	Gamma (8.00) ||	
HPA-1a antibody screening	€75.00	Gamma (3.75) †	
Risk typing (antibody titre)	€150.00	Gamma (7.50) †	
Platelet count	€22.39[∞]	Gamma (2.24) ‡	Dutch rate decision [49]
Order rate	€9.01[∞]	N/A	Dutch rate decision [49]

† SE of 5%. ‡ SE of 10%. § SE of 15%. || SE of 20%. # SE of 50%.
Abbreviations: SE, standard error; HPA, human platelet antigen; N/A, not applicable; HLA, human leukocyte antigen

SUPPLEMENTAL TABLE 4. COSTS

Parameter name	Value	Distribution Gamma (SE)	Source
Antenatal treatment			
NaCl 500 ml 0.9%	€2.13	Gamma (0.11) †	Medicijnkosten.nl[26]
IVIg 0.1g/ml, 25 ml vial	€223.45	Gamma (11.17) †	Medicijnkosten.nl[26]
IVIg administration in hospital	€304.46 per administration	Gamma (60.89) ||	Manual for cost research[27]
Sanquin home service	€200 per administration	Gamma (40.00) ||	Estimated by Sanquin, personal communication MdH
Advanced fetal ultrasound	€851.48	Gamma (42.57) †	Passer-by rate[28] assuming the highest rate; costs updated to 2022 using Dutch CPI
Standard fetal ultrasound	€166.66	Gamma (8.33) †	Passer-by rate[28] costs updated to 2022 using Dutch CPI
Consult gynaecologist	€185.87	Gamma (9.29) †	Manual for cost research.[27]
Consult midwife	€31.54	Gamma (3.17) ‡	Manual for cost research.[27]
Postnatal treatment			
HPA matched platelet transfusion	€365.37	Gamma (17.65) †	Sanquin, personal communication TWdV
Cranial ultrasound	€100.35	Gamma (5.02) †	Liem *et al*.[29]
Admission maternal ward (day)	€449.86	Gamma (44.99) ‡	Liem *et a* .[29]
Admission high care neonatology	€1830.87	Gamma (183.09) ‡	Liem *et al*.[29]
Lifetime costs per health state			
Healthy state	€0	NA	-
Not disabled state	€0	NA	-
Disabled state (excl. informal costs)	€802,868		Kruse *et al*.[30]
Lifetime informal care costs (disabled state)	€340,999		Mitchell *et al*.[31]
Total lifetime costs disabled health state	€1,143,867	Gamma (571,933.62)#	Liem *et al*.[29] and Kruse *et al*.[30]
Death state	€0		-

† SE of 5%. ‡ SE of 10%. § SE of 15%. || SE of 20%. # SE of 50%.
Abbreviations: SE, standard error; NaCl, natriumchloride [sodiumchloride in English]; IVIg, intravenous immune globulins; ml, millilitre; CPI, consumer price index; HPA, human platelet antigen, excl., excluding.

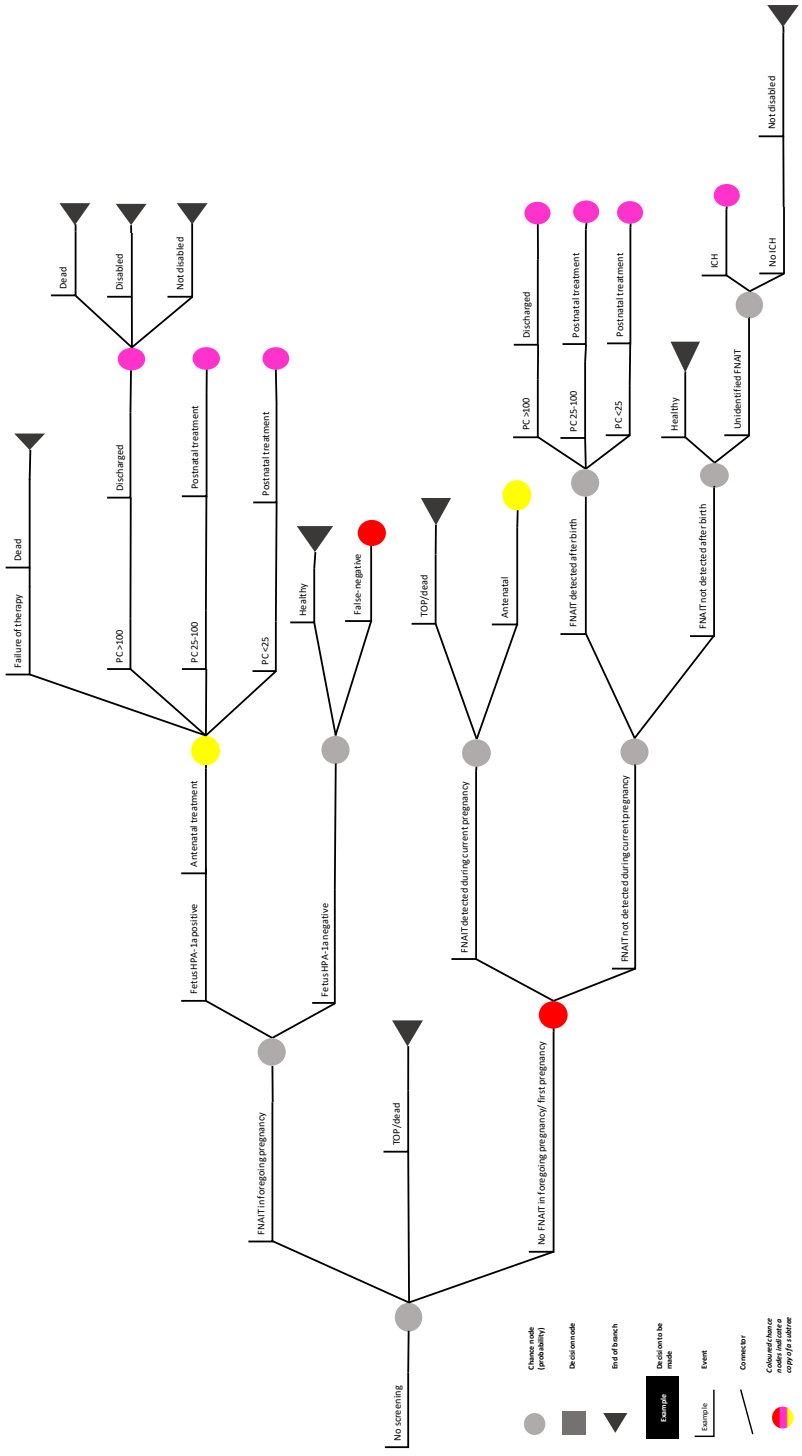
SUPPLEMENTAL TABLE 5. Utility, life expectancy and quality-life adjusted years

