Management of RhD-negative Pregnancies: Do New Technologies Make a Difference?

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Abstract

In this work we are modelling the management process of RhD negative pregnancies. The current practice is based on the use of anti-D as a prophylactic measure to prevent sensitisations (development of antibodies by the mother against fetal blood type). RhD NIPD is a diagnostics test designed to improve management of RhD negative pregnancies and to make the usage of anti-D prophylaxis more efficient. Despite the latter benefit, the need for the RhD NIPD technology introduction into clinical practice at the population level is questionable. This test is a technology push product rather than a market-driven development and is characterised by high implementation costs and no clinical impact on the decrease of sensitisations and HDFN (haemolytic disease of fetus and newborn) cases in countries where antenatal anti-D is implemented. However, scientists argue the importance of this test in clinical practice.

We employ systems thinking and simulation modelling to assess the potential and the impact of this test. This work describes the development of a game simulator for clinicians and policymakers. We hope it will serve as a useful decision-making tool for evaluation of RhD NIPD adoption scenarios.

Background

Before 1970s, haemolytic disease of fetus and newborn (HDFN) was a major cause of perinatal morbidity and mortality [2]. This disease is characterised by blood group incompatibility between mother and fetus. HDFN can be caused by various types of incompatibilities, but RhD is the most frequent (more than 50% of cases). The problem arises only when an RhD negative mother carries an RhD positive fetus. During such pregnancy or during birth a woman might become sensitised (develop antibodies against D). After a woman is sensitised, all her following pregnancies might be at risk, as these antibodies may attack the developing fetus and cause HDFN.

The prevalence of RhD negativity in Caucasian population is between 15 and 17%, it is less in other populations and rare in Asians (<1%) [1]. Therefore, a large number of pregnancies were affected by sensitisations and HDFN in the past. After the introduction of anti-D prophylaxis [1], trend towards smaller families, improved maternal and neonatal care, and changes in racial composition in the Western world, rhesus disease has been taken under control. However, ~10-12 deaths due to HDFN and ~600 of sensitizations continue to occur each year in the UK [2]. Other European countries show similar indicators.
(proportional to the population size) for HDFN and sensitisations. However, countries (Germany, France, USA, Australia, Spain) that adopted antenatal prophylaxis, in addition to postnatal, have fewer deaths and sensitisations than those which did not adopt or partially adopted antenatal prophylaxis (Italy, Poland, Austria1).

About 40% of RhD negative women carry an RhD negative fetus [2]. They are not at risk of sensitisations. Out of the remaining 60%, majority are not at risk either due to various reasons. One third of these women are actually non-responders, they do not respond to antigen challenge by producing anti-D. Furthermore, among the remaining every 5th is protected from sensitization by ABO-blood group incompatibility [3]. However, no antenatal tests for the above causes exist, thus it is considered that all women carrying an RhD positive child are at risk of sensitisation and should receive anti-D.

New Technology Description

RhD NIPD test has been in development since late 1990s and is designed to identify the fetal \textit{RHD} type by studying free fetal DNA extracted from maternal plasma of RhD negative women. It is recommended that blood is drawn for this test around the 26th week of pregnancy, which gives sufficient time to administer antenatal anti-D prophylaxis after it is determined that the woman is carrying an RhD positive fetus. However, there are a number of studies showing that fetal blood group can be determined as early as the 10th week of pregnancy [4,5]. A very high detection rate (99-100%) of fetal RhD type has been reported [6,7]. To date majority of studies present results based on a small sample size however, the Dutch study obtained promising results on about 2,500 samples [8]. A few other large clinical trials are currently in progress in Germany, UK, Spain, and France. The outcomes of these studies should provide valuable information for making an informed decision about bringing this technology into clinical practice. The Dutch study has reported that the test works equally well across ethnic groups however, some studies suggest that basic kits are not sensitive enough to be applied at the population level due to different gene expression in different populations [9].

As of now, there are no population level studies indicating the 100% sensitivity of RhD NIPD test and the large number of variations in the \textit{RHD} gene makes it difficult for primers to detect 100% of RhD variants using currently available technologies. Thus, a small percentage of misdiagnoses are unavoidable. The main disadvantage is linked to \textit{false negatives}, with the associated risk that a small number of women may not receive antenatal (and even postnatal\textsuperscript{2}) anti-D, even though the fetal-maternal gene set-up would require it.

