Neonatal jaundice

Health Economics Appendices

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Health Economics Appendix

Part i
Economic evaluation of alternative testing strategies in the detection of hyperbilirubinaemia

Introduction

Jaundice (a yellow colouration of the skin) is caused by hyperbilirubinaemia and is common in the newborn baby. Rarely, if bilirubin levels are sufficiently high, bilirubin can cross the blood brain barrier and cause a brain damaging condition called kernicterus, a lifelong disabling neurological problem with manifestations of cerebral palsy and deafness with high costs of care. Hyperbilirubinaemia can also cause deafness without cerebral palsy and other adverse outcomes have been described. Levels of bilirubin can be controlled with phototherapy, but the only way to reduce very high levels in an emergency is with an exchange transfusion. This is a costly intensive care procedure which carries a mortality risk \(^1\). Phototherapy is generally effective in controlling bilirubin levels, preventing them from rising to a level at which kernicterus occurs, hence some clinicians have called for kernicterus to be classified as a “never event”. There is some evidence to show that cases of kernicterus have risen recently, probably a result of earlier discharge following childbirth \(^2,3\).

Current practice in England and Wales is varied but the GDG estimate that less than 10% of babies undergo specific testing of their bilirubin levels following visual examination. At present, babies who develop kernicterus often present late and with bilirubin levels already in the toxic range. The key to prevention of kernicterus is early detection of cases at a time when phototherapy can be effective. Any guideline recommendation which requires more widespread testing will have important resource implications for the NHS as well as requiring a change in practice in many places. Therefore the guideline recommendation regarding identification of cases by testing for hyperbilirubinaemia was highlighted by the GDG as an important priority for economic analysis. The NHS operates within resource constraints and a more intensive testing and treatment strategy can only
be justified if it represents a better use of scarce resources than could be obtained in some alternative use of those resources.
Literature review

A literature search was undertaken to assess the economic evidence base for strategies to prevent kernicterus in newborn babies. This initial search yielded 33 papers and the abstracts of these papers were read to exclude papers that were clearly not relevant. As a result of this initial screen, 5 papers were retrieved of which only one was identified as a relevant economic evaluation.

This was a US study which compared the cost-effectiveness of four strategies against current practice to prevent kernicterus in newborn infants. Incremental cost-effectiveness was undertaken using a decision analytic framework. The strategies were modelled for a population of healthy, term infants who were being discharged within 48 hours of an uncomplicated vaginal birth.

The strategies were: 1) current practice – physicians and nurses assess the need for serum bilirubin testing after delivery and prior to discharge based on a review of clinical history and physical exam, including visual inspection of skin colour. Clinical judgement and assessment of risk are used to determine the timing of follow-up. 2) Universal follow-up one to two days after early discharge, but in other respects similar to the first strategy. 3) Routine serum bilirubin testing prior to discharge with follow-up within two days of discharge if the bilirubin measurement is greater than the 40th percentile value on the nomogram. 4) Routine transcutaneous bilirubin testing prior to discharge with the percentile value on the nomogram developed by Bhuthani et al. guiding decisions about the need for serum bilirubin testing before discharge and subsequent follow-up. In strategies 2-4 the threshold for laboratory testing is lowered in recognition of the unreliability of visual estimation of bilirubin.

The authors estimated that with current practice 2.3% of infants would receive phototherapy compared with 8.1%, 5.6%, and 7.8% for strategies 2-4 respectively. The savings from an averted kernicterus case were assumed to be $921,000 USD (at 2003 prices). The authors assumed that strategies 2-4 would be equally effective at preventing kernicterus cases and their primary outcome was to estimate the cost per kernicterus case averted in each of those strategies with a relative risk reduction of 0.7, an assumption made in the absence of data.

The results suggested that routine serum bilirubin was the cheapest strategy at $5.75 million USD per case averted. Using transcutaneous bilirubin meters prior to discharge gave a cost per averted kernicterus case of $9.19 million USD. Universal screening was the most expensive strategy with a cost per case averted of $10.32 million USD. One way sensitivity analysis suggested that the magnitude of these costs were sensitive to incidence of kernicterus although this did not alter the ranking of the strategies in terms of costs. The authors concluded that their data suggested that it would be premature to implement large scale routine bilirubin screening.

However, there are often difficulties in generalising the result of an economic evaluation from one setting to another. In particular the US hospital charges seem unlikely to accurately reflect NHS costs and the costs of a kernicterus case may have been understated. Furthermore, the GDGs remit did not cover screening. Therefore, a de novo economic model was developed to reflect the UK context and to enable the GDG to consider cost-effectiveness issues in making their recommendations.

Background to the economic evaluation
Kernicterus is a largely preventable disease if severe hyperbilirubinaemia is identified early and promptly treated (using phototherapy or, for more acute cases, exchange transfusion). Therefore, early identification of raised (or rapidly rising) bilirubin levels is the key to reducing severe morbidity.

