Screening of pregnant women for fetal neonatal alloimmune thrombocytopenia: a cost-utility analysis

Thijs W. de Vos1,2, Ilonka Tersteeg3, Enrico Lopriore1, Dick Oepkes4, Leendert Porcelijn5, C. Ellen van der Schoot2, E. Joanne T. Verweij4, Dian Winkelhorst2,4, Masja de Haas2,5,6\*, M. Elske van den Akker-van Marle3\*

\*Last authors contributed equally

1. Willem-Alexander Children’s Hospital, Department of Pediatrics, Division of Neonatology, Leiden University Medical Center, the Netherlands.
2. Department of Experimental Immunohematology, Sanquin Research, Amsterdam, the Netherlands.
3. Department of Biomedical Data Sciences, Section Medical Decision Making, Leiden University Medical Center, Leiden, the Netherlands.
4. Department of Obstetrics and Gynecology, Leiden University Medical Center, the Netherlands.
5. Department Immunohematology Diagnostics, Sanquin Diagnostic Services, Amsterdam.
6. Department of Hematology, Leiden University Medical Center, Leiden.

**Corresponding author:** Thijs W. de Vos, Division of Neonatology, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden

**Funding:** Process and Product Development Diagnostic Services, Sanquin (SQI/00034).

**Running title:** Cost-utility analysis of screening for FNAIT

**Word count**:3500

# Abstract

**Objective:** 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 ICH. We aim to assess the cost-effectiveness of adding screening for anti-HPA-1a to the prenatal screening program.

**Design:** A decision analysis model was developed.

**Setting:** The Netherlands.

**Population:** 171,713 pregnant women.

**Methods:** Lifetime costs and effects of antenatal anti-HPA-1a screening with subsequent diagnostic and treatment interventions were 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.

**Main Outcome Measures:** Incremental cost-effectiveness ratio (ICER).

**Results:** Adding screening for HPA-1a antibodies to the current antenatal screening program of the Netherlands will lead to an additional cost of 4.7 million euro and a gain of 226 Quality-Adjusted Life Years (QALY) per year, indicating an ICER of €20,782 per QALY gained. One-way sensitivity analysis 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, a pilot screening program is warranted.

**Funding:** Sanquin

**Keywords:** cost-effectiveness analysis, fetal and neonatal alloimmune thrombocytopenia, screening.

# Funding

This study was partly funded by a grant from the Process and Product Development Diagnostic Services at Sanquin (SQI/00034). The grant (SQI/00034) was awarded to Masja de Haas. The funder had no role in the conduct of this study and/or the decision to publish it.

# 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 ICH, and its life-long neurological sequelae.2-8

Over the last decades several cost-effectiveness studies on HPA-screening were performed.5-8 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 study6 focused on postnatal screening whereas later became apparent that 63% of the ICH are diagnosed during pregnancy in first-born children.9 In 1998, Williamson *et al*.10 proposed to select high-risk pregnancies with serial antibody measurements during pregnancy because primigravida women may produce clinically relevant HPA-1a antibodies during pregnancy and in multigravida women antibody levels may decline to non-relevant quantities.10 Based on these insights Turner *et al.7* calculated the diagnostics test costs for antenatal screening, however their study had a relatively limited sample size. Finally, Killie *et al.*8 performed a cost-effectiveness study based on a large screening study11 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 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. 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%.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 in Figure S1). 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 Netherlands16 and the results of previous antenatal screening studies summarised in a systematic review.17

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, of which 0.9 cases/year diagnosed with ICH18) was based on a study of the national reference laboratory and clinical expertise centre in The Netherlands (2002-2019).18 Probabilities on the postnatal outcome (e.g. platelet count) of newly diagnosed FNAIT cases were retrieved from an international multicentre study.19

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 Netherlands18). 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 that was diagnosed with FNAIT (estimated on 4.2 cases/year in The Netherlands).18 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.20 Probabilities of the situation without screening are listed in Table S1.

### Antenatal screening

The situation with HPA-1a screening is visualised in Figure 1B (decision tree in Figure S2). In the situation with HPA-1a screening, all pregnant women will be typed for HPA-1a early in pregnancy. In HPA-1a negative women HLA-typing will be performed because women negative for HLA DRB3\*01:01 rarely develop high levels of anti-HPA-1a.21 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 will be performed to confirm fetal-maternal incompatibility. 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 based on the Norwegian screening study.22 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).