Parameter name	Value	Distribution Gamma (SE)	Source
		Utility per health state	
Dead	0	N/A	By definition
Disabled	0.550	Beta (0.110)||	Jarl *et al.*[32]; Macedo *et al.*[33]; Langelaan *et al.*[34]; Kirkham *et al.*[35]
Not disabled	0.910	Beta (0.046) †	Janssen *et al.*[36]
Healthy	0.910	Beta (0.046) †	Jansen *et al.*[36]
		Life expectancy per health state	
Dead	0	N/A	By definition
Disabled	50	Gamma (10)||	Strauss *et al.*[37]
Not disabled	81.66	Gamma (4.083) †	CBS[38]
Healthy	81.66	Gamma (4.083) †	CBS[38]

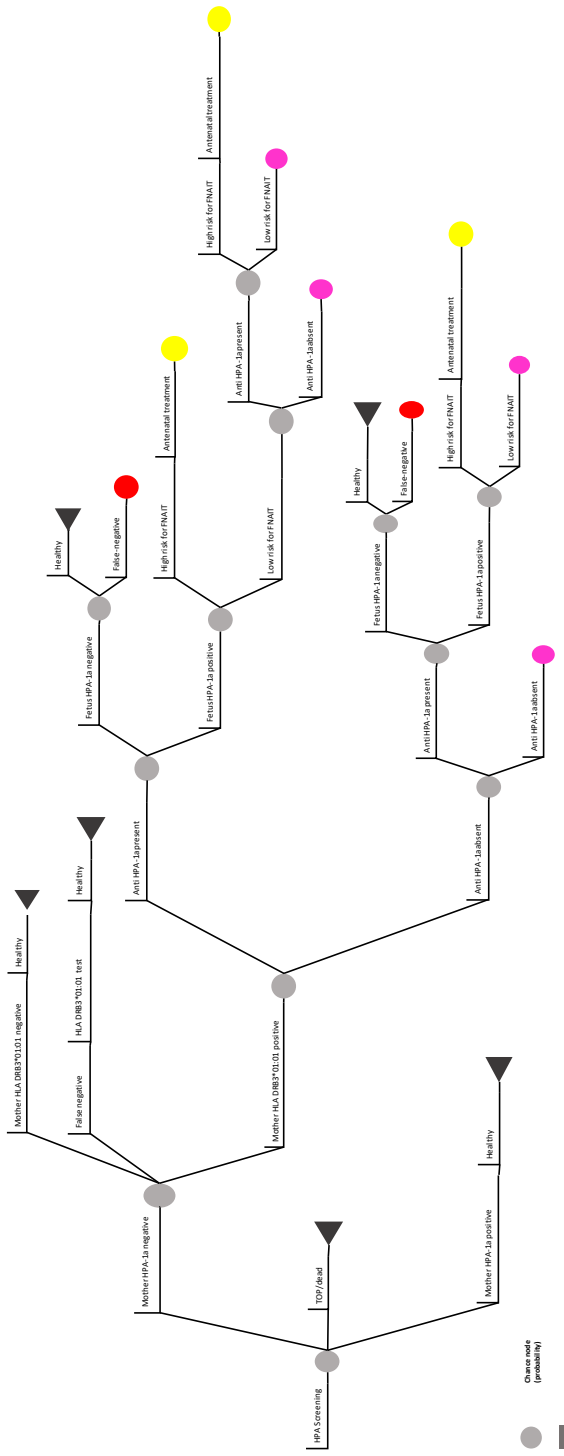
† SE of 5%. ‡ SE of 10%. § SE of 15%. || SE of 20%. # SE of 50%.
Abbrevation: SE, standard error.

SUPPLEMENTAL TABLE 6. Quality-adjusted life years per health state

Health state	Value - undiscounted	Value - discounted
Dead	0	0
Disabled	27.5	19.54
Not disabled	74.31	43.41
Healthy	74.31	43.41



SUPPLEMENTAL FIGURE 1. Situation without screening - decision tree



SUPPLEMENTAL FIGURE 2. HPA-1a screening - decision tree