There are studies which demonstrate that more intensive monitoring reduces the need for exchange transfusions. Evidence from the United States reports that during the 1970s, kernicterus was practically eradicated, which was probably due to the liberal use of phototherapy. The disease re-emerged in the 1990s, largely among babies cared for in the home environment in the neonatal period often with limited medical supervision during the first week after birth. Kernicterus has fallen again in the US since the adoption of the 1994 AAP guidelines; estimates are that the rate has fallen from 5.1 per 100,000 in 1988 to 1.5 per 100,000.

In the UK, babies are discharged earlier and are monitored less often than in previous decades. Reduced contact with experienced midwives and reliance on intermittent visual examination to assess bilirubin levels may be one of the reasons for the failure to detect babies with significantly elevated serum bilirubin levels. A newborn baby might only be visited once by a midwife in the post natal period if there are no risk factors, although the norm is currently around two or three visits in the first week. Visual examination by a midwife to assess for jaundice during these post-natal visits is currently the standard of care, with a small proportion of these jaundiced children subjected to a total serum bilirubin blood test (TSB) based on clinical visual assessment of the level of bilirubin. This is known to be unreliable. There is strong evidence that visual examination alone cannot be used to assess the level of bilirubin in a baby (see chapter 5). The inaccuracy of visual assessment for the detection of bilirubin levels, particularly in babies with dark skin tones, is likely to be a major factor responsible for the late presentation of babies with significant hyperbilirubinaemia. Therefore a more reliable strategy for the detection of babies who require treatment with phototherapy may be required if it is cost-effective.

The cost of care of people with kernicterus throughout their lives runs to millions of pounds. If resources were invested in a testing strategy that was effective in reducing the number of cases of kernicterus annually by one case per year, it would be cost saving if the total annual cost of the strategy was less than the discounted lifetime cost of caring for one individual with the disease. Since kernicterus is a lifetime condition with poor
quality of life, the value that the NHS places on preventing a case of kernicterus is not only calculated as the cost saved by preventing the downstream costs but also the £20,000 per QALY over the lifetime of the condition. Clearly, if the intervention was more successful in preventing kernicterus, then more NHS resources could be used to identify hyperbilirubinaemia and still be cost-effective.

It seems plausible that a more intensive testing strategy could be clinically effective if it overcame the limitations of visual examination alone, thereby leading to better detection and treatment. Currently, there are two methods of testing: a total serum bilirubin blood test (TSB) and a transcutaneous bilirubinometer (TCB) which is a non-invasive test on the surface of the skin. TCB is not accurate above a threshold level of 250 micromol/L of bilirubin so that TSB testing is required in babies whose TCB is above this threshold level. Hence a strategy involving more bilirubin measurements could be based on TSB alone or TCB with TSB only required for those babies whose TCB level was higher than the threshold value. Current evidence does not favour one strategy over the other for the detection of babies with bilirubin levels under 250 micromols/L. That is, even though TSB is the gold standard test, both strategies when used correctly as part of a assessment and management process to test babies who are visibly jaundiced, would be equally effective at detecting hyperbilirubinaemia and preventing kernicterus. Both methods are in use in the NHS. The TSB can be analysed in hospital labs without the need for additional equipment. The TCB requires the purchase of hand held devices, sufficient for one to be available for each community midwife undertaking post natal visits on any particular day.

The economic evaluation was undertaken to determine the conditions under which increased testing would be cost-effective, and to explore which testing strategy would be cost-effective under different circumstances.

Method

In this analysis we evaluate the cost-effectiveness of moving from current practice to a more intensive test strategy in England and Wales subject to the limitations of the published evidence.

The following strategies are compared:

1. “Current practice”
   - A visual examination followed by TSB in 10% of visually jaundiced babies

2. TSB
• A TSB on all babies with a positive visual examination
3. TCB followed by TSB if positive TSB
• A TCB on all babies with a positive visual examination, with a TSB on those babies with a positive TCB

Visual examination has a high negative predictive value which means that babies who do not appear visually jaundiced are very unlikely to have clinically significant jaundice. However, visual examination has been shown to be unreliable in detecting the severity of hyperbilirubinaemia. Therefore, visual examination alone as a basis for detecting jaundice requiring phototherapy has poor sensitivity which may put jaundiced babies at a higher risk of developing kernicterus.

Detection of hyperbilirubinaemia requiring treatment or further monitoring can be better assessed using a transcutaneous bilirubin test (TCB) or a blood test to measure the total serum bilirubin levels (TSB). The TCB is done with a handheld device (e.g. Minolta JM103 or Bilicheck) which is simple to use and is placed on the baby’s skin. The TSB is the gold standard test but is more invasive and distressing to the baby since it requires a blood sample. Both tests can be carried out by the midwife during the home visit or in hospital if the baby hasn’t been discharged.