The proportion of HPA-1a negativity was (2.4%) was based on the results of a Dutch screening study.16 The probability of being HLA DRB3\*01:01 positive (33%) was based on data of two cohorts of healthy blood donors.23, 24 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.22 Probabilities of the situation with HPA screening are shown in Table S2.

## Costs

### Diagnostics test costs

Costs of diagnostic tests are shown in Table S3. 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.25, 26 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 (MdH and LP). Costs used for the screening setting in the base case were €15 for maternal HPA-1 typing (including costs for logistics and the reports), €40 for maternal HLA typing, €75 for HPA antibody screening and €150 for antibody quantitation.

### Treatment costs

Treatment costs are presented in Table S4. Antenatal treatment costs consist of both administration costs and medication costs for weekly administration of IVIg (€223 per vial of 2.5 g27). Every first IVIg dosage during pregnancy is given in the hospital on day-care basis (€30428), subsequent dosages are administered by home-care nurses (€200 per administration). Additionally, costs for healthcare resource use were calculated including outpatient clinic visits28 with costs of advanced fetal ultrasounds (€85129) 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.

Postnatal treatment costs depend on postnatal platelet counts, which were categorised in three groups. Neonates with platelet count >100×109/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 × 109/L will be admitted for clinical surveillance to the maternity ward (3 days, €449 per day30) including daily measurements of platelet counts. In addition, cranial ultrasound (€10030) will be performed to screen for ICH. Neonates with platelet count <25×109/L will be admitted to the neonatology ward (high care, €1830 per day30) and receive one HPA-matched platelet transfusion (€365). 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 loss of 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 Table S4. 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 Denmark31 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 these lifetime costs as in this study the friction cost approach is used.28 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 conditions32 and the cost per hour of caregiving.28

## Effects

In Table S5 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 CP, 40% had severe visual impairment and 40% was diagnosed with epilepsy.14 Therefore, literature on the utility scores of children diagnosed with CP33, visual impairment34, 35 and epilepsy36 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).37 Life expectancy of disabled children was assumed to be 50 years38 and 81.7 years for children not disabled.39

## Assumptions

In the base case we assumed no failure of antenatal treatment, it was also assumed that all cases at risk for FNAIT-related ICH develop antibodies with levels >3 IU/ml at 27th weeks or earlier.

## 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 costs and QALYs. To perform these analyses beta, gamma and Dirichlet distributions were used around the parameters. Beta distribution was applied to all parameters values that needed to stay within the 0-1 range, thus for the probabilities and utilities. Gamma distribution applies to parameters that are not allowed to drop below 0 (e.g. costs, 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 (TdV and MdH). 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. 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.

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

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 could lead to missing cases with ICH, but the number of ICH missed by increasing this threshold is unknown.

### Scenario analysis 3 – Reduced sensitivity of risk stratification

In general, cases with ICH in prospective screening studies had high antibody levels.10, 11, 40, 41 However, antibody quantitation is doubted as single predictor for disease severity because in retrospective studies cases were identified with ICH and low antibody levels.42 To address this uncertainty, we performed a scenario analysis in which yearly one out of 194 pregnancies classified as low-risk at 27weeks gestational age, ended with the delivery of a child with ICH.

### Scenario analysis 4 – Reduced effectivity of IVIg treatment

The efficacy of IVIg treatment in immunised pregnancies identified via antenatal screening was never proven in a randomised controlled trial. Therefore, a fourth scenario analysis was performed that presumed that in 20% of pregnancies IVIg is not effective and the risk of ICH would be equal to the risk in the group with unidentified FNAIT.

# 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 a situation without screening.

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 per year. Due to the earlier HPA-antibody detection and antenatal treatment, we expect to prevent all FNAIT related disability and death: a yearly gain of 226 QALYs was expected (discounted). The number needed to treat is 10.2 (75.4/7.4) to prevent one ICH. Total annual 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.

## 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 (Tables S1–S5). 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. If the efficacy of IVIg treatment would be lower (scenario analysis 4), a gain of 183 QALY was expected resulting in a cost-utility ratio of €28,483 per QALY gained.