Today antenatal anti-D is given to RhD negative pregnant women regardless of whether they are carrying a positive or a negative fetus. The assumption is that the introduction of

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1 In many countries no centralised antenatal anti-D program exists, but some women choose to buy anti-D in pharmacies and bring to their physicians for administration.
2 Clinicians believe that if RhD NIPD is implemented at the population level, cord blood testing determining newborn’s blood group will be voided (as costly and redundant procedure). Hence, if the fetus has been misdiagnosed in utero, it is unlikely blood group testing will take place after birth.
RhD NIPD technology to the market and its application at the population level will decrease the use of anti-D prophylaxis by making it available only to women pregnant with RhD positive fetuses. In turn, it will decrease the amount of money spent on the management of RhD negative pregnancies and allow the donor blood to be saved for other valuable products. RhD NIPD test is also very useful for already sensitised women. If it is determined that a sensitised woman is carrying an RhD negative child, there will be no need to monitor her as those sensitised women who carry an RhD positive child. Anti-D is not given to already sensitised women, but prenatal procedures for monitoring such pregnancies can be very costly.

RhD NIPD will not have any impact on further reduction of sensitisations or HDFN cases if it is offered in systems with fully adopted antenatal anti-D prophylaxis. However, in countries where antenatal anti-D prophylaxis has not been introduced, RhD NIPD technology will increase the usage of anti-D (antenatal) up to 60% and thus help decrease sensitisations and HDFN cases as a result.

This new technology presents a number of benefits but it is not a panacea for perfectly managing all RhD negative pregnancies. RhD NIPD is a very important development in prenatal diagnostics as it can serve as a basis for the development of other tests (non-invasive detection of X-linked and chromosome disorders), but it is one of a few technologies which implementation might be considered at the population level. Thus, all pros and cons of this technology must be carefully evaluated to assess its socio-economic potential. In addition to economic modelling studies, which are being carried out in the number of European countries, we decided to use systems thinking and simulation modelling approach to study this problem and create a game simulator for policymakers.

**Problem Description**

According to most clinicians, RhD negative pregnancies are easily managed these days and sharply decreased cases of sensitisation and HDFN remove a great share of attention from this subject. Based on our survey results, clinicians are not expressing the need for the new technology and are happy with the performance of anti-D [2]. But is it enough to conclude that pregnancies of RhD negative women no longer pose a problem? If the need for the technology is not market driven, can we conclude that technology is not valuable?

In contrast to the clinicians’ point of view, the scientific and commercial communities are more optimistic about bringing the RhD NIPD test to public. Many European laboratories have been involved in the development of this test and there are many people interested in seeing this technology implemented. The lobbying for the importance and necessity of this test promises to be strong. Currently, Sequenom, Inc in the United States holds exclusive licensing for RhD NIPD in the US and for other non-invasive tests based on the same technology in most countries around the world. L’Institut de Biotechnologies Jacques Boy in France holds exclusive rights to RhD NIPD in Europe. Hence, either all European countries will have to use the French kit or other producers of kits need to negotiate royalty payments to L’Institut de Biotechnologies Jacques Boy. This is a disappointing fact to
many European laboratories which have been working on the kit development for a number of years.

As the introduction of RhD NIPD technology is concerned, a few interesting questions arise. Which decision each country is going to make regarding RhD NIPD? Where is it going to become a routine test? Where is it going to be used for sensitised pregnancies only? Where is it going to help introduce antenatal prophylaxis? Which countries are going to refuse the implementation of this test? On what grounds? Will the introduction of this technology result in any paybacks? What are the long-term benefits? Who will dominate the market?

The main problem of this technology is that the implementation at the population level carries very unclear economic consequences and limited clinical benefits. RhD NIPD’s potential of reducing the usage of anti-D and better managing sensitised pregnancies is convincing however, from the clinical point of view, this test is not fixing the problem of sensitisations and HDFN. The introduction of anti-D prophylaxis in the 1960s was a major break through in the field and it significantly reduced fetal and neonatal mortality and prevented many sensitisations [1]. Introduction of antenatal anti-D further decreased the number of sensitisations and HDFN cases [2]. RhD NIPD does not promise much improvement in that front especially in systems where antenatal anti-D prophylaxis is implemented at the population level.

Approximate costs of the test have been calculated and suggested to be similar to one dosage of anti-D, which means that if, by using RhD NIPD we can save on 40% of anti-D, this money can partially pay for the new test which would be given to 100% of RhD negative women. The management will change, however clinical results will remain the same. Systems which decide to introduce RhD NIPD, have to come up with significant working capital to offer the test in their country, as well as additional capital to start offering antenatal anti-D to women who require it.