Diagnostic tests are usually evaluated according to their sensitivity and specificity and these characteristics can be used to generate probabilities in decision analytic models. Initially, we intended to compare the alternative strategies using such an approach. However, the decision making process in this context is far more complicated than that implied by the outcomes for a “two by two table”. Rather than the test result dividing the patient population neatly into positives and negatives for hyperbilirubinaemia, ‘raised bilirubin level’ is measured on a continuum from normal to severe disease and different test thresholds are used to stratify patients into groups requiring immediate treatment, further monitoring or transfer back to routine care. Decision making is affected implicitly in a Bayesian manner by the impact of the bilirubin level on the post-test probability of disease. The decision making is complicated further as a number of other factors, such as family history of jaundice, will also be taken into account. Furthermore, monitoring can occur at many points in time and this temporal aspect is important because thresholds for clinically significant jaundice change and the evidence base to track changes in diagnostic accuracy over the relevant time periods is lacking. Therefore, it was ultimately
decided that there was not sufficient published evidence to populate such a decision model. Furthermore, it was felt that the GDG would not be able to estimate the vast array of model parameters to reflect the actual micro decision-making process that occurs in actual clinical practice.

The GDG have set a higher bilirubin threshold as a basis for treatment and a lower bilirubin threshold for further monitoring. The rationale for this is to avoid unnecessary phototherapy (i.e. a high specificity or false positive rate in terms of treatment) whilst avoiding missed cases by continued monitoring in babies who have an intermediate bilirubin level (i.e. a high sensitivity or false negative rate in terms of monitoring). Whilst, the TCB is not thought to be reliable at high bilirubin levels (hence the need for TSB if TCB is positive) it is nevertheless thought to be accurate at the more intermediate levels.

The GDG opinion is that, using the thresholds defined in this guideline, either method of testing would be effective in detecting hyperbilirubinaemia and avoiding new cases of kernicterus. Therefore, the cost-effective strategy was estimated using a cost minimisation approach which assumes no difference in effectiveness between testing strategies. As noted earlier, there is insufficient evidence to estimate the incremental benefit of moving from “current practice” to a more intensive testing regime, although evidence on the limitations of visual examination suggests that some benefit is likely. Therefore, threshold analyses were undertaken to determine the number of kernicterus cases that a more intensive testing approach would have to avert in order for this to be considered cost-effective.

**Model parameters and assumptions**

The cost analysis was undertaken from the perspective of the NHS and personal social services which is in accordance with the NICE guidelines manual (http://www.nice.org.uk/media/5F2/44/The_guidelines_manual_2009_-_All_chapters.pdf). The costs were estimated using a bottom-up or “ingredients” approach which involves detailing the physical quantity of resources used in providing treatment alongside the unit cost of those resources. From this it is possible to estimate the total cost of treatment.

It was assumed that visual examination is undertaken in the first instance in all strategies. In the “current practice” strategy it was additionally assumed that visual examination is used to determine the severity of hyperbilirubinaemia with a proportion of these having a TSB blood test as a precursor to possible phototherapy. No cost has been applied to the
visual examination as it is assumed this would occur as part of the standard home visit carried out by a midwife or as part of standard hospital care if the baby had not been discharged.

The population characteristics for this analysis are shown in Table B.1. Economic parameters used in the assessment of cost benefit (other than the costs of the test strategies) are shown in Table B.2. It should be noted that the base case values for the cost and QALY loss of a kernicterus case should not be considered point estimates in a conventional sense. Considerable uncertainty surrounds both values and therefore, as part of sensitivity analysis, both are varied simultaneously to derive a cost-effectiveness threshold across a wide combination of values.

The base case estimate of the lifetime cost of kernicterus is based on a legal settlement and, as such, may include costs over and above those which are deemed relevant for the perspective used by NICE in economic evaluation. A US study used mean lifetime direct and indirect costs of cerebral palsy as a proxy for kernicterus costs and as a result used a cost of $921,000 US dollars (at 2003 prices). However, this method may underestimate the costs as kernicterus is associated with severe cerebral palsy. Also, untreated hyperbilirubinaemia can also cause hearing loss without cerebral palsy with a need for cochlear implants and these potential cost savings are not explicitly considered within the model. The base case QALY loss of a kernicterus case can be considered as an upper bound estimate as it is based on assuming a health state that is as bad as death.