# Discussion

## Main Findings

Based on our model we calculated that addition of HPA-1a-antibody screening to the current antenatal screening program of the Netherlands will lead to additional cost of 4.7 million euro and a gain of 226 QALY per year. Thus, the incremental cost-effectiveness ratio was €20,782 per QALY gained. 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.

## Interpretation

Turner *et al.*7 calculated $71,067 (€84,747 price level 2022) 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 and prevention of disability into account. Therefore, no effect 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 their screening study,11 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.43 The Norwegian study8 estimated that screening of 100,000 women would lead to 210-230 gained QALYs (discounted rate). This was higher compared to our study (132 QALYs per 100,000 pregnant women). This difference can be explained by using different probabilities 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.44 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-1a and HLA typing are stored in a central database, this information can be used for subsequent pregnancies, avoiding unnecessary retesting. Additionally, if prophylaxis may become available in future, immunisation can be prevented. This may reduce the number of immunised and high-risk pregnancies requiring (expensive) IVIg treatment.45

## Strengths and limitations

Our study has several limitations. Most importantly, our study was based on the assumption 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 unknown if IVIg also reduces the risk of bleeding in *first* HPA-1a immunised pregnancies. The impact of this assumption was explored in a scenario analysis in which the effectiveness of IVIg treatment was lower. The only way to obtain more knowledge on this subject is to introduce population-based screening in a study setup with a control group. Such a pilot screening could also provide information about risk stratification within HPA-1a immunised pregnant women. Possibly, determination of Fc core fucosylation of anti-HPA-1a46 or the presence subtypes of anti-HPA-1a47 could be used to improve risk stratification. 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. The threshold of 3 IU/ml was designed to detect cases with severe thrombocytopenia (platelet count <50×109/L).22 However, severe thrombocytopenia does not always lead to ICH and most cases with ICH in prospective studies have antibody thresholds above 10 IU/ml.10, 11, 40, 41 Possibly, cases with ICH will be missed by using a higher threshold, however screening is not necessarily intended to find all cases, but to find as many as possible in a cost-effective way. 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.

# Acknowledgements

We would like to thank Jens Kjeldsen-Kragh and Mette Kjær for providing additional data regarding antibody levels at multiple time points during pregnancy.

# Disclosure of Interests

DO is funded as a research consultant by Janssen Pharmaceuticals Inc and participates on the Advisory Board of Janssen Pharmaceuticals Inc. EL reports a consultancy fee from Janssen Pharmaceuticals Inc as member of the Advisory Board on FNAIT. The other authors report no conflicts of interest.

# Contribution to Authorship

Conceptualisation, TWdV, MdH and EvdAvM; Formal analysis, IT and TWdV; Funding acquisition, MdH; Methodology, TWdV, IT, MdH, EvdAvM; Investigation, EL, DO, LP, CEvdS, EJTV, DW; Supervision, MdH and EvdAvM; Visualisation, IT and TWdV; Writing – original draft, TWdV; Writing – review and editing, IT, EL, DO, LP, CEvdS, EJTV, DW, MdH, EvdAvM.

# Details of Ethics Approval

This study did not involve human or animal subjects, or medical records. Therefore ethical approval was not applicable.

# Figure legends

## Figure 1: Diagram of the situation without HPA-1a screening and the situation with HPA-1a screening.

## Figure 1A: No screening

## Figure 1B: HPA-1a screening

Flowchart of the situation without HPA-1a screening during pregnancy (Figure 1A) and the situation with HPA-1a screening in pregnancy (Figure 1B).

HPA, human platelet antigen; FNAIT, fetal and neonatal alloimmune thrombocytopenia; IVIg intravenous immune globulins; HLA, human leukocyte antigen;

## 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).

ICH, intracranial haemorrhage; FNAIT, fetal and neonatal alloimmune thrombocytopenia; GA, gestational age; IVIg, intravenous immune globulins.

## 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.

QALY, Quality-Adjusted Life Years.

## 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.

QALY, Quality-Adjusted Life Years; ICER, incremental cost-effectiveness ratio.

# Table

## 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 screening *vs* no screening** |
| 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 |

# References

1. Davoren A, Curtis BR, Aster RH, McFarland JG. Human platelet antigen-specific alloantibodies implicated in 1162 cases of neonatal alloimmune thrombocytopenia. Transfusion. 2004;44(8):1220-5.