As anti-D is concerned, there are also a number of issues to consider:
- overuse of anti-D (majority of RhD negative women are not at risk of sensitisation and do not require anti-D) [11];
- anti-D is a blood product (risk of infections, adverse reaction to the product, possible effect on fetuses is reportedly very low (0.54%), but cannot be ruled out) [11];
- high cost of anti-D [1];
- production of anti-D: often healthy RhD negative male donors are used who are injected with RhD positive blood which carries along a small risk of infections or adverse reactions [11].

The population level demand for RhD NIPD could be great (about 400,000 tests annually in the US and about 115,000 tests in the UK). So, if such technology is available, is it ethical not to offer it to women and continue to blindly give them anti-D? While in some countries
this question might be easily resolved by the out-of-pocket payments or insurance companies, in Europe with centralised public healthcare systems such decision should be made at the policy level.

Finally, the test is 99.4% accurate, but the kit standardisation is still in progress, and it is unclear whether the test will perform equally well in all ethnic groups.

**Modelling Process**

There are a few reasons why we decided to use system dynamics as a modelling tool for the above described problem. First of all, we have very limited data and the problem can be easily described by a number of aggregate parameters. We are not interested in modelling condition of or service provided to each woman, but we are interested in tracing the flow of RhD negative pregnancies through a number of years and tracking how different management policies affect outcomes. Second, pregnancy is an interesting state to model using system dynamics, as it easily integrates into the population growth models. Third, we are interested in finding new potential insights while modelling the problem using system thinking. Finally, the ultimate goal is to create a simulation game for policymakers, which they can use to enter their national data and evaluate the impact of the NIPD test in their respective healthcare systems.

Preliminary simulation model was developed using systems thinking approach. Figure 1 shows the causal loop diagram which depicts the impacts of the two technologies: antenatal anti-D and NIPD on other parameters.

**Figure 1. Causal Loop Diagram**
Antenatal anti-D decreases sensitisations. As sensitisations lead to HDFN, the prevalence of the latter requires a better use of anti-D. Since anti-D is a blood product, it may result in transmission of infection. It is an important concern which triggers the need for a new technology that can optimize the use of anti-D. This new technology is RhD NIPD. It narrows down the use of antenatal anti-D only to women who carry RhD positive babies and eliminates the need for an invasive test such as amniocentesis for sensitised women. The NIPD test also decreases the number of post-birth cord blood tests. Amniocentesis is a procedure associated with miscarriages. In order to avoid the latter there is a need for a technology which can replace an invasive test (amnio).

Based on the above presented causal loop diagram, the advantages of NIPD seem to be obvious however, if we introduce the reality of the clinical situation, it becomes clear that some of these benefits, while important, are marginal. Invasive test is given only to a small percentage of already sensitised women (~600 in the UK). Cord blood test which can be replaced by NIPD costs ~10 times less than the NIPD test. The only real way to remove the risk of infection from anti-D is not to limit its use but to replace the blood product with a recombinant product (in development). Most importantly, it is anti-D that in the end prevents sensitisations and not NIPD. The RhD NIPD test has a high clinical value for testing sensitised pregnancies and it has an interesting application for the rest of RhD negative pregnancies however, financial implications need to be weighed against the clinical benefits. Thus, we are developing a simulation model to better understand the latter in different healthcare systems.

Powersim software was used for modelling and simulation. Figure 2 presents the stock and flow structure. While for this model it is unnecessary to include population and total pregnancies stocks, we chose to do so in order to make the game interface more user-friendly. Most policymakers will have on hand the actual population data and prevalence rates rather than fractions thus, it would be easier for them to enter all the necessary parameters to simulate new technology uptake within their health systems.

The main feedback loops are the repeated pregnancies after adverse events (miscarriages, abortions, stillbirths) and births. If for a woman it is a final pregnancy, she exits the system however, all women who become pregnant again represent the stock significantly influencing the pools of Non-sensitised and Sensitised pregnant women.

We chose the time horizon of 10 years. It is sufficient to implement the new technology in the most economically efficient way and see how the dynamics of sensitisations and HDFN cases is affected over time.