<table>
<thead>
<tr>
<th>Item</th>
<th>Value</th>
<th>Source</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Births</td>
<td>690,000</td>
<td>ONS (2008)</td>
<td>Based on 2007 births</td>
</tr>
<tr>
<td>Babies identified as jaundiced on visual exam</td>
<td>60%</td>
<td>GDG</td>
<td></td>
</tr>
</tbody>
</table>
Babies currently tested for jaundice on basis of visual exam

<table>
<thead>
<tr>
<th>Item</th>
<th>Value</th>
<th>Sensitivity Analysis</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kernicterus case</td>
<td>£5.5 million</td>
<td>£0 - £10 million</td>
<td>JMW Clinical Negligence Solicitors <a href="http://www.jmw.co.uk/kernicterus_bilirubinaemia">http://www.jmw.co.uk/kernicterus_bilirubinaemia</a></td>
</tr>
<tr>
<td>Discount rate</td>
<td>3.5%</td>
<td>NICE Guidelines Manual (2009)</td>
<td>Both costs and QALYs are discounted</td>
</tr>
<tr>
<td>QALY gained per kernicterus case avoided</td>
<td>25</td>
<td>0 – 25</td>
<td>Calculation</td>
</tr>
</tbody>
</table>

The resource ‘ingredients’ and their unit costs for TSB and TCB are shown in Table B.3 and Table B.4 respectively. The resource items include any the additional staff time required to undertake a test as part of a routine post natal visit. It also includes equipment costs and consumables, those resources that are used up in the provision of the test that cannot be reused.

### Table B.3 TSB resources and costs

<table>
<thead>
<tr>
<th>Resources</th>
<th>Unit cost</th>
<th>Source</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical nurse specialist</td>
<td>£69.00</td>
<td>PSSRU (2008) <a href="http://www.pssru.ac.uk/pdf/uc/uc2008/uc2008.pdf">http://www.pssru.ac.uk/pdf/uc/uc2008/uc2008.pdf</a></td>
<td>It is assumed that it would take 10 minutes to undertake this test</td>
</tr>
<tr>
<td>Venous blood test</td>
<td>£7.00</td>
<td>GDG estimate</td>
<td>One per test</td>
</tr>
</tbody>
</table>

A TCB positive followed by a TSB is considered as a single test for the purposes of this analysis.
Gloves | £0.06 | medisave.co.uk accessed 16 July 2009 | £6.27 per 100 One pair per test

Table B.4 TCB resources and costs

<table>
<thead>
<tr>
<th>Resources</th>
<th>Unit cost</th>
<th>Source</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical nurse</td>
<td>£69.00</td>
<td>PSSRU (2008)</td>
<td>It is assumed that it would take 1 minute to undertake this test</td>
</tr>
<tr>
<td>specialist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCB meter</td>
<td>£3,400</td>
<td>Manufacturer, JM103</td>
<td>No consumables required</td>
</tr>
<tr>
<td></td>
<td>£3,600</td>
<td>Manufacturer, Bilichek</td>
<td></td>
</tr>
<tr>
<td>Calibration tips</td>
<td>£5.50</td>
<td>Manufacturer, Bilichek</td>
<td></td>
</tr>
<tr>
<td>TSB</td>
<td>£18.56</td>
<td>Marginal cost of TSB</td>
<td>It is estimated that 25% of TCB tests would be positive leading to a TSB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(see Table B.3)</td>
<td></td>
</tr>
</tbody>
</table>

Comment [P4]: Very important. Factual accuracy check – need to double check these. Manufacturers will not be happy if the price of their product is over-estimated but I think an e-mail from HRD to PJ on 12/08/2009 is relevant + e-mail PJ sent to Paula Prior on 28/03/2010.
The purchase of medical equipment, TCB meters in this case, carries an opportunity cost which differs from operating costs such as labour and consumables in certain respects. The purchase of TCB meters involves an upfront payment before use. However, that cost is fixed as it does not vary with the quantity of treatment provided. The equipment can often be used over a number of years before it needs to be replaced.

The equipment costs have two facets:

- **Opportunity cost** – the money spent on the equipment could have been invested in some other venture yielding positive benefits. This is calculated by applying an interest rate to the sum invested in the equipment.

- **Depreciation cost** – the equipment has a certain lifespan and depreciates over time. Eventually, the equipment has to be replaced.

In economic evaluation, the usual practice is to annuitise the initial capital outlay over the expected life of the equipment to give an ‘equivalent annual cost’. Calculating the equivalent annual cost means making an allowance for the differential timing of costs, using discounting.

The formula for calculating the equivalent annual cost is given below:

\[
E = \frac{(K - [S - (1 + r)^n])}{A(n, r)}
\]

where:
- \(E\) = equivalent annual cost
- \(K\) = purchase price of equipment
- \(S\) = resale value
- \(r\) = discount (interest rate)
- \(n\) = equipment lifespan
- \(A(n, r)\) = annuity factor* (n years at interest rate \(r\))

To calculate the equivalent annual cost we have assumed that the meters last 5 years and have no resale value. However, the total annual equivalent cost would depend on the actual number of meters that were necessary to deliver the strategy. This is not known and service delivery is not generally part of the remit of NICE guidelines. Therefore, the results are presented as a threshold analysis, with the threshold being the number of meters at which the TSB strategy (strategy 2) would be equivalent in cost to the TCB strategy (strategy 3).