2. Husebekk A, Killie MK, Kjeldsen-Kragh J, Skogen B. Is it time to implement HPA-1 screening in pregnancy? Current opinion in hematology. 2009;16(6):497-502.

3. Kjeldsen-Kragh J, Husebekk A, Killie MK, Skogen B. Is it time to include screening for neonatal alloimmune thrombocytopenia in the general antenatal health care programme? Transfusion and apheresis science : official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis. 2008;38(3):183-8.

4. Winkelhorst D, de Vos TW, Kamphuis MM, Porcelijn L, Lopriore E, Oepkes D, et al. HIP (HPA-screening in pregnancy) study: protocol of a nationwide, prospective and observational study to assess incidence and natural history of fetal/neonatal alloimmune thrombocytopenia and identifying pregnancies at risk. BMJ open. 2020;10(7):e034071.

5. Gafni A, Blanchette VS. Screening for neonatal alloimmune thrombocytopenia: an economic perspective. Current studies in hematology and blood transfusion. 1988(54):140-7.

6. Durand-Zaleski I, Schlegel N, Blum-Boisgard C, Uzan S, Dreyfus M, Kaplan C. Screening primiparous women and newborns for fetal/neonatal alloimmune thrombocytopenia: a prospective comparison of effectiveness and costs. Immune Thrombocytopenia Working Group. American journal of perinatology. 1996;13(7):423-31.

7. Turner ML, Bessos H, Fagge T, Harkness M, Rentoul F, Seymour J, et al. Prospective epidemiologic study of the outcome and cost-effectiveness of antenatal screening to detect neonatal alloimmune thrombocytopenia due to anti-HPA-1a. Transfusion. 2005;45(12):1945-56.

8. Killie MK, Kjeldsen-Kragh J, Husebekk A, Skogen B, Olsen JA, Kristiansen IS. Cost-effectiveness of antenatal screening for neonatal alloimmune thrombocytopenia. BJOG : an international journal of obstetrics and gynaecology. 2007;114(5):588-95.

9. Tiller H, Kamphuis MM, Flodmark O, Papadogiannakis N, David AL, Sainio S, et al. Fetal intracranial haemorrhages caused by fetal and neonatal alloimmune thrombocytopenia: an observational cohort study of 43 cases from an international multicentre registry. BMJ open. 2013;3(3).

10. Williamson LM, Hackett G, Rennie J, Palmer CR, Maciver C, Hadfield R, et al. The natural history of fetomaternal alloimmunization to the platelet-specific antigen HPA-1a (PlA1, Zwa) as determined by antenatal screening. Blood. 1998;92(7):2280-7.

11. Kjeldsen-Kragh J, Killie MK, Tomter G, Golebiowska E, Randen I, Hauge R, et al. A screening and intervention program aimed to reduce mortality and serious morbidity associated with severe neonatal alloimmune thrombocytopenia. Blood. 2007;110(3):833-9.

12. Versteegh M, Knies S, Brouwer W. From Good to Better: New Dutch Guidelines for Economic Evaluations in Healthcare. PharmacoEconomics. 2016;34(11):1071-4.

13. van der Ploeg CPB, Oomen P, van Lent M. Prenatale Screening Infectieziekten en Erytrocytenimmunisatie (PSIE). 2021.

14. Winkelhorst D, Kamphuis MM, Steggerda SJ, Rijken M, Oepkes D, Lopriore E, et al. Perinatal Outcome and Long-Term Neurodevelopment after Intracranial Haemorrhage due to Fetal and Neonatal Alloimmune Thrombocytopenia. Fetal diagnosis and therapy. 2019;45(3):184-91.

15. Tiller H, Killie MK, Skogen B, Øian P, Husebekk A. Neonatal alloimmune thrombocytopenia in Norway: poor detection rate with nonscreening versus a general screening programme. BJOG : an international journal of obstetrics and gynaecology. 2009;116(4):594-8.

16. de Vos TW, Winkelhorst D, Porcelijn L, Beaufort M, Oldert G, van der Bom JG, et al. The natural history of human platelet antigen (HPA)-1a alloimmunised pregnancies: a prospective observational cohort study. manuscript is currently under review ed2022.

17. Kamphuis MM, Paridaans N, Porcelijn L, De Haas M, Van Der Schoot CE, Brand A, et al. Screening in pregnancy for fetal or neonatal alloimmune thrombocytopenia: systematic review. BJOG : an international journal of obstetrics and gynaecology. 2010;117(11):1335-43.