Only women who already have been pregnant can add to the stock of Sensitised pregnancies. A small share of women from the Non-sensitised stock in the consecutive pregnancy transfers to the Sensitised stock. Also, the inflow into the Sensitised stock comes from women who had adverse events in pregnancy and all women who previously were in the Sensitised stock.
Figure 2. Stock and Flow Structure. Management of RhD-negative Pregnancies.
Figure 3 depicts another part of the stock and flow diagram. It traces the number of procedures given to RhD negative women (postnatal anti-D, antenatal-anti-D, anti-D after adverse event, cord blood test and NIPD test) and costs of these procedures. With this model we can trace the usage of anti-D in the given country, expenditures on specific interventions and combined expenditures. At later stages we plan to expand this model to include recombinant (non-blood based product) anti-D into the system.

Figure 3. Stock and Flow Structure. The Economics of RhD Negative Pregnancies.
Parameter Estimation

The economic modelling is being undertaken in five countries: Germany, India, the Netherlands, UK, and France. As of now, we have results of the large clinical trial (~2,500 samples) of RhD NIPD in the Netherlands. The German trial (~1,000 samples) will be finished in September 2007, the UK trial (~5,000 samples) is underway, as well as the Scottish trial (~1,000 samples) [2]. Results of these studies should provide us with valuable information on the performance of the automated technology and sensitivity and specificity rates. Cross-comparison of such information would be very interesting in order to determine the best technologies on the market, throughput, costs, associated with the test, and of course, the accuracy.

One of the main activities of the economic modelling exercise is to establish the cost of the RhD NIPD test. Economists in Germany, France, Spain, and the Netherlands are devising their estimates. We have been working on establishing the RhD NIPD cost for the UK. The latter depends on a number of parameters; specifically: type of equipment used, throughput, royalties on associated patents, overhead costs, blood sample, transportation, etc. If the test is done in the UK laboratories with high throughput (~880/samples per week per lab), the cost per sample would be ~£13. However, this scenario is not possible. The UK either needs to negotiate royalty payments with L’Institut de Biotechnologies Jacques Boy, which would significantly increase the cost of the test, or use the patented French kit, which is currently priced at ~€38/sample, but includes only controls and primers. Thus, the laboratory using the kit needs to add equipment, labor, assay costs, and other expenses. If French kits are used, the cost of the test is about £40. In our calculations final cost does not include overhead costs, educational or training materials for physicians, midwives, nurses, and/or lab technicians.

Based on the results from other countries, the price of £40/test seems to be quite an accurate estimate at this stage and it is unlikely it could be brought down even using the economies of scale, unless UK negotiates low royalty payments. This uncertainty we cannot build into the model at this stage.

We have collected data on sources, costs, and usage of anti-D in different countries. Most countries using antenatal anti-D offer 1 dose between weeks 28 and 30 however, there are countries offering two doses (UK, Australia) during weeks 28 and 32 [1]. Dosages vary as well as costs per dose. Different products are being used. Anti-D can be local or imported. Often, if anti-D is produced in the country, plasma can be imported. These differences influence the cost of anti-D. The average cost around Europe is about ~€62/dose [2]. We also tried to collect information on recombinant anti-D, which is in development, and may enter the market in a few years. It is an artificial blood product which promises to be safe but more expensive.

The administration of postnatal anti-D to RhD negative women giving birth to RhD positive babies is estimated to be close to 100%. Very limited data exists on abortions and
other adverse events in RhD negative women and administration of anti-D after an adverse event. However, we are attempting to make the necessary estimates.

We collected most of the necessary demographic data such as number of RhD negative pregnancies per year, ethnic composition in the country, and availability of antenatal anti-D. This also includes data on the number of sensitisation cases annually as well as HDFN cases. Table 1 presents data (main parameters only) for the UK which has been used in the model. All of these parameters are constants which can be changed by the user of the simulator to input proper values for another healthcare system or adjust the values for the UK. We used the adoption curve to reflect the 80% adoption of the RhD NIPD technology by the year 2015. Policymakers have an option of setting their own adoption level of RhD NIPD technology for their countries and tracing the impact of such intervention.

Table 1. UK data on the management of RhD negative pregnancies (2006 estimates)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>61,000,000</td>
</tr>
<tr>
<td>UK birth rate</td>
<td>10.67/1000 population</td>
</tr>
<tr>
<td>RhD negativity</td>
<td>~16%</td>
</tr>
<tr>
<td>Total number of RhD negative pregnancies/year</td>
<td>~115,000</td>
</tr>
<tr>
<td>Sensitisations/year</td>
<td>~600</td>
</tr>
<tr>
<td>HDFN cases/year</td>
<td>~500</td>
</tr>
<tr>
<td>Anti-D cost</td>
<td>£27/dose</td>
</tr>
<tr>
<td>Anti-D policy</td>
<td>2 antenatal doses, 1 postnatal</td>
</tr>
<tr>
<td>Antenatal anti-D coverage</td>
<td>~70%</td>
</tr>
<tr>
<td>Postnatal anti-D coverage</td>
<td>~100%</td>
</tr>
<tr>
<td>Cord-blood test cost</td>
<td>£3</td>
</tr>
<tr>
<td>RhD NIPD test cost</td>
<td>~£40</td>
</tr>
</tbody>
</table>