**Results**
The marginal cost per test (excluding equipment) was estimated to be £18.56 for TSB and £5.87 for TCB for a test requiring no consumables and £11.37 for a test requiring calibration tips. Using these figures the cost per strategy was calculated as follows for the model’s default input values:

### Calculation of total costs per annum of each strategy

1. **Current practice**

<table>
<thead>
<tr>
<th>Description</th>
<th>Calculation</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>690,000</td>
<td></td>
</tr>
<tr>
<td>Tested with TSB</td>
<td>690,000 x 0.1 x 0.6 = 41,400</td>
<td></td>
</tr>
<tr>
<td>TSB tests</td>
<td>41,400 x 1.33 = 55,062</td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td>55,062 x £18.56 = £1.02 million</td>
<td></td>
</tr>
</tbody>
</table>

   **Strategy 2 (TSB to all visually jaundiced babies)**

<table>
<thead>
<tr>
<th>Description</th>
<th>Calculation</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>690,000</td>
<td></td>
</tr>
<tr>
<td>Visibly jaundiced</td>
<td>690,000 x 0.6 = 414,000</td>
<td></td>
</tr>
<tr>
<td>TSB tests</td>
<td>414,000 x 1.33 = 550,620</td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td>550,620 x £18.56 = £10.22 million</td>
<td></td>
</tr>
</tbody>
</table>

2. **Strategy 3 (TCB to all visually jaundiced babies followed by TSB if TCB is positive)**

<table>
<thead>
<tr>
<th>Description</th>
<th>Calculation</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>690,000</td>
<td></td>
</tr>
<tr>
<td>Visibly jaundiced</td>
<td>690,000 x 0.6 = 414,000</td>
<td></td>
</tr>
<tr>
<td>TCB tests</td>
<td>414,000 x 1.33 = 550,620</td>
<td></td>
</tr>
<tr>
<td>TSB tests</td>
<td>550,620 x 0.25 = 137,655</td>
<td></td>
</tr>
<tr>
<td>Cost (BiliChek®)</td>
<td>(550,620 x £11.37)</td>
<td>£6.26 million plus annual equivalent equipment cost</td>
</tr>
<tr>
<td>Cost (Minolta®)</td>
<td>(550,620 x £5.87)</td>
<td>£3.33 million plus annual equivalent equipment cost</td>
</tr>
</tbody>
</table>

Figure B.1 shows how the incremental costs of the TCB strategy (for two different types of meter) relative to the TSB strategy vary according to the number of meters that would be necessary to deliver a strategy of TCB testing. The point where the lines plotting the incremental costs of TCB cross the horizontal axis gives the threshold number of meters for cost neutrality between TCB and

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2 The marginal cost of TCB reflects that 25% of tests will be followed by TSB
TSB. If the TCB strategy can be delivered with fewer meters than implied by this threshold then it would be cheaper than the TSB strategy. With the other model values held constant at their default values, Figure B.1 suggests that a TCB strategy using the cheaper meter will cost less than the TSB strategy providing that it can be delivered with less than 9,200 meters.

**Figure B.1:** A graph to compare the incremental costs of TCB with TSB varying the number of TCB meters needed to deliver the strategy

Figure B.2 shows the test costs of all three strategies in a scenario where 9,200 meters are needed to deliver the TCB strategy.

**Figure B.2:** Total test costs of the different strategies with the model’s default input values and assuming 9,200 TCB meters

*Comment [P5]:* In meningitis guideline, a stakeholder suggested 3D graphs of this type had no place in a scientific publication.
Figure B.2 strongly suggests that both the TSB and TCB strategies are more expensive than current practice in terms of test costs. This would be the case even if a much less than 9,200 TCB meters were required. The cost-effectiveness of this additional testing ultimately depends on any offsetting savings and health gains derived as a result of improved outcomes, i.e. averted kernicterus cases. This is an unknown but the “what-if” analysis presented in Figure B.3 shows the minimum number of kernicterus cases that would need to be averted for cost-effectiveness using the model’s default input values and varying the number of TCB meters.

**Figure B.3: A graph to show the minimum number of kernicterus cases to be averted at different incremental costs of more intensive testing.**

Figure B.3 shows the total additional cost to the NHS of more intensive testing between a minimum of 1,000 TCB meters and a maximum of 9,200. The cost on the x-axis is the incremental cost difference between ‘current practice’ and more intensive testing. In this figure, the comparator with current practice is always TCB. If 9,200 meters or fewer are purchased, the cheaper option is always TCB. If more meters are required, then the TSB strategy should be preferred on cost-effectiveness grounds. The figure shows that the total cost of using 9,200 meters would require an additional £9.14 million per year. The number of kernicterus cases to be averted would have to be at least 1.52 per year for this additional cost of testing to be cost-effective compared with current practice. Buying only an additional 1,000 meters, the total additional cost would be £2.96 million per year and 0.49 cases of kernicterus would need to be averted per year for TCB to be more cost-effective than current practice.
Sensitivity Analysis

Sensitivity analysis is used in economic evaluation to assess how sensitive the results of the model are to the assumptions made about the model parameters, particularly those parameters where considerable uncertainty exists as to their actual value. One-way sensitivity analysis involves altering the value of a single parameter, holding all the others constant, to determine how sensitive the cost-effectiveness conclusion is to the assumptions made about that particular parameter.