18. de Vos TW, Porcelijn L, Hofstede-van Egmond S, Pajkrt E, Oepkes D, Lopriore E, et al. Clinical characteristics of human platelet antigen (HPA)-1a and HPA-5b alloimmunised pregnancies and the association between platelet HPA-5b antibodies and symptomatic fetal neonatal alloimmune thrombocytopenia. British journal of haematology. 2021;195(4):595-603.

19. de Vos TW, Winkelhorst D, Árnadóttir V, van der Bom JG, Canals Surís C, Caram-Deelder C, et al. Postnatal treatment for children with fetal and neonatal alloimmune thrombocytopenia: a multicentre, retrospective, cohort study. The Lancet Haematology. 2022;9(11):e844-e53.

20. de Vos TW, de Haas M, Oepkes D, Tan R, van der Schoot CE, Steggerda SJ, et al. Long-term neurodevelopmental outcome in children after antenatal intravenous immune globulin treatment in fetal and neonatal alloimmune thrombocytopenia. American journal of obstetrics and gynecology. 2022.

21. Kjeldsen-Kragh J, Fergusson DA, Kjaer M, Lieberman L, Greinacher A, Murphy MF, et al. Fetal/neonatal alloimmune thrombocytopenia: a systematic review of impact of HLA-DRB3\*01:01 on fetal/neonatal outcome. Blood advances. 2020;4(14):3368-77.

22. Killie MK, Husebekk A, Kjeldsen-Kragh J, Skogen B. A prospective study of maternal anti-HPA 1a antibody level as a potential predictor of alloimmune thrombocytopenia in the newborn. Haematologica. 2008;93(6):870-7.

23. Gleadall NS, Veldhuisen B, Gollub J, Butterworth AS, Ord J, Penkett CJ, et al. Development and validation of a universal blood donor genotyping platform: a multinational prospective study. Blood advances. 2020;4(15):3495-506.

24. Timmer TC, de Groot R, Habets K, Merz EM, Prinsze FJ, Atsma F, et al. Donor InSight: characteristics and representativeness of a Dutch cohort study on blood and plasma donors. Vox sanguinis. 2019;114(2):117-28.

25. Diagnostics S. Foetale HPA-1a genotypering in maternaal plasma - Diagnostische testen 2022 [Available from: <https://www.sanquin.org/nl/producten-en-diensten/diagnostiek/diagnostische-testen/index/name/t012-foetale-hpa-1a-genotypering-in-maternaal-plasma>.

26. Diagnostics S. Trombocytopenie van de pasgeborene (of foetus) 2022 [cited 2022 19-06-2022]. Available from: <https://www.sanquin.org/nl/producten-en-diensten/diagnostiek/diagnostische-testen/index/name/t911-trombocytopenie-van-de-pasgeborene-of-foetus>.

27. Nederland Z. Medicijnkosten.nl [translated into English: medicinecosts.nl] 2022 [Available from: <https://www.medicijnkosten.nl/>.

28. Kanters TA, Bouwmans CAM, van der Linden N, Tan SS, Hakkaart-van Roijen L. Update of the Dutch manual for costing studies in health care. PloS one. 2017;12(11):e0187477.

29. LUMC. Passanten prijslijst DBC-zorgproducten en overige zorgproducten jaar 2021.

30. Liem SM, van Baaren GJ, Delemarre FM, Evers IM, Kleiverda G, van Loon AJ, et al. Economic analysis of use of pessary to prevent preterm birth in women with multiple pregnancy (ProTWIN trial). Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2014;44(3):338-45.

31. Kruse M, Michelsen SI, Flachs EM, Brønnum-Hansen H, Madsen M, Uldall P. Lifetime costs of cerebral palsy. Developmental medicine and child neurology. 2009;51(8):622-8.

32. Mitchell LA, Hirdes J, Poss JW, Slegers-Boyd C, Caldarelli H, Martin L. Informal caregivers of clients with neurological conditions: profiles, patterns and risk factors for distress from a home care prevalence study. BMC health services research. 2015;15:350.

33. Jarl J, Alriksson-Schmidt A, Rodby-Bousquet E. Health-related quality of life in adults with cerebral palsy living in Sweden and relation to demographic and disability-specific factors. Disability and health journal. 2019;12(3):460-6.