**Results**

Our preliminary calculations show that the gradual introduction of RhD NIPD technology into the healthcare system is less financially straining, but the benefits of such introduction are less clear since a large percentage of women will continue to receive anti-D unnecessarily and those women who might need anti-D will not be offered it antenatally at all due to the lack of services in their area.

The Dutch study reports that RhD NIPD could possibly be marginally cost-effective (about €100,000 in savings) in the Netherlands. However, the economists make a clear statement that the small variation in the cost of the test may easily turn savings into losses. Healthcare systems within Europe and around the world differ significantly, thus a technology which seems cost-effective in one country, might be prohibitively expensive in another.
If we run the simulation model for the UK using the data from Table 1, we can see (Figure 4) that the increase in the number of RhD NIPD procedures (tests) leads to the decrease in the number of anti-D dosages (injections). This is a positive dynamics, but financially it is interpreted differently if we examine Figure 5.

**Figure 4. Anti-D injections and RhD NIPD tests**

Annual costs for anti-D will be gradually decreasing as RhD NIPD tests (at ~£40/test) are being used more widely but the annual costs for RhD NIPD are increasing significantly over time. Now the healthcare system has to pay for both interventions. The blue line shows the combined expenditure which will be needed annually to manage RhD negative non-sensitised pregnancies. Expenditure of close to £7 million by the year 2013 (inflation not included) is a significant increase for the NHS budget, considering the new technology brings very limited or no clinical benefit.

**Figure 5 Economic impact of RhD NIPD technology.**

RhD NIPD technology has not demonstrated a potential in lowering the number of sensitisations or HDFN cases. Figure 6 depicts two runs showing identical growth in sensitisations in the UK over the 10 year period. This growth is due to population growth and gradually increasing number of pregnancies. In both scenarios antenatal anti-D coverage is at 70% and postnatal anti-D coverage is at 100%, however, in the current run,
the adoption of RhD NIPD was changed from gradual increase to 80% to constant 20% adoption level.

**Figure 6. Sensitisations**

![Graph showing sensitisation levels over time.](image)

We expect that for some countries the model will demonstrate marginal savings while for others it will help estimate required expenditures for future management of RhD negative pregnancies.

**Limitations**

The current model reflects the basic population and financial flows. The model needs to be expanded to include other interventions which may affect the management of RhD negative pregnancies: recombinant anti-D, procedures for sensitised women. Not all stakeholders have evaluated the model so far and necessary adjustments will be made based on their recommendations. Additional work needs to be done to validate the model before the game simulator is distributed to policymakers in other countries.

We believe that RhD NIPD technology will have a beneficial socio-economic impact on management of sensitised pregnancies. This model needs to be expanded to include more parameters such as the amniocentesis procedure and cost of management of sensitised pregnancies.

**Conclusions**

System dynamics approach is an efficient way to analyze a myriad of scenarios which are associated with the implementation of the RhD NIPD technology. It is also the most economic way to conduct the study rather than subcontract with health economists in different healthcare systems to do their own calculations.

This is the work in progress and the simulator will be undergoing necessary changes in the near future to take into consideration the feedback from the stakeholders however, we already now anticipate that it is shaping up into a useful tool which will help promote
harmonization of policymaking across EU states as RhD NIPD technology is concerned. The simulator can be used by any country regardless of their current anti-D policy.

We suppose that RhD NIPD can serve as a pioneer technology in the development of a battery of NIPD tests for X-linked disorders, chromosome abnormalities, etc. Initially, the idea of developing non-invasive prenatal diagnostic technologies based on the evaluation of fetal DNA extracted from maternal blood was driven by the desire to replace currently used invasive technologies (amniocentesis, CVS). The latter are associated with miscarriage rate of 0.5-2%, thus it would be very useful to be able to diagnose fetuses without putting women at risk. However, invasive tests are not used to determine fetal blood type in non-sensitised pregnancies, so such major benefit as the replacement of invasive procedure is not going to be addressed by the introduction of the RhD NIPD test.

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References