The base-case results above were presented as threshold analyses reflecting uncertainty about the number of meters that would be needed for the TCB strategy and the number of kernicterus cases that would need to be averted in order for the additional costs of more intensive costing to be deemed an efficient use of scarce NHS resources. However, the sensitivity analyses below explore how changes in other model parameters would affect results.

i. Varying the cost of meters

In this sensitivity analysis the cost of the meters is varied between £600 and £3,600. It is assumed that the meter is a Minolta® and does not therefore require a new calibration tip for each test. The analysis additionally considers how this affected by the number of meters needed to deliver the TCB testing strategy.

Figure B.4: A graph to compare the incremental costs of TCB with TSB varying the number of TCB meters needed to deliver the strategy and the cost of the TCB meter

Figure B.4 shows that the cost of meters is likely to be an important determinant of the cost-effectiveness of TCB relative to TSB. As the cost of meters falls, the number of meters has far less impact in determining the incremental costs of the TCB strategy.
ii  **Varying the mean number of tests per baby tested**

In this sensitivity analysis the mean number of tests per baby tested is varied between one and two tests. The analysis is repeated for different numbers of TCB meters.

**Figure B.5: A graph to compare the incremental costs of TCB with TSB varying the number of TCB meters needed to deliver the strategy and the mean number of tests per baby tested**

Figure B.4 shows that the incremental costs of the TCB test strategy relative to the TSB test strategy fall as the average number of tests per baby increase. This simply reflects that TSB test has the higher marginal cost. If just one test per baby were required then the threshold number of meters for cost neutrality would be approximately 7,000. However, if babies were tested twice on average then that cost neutrality threshold would rise to approximately 14,000 meters. It should be noted that whilst more testing improves the cost-effectiveness of TCB relative to TSB the opposite is the case with respect to current practice.

iii  **Simultaneously varying the QALY gain and cost averted of a kernicterus case**

These are important unknowns because together with effect size they are fundamental determinants of whether increased testing costs represent a good use of scarce NHS resources. The greater the QALY gain associated with a kernicterus case, the greater the NHS would be willing to pay for such a gain. The greater the saving from an averted kernicterus case, the more the additional costs of testing will be offset by a reduction in “downstream” treatment costs.
Figure B.6. A graph to show the thresholds for cost-effectiveness according to the number of kernicterus cases averted and the savings and QALY gain from an averted kernicterus case based on 2,000 TCB meters

Figure B.7. A graph to show the thresholds for cost-effectiveness according to the number of kernicterus cases averted and the savings and QALY gain from an averted kernicterus case based on 9,200 TCB meters

Figures B.6 and B.7 show that the greater the savings from an averted kernicterus case has a big effect on reducing the number of kernicterus cases that would need to be averted in order for a TCB strategy to be considered relative to current practice. By comparison increasing the QALY gain associated with an averted case has only a relatively small impact on reducing the cost savings from averted kernicterus cases that would be necessary for cost-effectiveness as any given number of averted cases. These two figures together also show the large impact the number of meters has on these cost-effectiveness thresholds. For a given number of averted cases a much higher saving and
QALY gain is necessary for cost-effectiveness when the TSB strategy requires 9,200 meters compared to when 2,000 meters are required.

**Discussion**

The analysis compared the current testing strategy with an uplift in testing using alternative strategies. In the base case analysis, the current strategy of testing only 10% of babies using TSB was £1.02 million per year. The next cheapest strategy was to use Strategy 3 (TCB to all visually jaundiced babies followed by TSB if TCB is positive) using a meter that does not require calibration tips which cost £10.16 million, or £13.25 million using a meter requiring a calibration tip. Using the TSB more intensively (on 60% babies who are visibly jaundiced) would cost £10.22 million per year. The cost difference between TSB and TCB is mainly due to the increased time to do a blood test compared with a skin test.

An important question is whether any change from current practice can be justified on cost-effectiveness grounds. In part this depends on the fixed costs, that is the number of TCB meters needed to deliver strategy 3. This determines the incremental costs of increased testing if the TCB strategy is deemed more cost-effective than TSB, that is, the strategy with the lowest cost since this is a cost minimization analysis. In the base-case analysis, the results estimate that the maximum incremental cost of more intensive testing is around £9.14 million which is the incremental cost of an enhanced testing strategy using TSB alone relative to current practice. If the strategy using the TCB could be delivered with the purchase of only 1,000 additional bilirubinometers (which would be a highly conservative estimate) then the incremental cost would be £2.96 million. Figure B.3 suggests that 1.52 cases of kernicterus would have to be averted for more intensive testing to be considered cost-effective if the incremental testing costs were £9.14 million. If fewer resources were required (fewer bilirubinometers purchased) then fewer cases would need to be averted. This assumes a threshold QALY value of £20,000. At a higher threshold, say £30,000 per QALY, the number of cases of kernicterus averted in order for more intensive testing to be cost-effective would be fewer.