34. Macedo AF, Ramos PL, Hernandez-Moreno L, Cima J, Baptista AMG, Marques AP, et al. Visual and health outcomes, measured with the activity inventory and the EQ-5D, in visual impairment. Acta ophthalmologica. 2017;95(8):e783-e91.

35. Langelaan M, de Boer MR, van Nispen RM, Wouters B, Moll AC, van Rens GH. Impact of visual impairment on quality of life: a comparison with quality of life in the general population and with other chronic conditions. Ophthalmic epidemiology. 2007;14(3):119-26.

36. Kirkham FJ, Vigevano F, Raspall-Chaure M, Wilken B, Lee D, Le Reun C, et al. Health-related quality of life and the burden of prolonged seizures in noninstitutionalized children with epilepsy. Epilepsy & behavior : E&B. 2020;102:106340.

37. Janssen MF, Szende A, Cabases J, Ramos-Goñi JM, Vilagut G, König HH. Population norms for the EQ-5D-3L: a cross-country analysis of population surveys for 20 countries. The European journal of health economics : HEPAC : health economics in prevention and care. 2019;20(2):205-16.

38. Strauss D, Brooks J, Rosenbloom L, Shavelle R. Life expectancy in cerebral palsy: an update. Developmental medicine and child neurology. 2008;50(7):487-93.

39. Statline C. Levensverwachting leeftijd in jaren 2022 [cited 2022 19-06-2022]. Available from: <https://opendata.cbs.nl/statline/#/CBS/nl/dataset/37360ned/table?fromstatweb>.

40. Maslanka K, Guz K, Zupanska B. Antenatal screening of unselected pregnant women for HPA-1a antigen, antibody and alloimmune thrombocytopenia. Vox sanguinis. 2003;85(4):326-7.

41. Blanchette VS, Chen L, de Friedberg ZS, Hogan VA, Trudel E, Décary F. Alloimmunization to the PlA1 platelet antigen: results of a prospective study. British journal of haematology. 1990;74(2):209-15.

42. Bessos H, Killie MK, Seghatchian J, Skogen B, Urbaniak SJ. The relationship of anti-HPA-1a amount to severity of neonatal alloimmune thrombocytopenia - Where does it stand? Transfusion and apheresis science : official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis. 2009;40(2):75-8.

43. Fretheim A. Cost-effectiveness analysis of screening for neonatal alloimmune thrombocytopenia was based on invalid assumption. BJOG : an international journal of obstetrics and gynaecology. 2008;115(3):412-3; author reply 3-4; discussion 4.

44. Cameron D, Ubels J, Norström F. On what basis are medical cost-effectiveness thresholds set? Clashing opinions and an absence of data: a systematic review. Global health action. 2018;11(1):1447828.

45. Bussel JB, Vander Haar EL, Berkowitz RL. New developments in fetal and neonatal alloimmune thrombocytopenia. American journal of obstetrics and gynecology. 2021;225(2):120-7.

46. Kapur R, Kustiawan I, Vestrheim A, Koeleman CA, Visser R, Einarsdottir HK, et al. A prominent lack of IgG1-Fc fucosylation of platelet alloantibodies in pregnancy. Blood. 2014;123(4):471-80.

47. Santoso S, Wihadmadyatami H, Bakchoul T, Werth S, Al-Fakhri N, Bein G, et al. Antiendothelial αvβ3 Antibodies Are a Major Cause of Intracranial Bleeding in Fetal/Neonatal Alloimmune Thrombocytopenia. Arteriosclerosis, thrombosis, and vascular biology. 2016;36(8):1517-24.

48. Chitty LS, Finning K, Wade A, Soothill P, Martin B, Oxenford K, et al. Diagnostic accuracy of routine antenatal determination of fetal RHD status across gestation: population based cohort study. BMJ (Clinical research ed). 2014;349:g5243.

49. Winkelhorst D, Porcelijn L, Muizelaar E, Oldert G, Huiskes E, van der Schoot CE. Fast and low-cost direct ELISA for high-throughput serological HPA-1a typing. Transfusion. 2019;59(9):2989-96.

50. Tariefbeschikking. Tariefbeschikking 2022 [Available from: <http://www.pns.nl/documenten/tariefbeschikking-2022>.