Figure B.3 shows how this threshold of kernicterus cases that need to be averted for cost-effectiveness falls as the incremental costs of more intensive testing fall, as is the case with a smaller number of TCB meters. At this moment in time the evidence base is not sufficiently robust to assess whether more intensive testing would achieve such an incremental gain – there are approximately five to seven new kernicterus cases per annum in England and Wales. However, given the evidence about the limitations of visual examination, the GDG are opposed to relying on observations which have been demonstrated to be unreliable in the detection of severe
hyperbilirubinaemia. It does seem plausible that a more intensive testing strategy using tests which are known to have greater reliability in detection of severe hyperbilirubinaemia would lead to more appropriate and timely intervention with a concomitant reduction in adverse outcomes.

The costs of the TCB testing strategy vary according to the cost of meter used. In the absence of evidence that health outcomes are different between types of meter used, the cheaper Minolta® meter should be preferred. The base-case results (see Figure B.2) suggest that, at current prices, the Minolta® meter would be about £3 million cheaper, assuming that the meters themselves are similarly priced. Therefore, in the remainder of the discussion it will be assumed that the analysis is based on the cheaper Minolta® TCB meter.

Figures B.1, B.3, B.4 and B.5 all show that the number of meters necessary to deliver the TCB strategy is important in determining the relative cost-effectiveness of the TCB strategy (strategy 3) to the TSB strategy (strategy 2). In the base-case analysis, TCB is cheaper than TSB providing the number of TCB meters is less than 9,200.

If it is decided that more intensive testing is likely to be cost-effective then a secondary decision is whether initial testing should be done using TCB or TSB. Factors such as convenience to the nurse and discomfort to the baby are not irrelevant to the decision but have not been included explicitly in this analysis because they are difficult to quantify and probably of a relatively small magnitude. This analysis suggests that the choice between TCB and TSB would depend on the number of meters that would be required. The NHS staff census as reported the NHS Information (http://www.ic.nhs.uk/statistics-and-data-collections/workforce/nhs-staff-numbers, accessed August 2009) reports the ‘head count’ figure for practicing midwives as 25,000 with 19,500 fulltime equivalents. The base-case analyses suggest that were all midwives required to have a TCB meter in order to implement a TCB strategy then TSB would be the cost-effective option. However, not all midwives do post-natal checks. It may be more useful to consider the number of post-natal checks undertaken per day.

If we assume that each birth has, on average, three post natal visits then amounts to:

\[(690,000 \times 3) \div 365 = 5,670 \text{ post natal visits per day}\]
Community midwives would typically do 6-10 postnatal visits per day which suggests that the postnatal workload is managed by approximately 1,000 midwives on any given day, which might suggest that the service could actually be delivered with less than 9,200 meters.

In interpreting this analysis there are a number of caveats to be considered in addition to the most important ones already highlighted concerning the lack of evidence. The analysis assumes that 25% of infants will require a confirmatory TSB before consideration of phototherapy. If this estimate were higher, then the total cost of the TCB strategy would be higher and the cost threshold at which TSB would be the preferred option would consequently be lower. The analysis also assumes that a move to more intensive testing does not lead to increased phototherapy. This might seem a counter-intuitive assumption as the efficacy of more intensive testing is ultimately predicated on not missing cases that could benefit from treatment. However, intervention rates may also be influenced by recommendations on thresholds for commencing treatment, where current practice varies. In some settings this might lead to lower, but more targeted, intervention than currently occurs.

The analysis also assumes that the different test strategies will not differ in terms of the amount of testing undertaken and the number of follow-up home visits undertaken. Of course, it is possible that the convenience of TCB could lead to additional “downstream” costs not considered here.

An important assumption in this analysis is that phototherapy rates would not change if a more intensive testing strategy was adopted. This is a strong assumption in the model since we do not know how many more cases of hyperbilirubinaemia would be correctly identified by a change in testing strategy.

**Conclusion**

Based on the published limitations of visual examination, the GDG strongly believe that a more intensive testing strategy is required in order to improve outcomes in neonatal jaundice. This will require more resources, but if this reduces the incidence of kernicterus by sufficient numbers, it would be cost-effective to implement in the NHS. Whilst the analysis presented here is unable to demonstrate that this would be cost-effective, it does
suggest that the actual number of kernicterus cases needed for more intensive testing to be cost-effective is relatively small, e.g. 0.49 cases per annum if the TCB strategy could be delivered with 1,000 meters up to 1.52 cases per annum if 9,200 meters are required. This is the cut-off above which the total cost of TSB strategy is cheaper than TCB. It is important to remember that these values are based on strong assumptions (for the lifetimes QALYs lost through kernicterus and lifetime cost of kernicterus) that are supported by the GDG but are not based on externally verifiable evidence. The number of cases of kernicterus that could be prevented is the critical unknown. However, reports from the US have shown a reduction of 4 cases per 100,000 births after the mid 1990s.

Determining which intensive testing strategy is cost-effective depends crucially on the number of meters which would have to be purchased in order to deliver TCB. The number of community midwives involved in home visits on any one day is far smaller than the total number working in the NHS at any one time. Therefore it seems plausible that the TCB strategy could be delivered with a number of transcutaneous meters that is sufficiently low to meet the threshold for cost-effectiveness. However, service delivery is not within the remit of this NICE guideline and local commissioners may want to opt for the strategy they believe can be delivered most cost-effectively in their area.

Reference List


Health Economics Appendix

Part ii
Cost-effectiveness of Intravenous Immunoglobulin (IVIG)

Introduction
The clinical evidence suggests that babies with rhesus and ABO haemolytic disease receiving IVIG are less likely to require exchange transfusion, an expensive procedure with associated morbidity and mortality. However, IVIG is also a relatively expensive therapeutic intervention and there is a shortage of global supply. Therefore an economic evaluation was undertaken to help guide GDG recommendations. The analysis compared giving IVIG as an adjunct to phototherapy in babies with rhesus haemolytic disease and ABO haemolytic disease where serum bilirubin is continuing to rise at more than 8.5 micromol/litre/hour against not giving IVIG to these babies.

Method
A simple decision analytic model was used to assess the cost-effectiveness of IVIG as an adjunct to multiple phototherapy in babies with haemolytic disease where bilirubin level continue to rise. The structure of this model is shown in Figure xx.1. Costs were taken from the perspective of the NHS and personal social services which is in accordance with the NICE guidelines manual (http://www.nice.org.uk/media/5F2/44/The_guidelines_manual_2009_-_All_chapters.pdf). The costs of multiple phototherapy was not included in the analysis as it common to both treatment alternatives. However, the costs of exchange transfusion are important as the rationale for IVIG is that the rates of exchange transfusion will vary according to treatment. Naturally the costs of IVIG are also an important cost input, as this is the treatment evaluated.

Health outcomes are measured in Quality Adjusted Life-Years (QALYs). Exchange transfusions is associated with mortality and morbidity and in this model the difference between the treatment alternatives in QALYs is assumed to only be a consequence of mortality arising from exchange transfusion. This was partly to simplify the analysis but
also because any impact on QALYs from morbidity would be small relative to that from assuming causation between exchange transfusion and mortality. We assume that IVIG would have no adverse effects that would have important long term morbidity.

Figure xx.1. Decision tree for IVIG cost-effectiveness model

**Model parameters**

The treatment cost of IVIG was estimated using the unit costs in Table xx.1.

<table>
<thead>
<tr>
<th>Resource</th>
<th>Unit cost</th>
<th>Source</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous immune globulin (IVIG)</td>
<td>£1,000</td>
<td>GDG estimate</td>
<td></td>
</tr>
<tr>
<td>Specialty doctor per hour</td>
<td>£54</td>
<td>PSSRU (2008)</td>
<td>15 minutes set up time</td>
</tr>
<tr>
<td>Nurse, day ward per hour of patient</td>
<td>£43</td>
<td>PSSRU (2008)</td>
<td>2 hours of nurse time</td>
</tr>
<tr>
<td>Non-elective inpatient bed day</td>
<td>£430</td>
<td>NHS ref costs 2007/08 Currency code PB01Z</td>
<td>Inpatient cost estimated as an excess bed day for non-elective patient with a major neonatal diagnosis</td>
</tr>
</tbody>
</table>

It takes 2 hours to administer IVIG and it was assumed that the drip was set-up by a specialist registrar but that a nurse would supervise the treatment for the 2 hours. The treatment is provided as an inpatient procedure and therefore treatment also includes the resources involved in the occupation of a hospital bed. This was estimated by using
the 2007-08 NHS Reference Cost Excess bed-day cost for a non-elective inpatient with a major neonatal diagnosis.

The cost of an exchange transfusion was estimated using the 2007-08 NHS Reference costs and the category on non-elective inpatient with a major neonatal diagnosis. The costs of treatment are summarised in Table xx.2.

Table xx.2  Treatment costs

<table>
<thead>
<tr>
<th>Resource</th>
<th>Unit cost</th>
<th>Source</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exchange Transfusion</td>
<td>£2,108</td>
<td>NHS reference cost 2007/08 currency code PB01Z</td>
<td>Non-elective inpatient, with a major neonatal diagnosis</td>
</tr>
<tr>
<td>IVIG</td>
<td>£1,500</td>
<td>Based on the unit costs in Table xx.2</td>
<td></td>
</tr>
</tbody>
</table>

The efficacy of treatment relates to the number needed to treat (NNT) with IVIG to avoid an exchange transfusion. This in turn influences the number of babies who avoid an exchange transfusion and its associated mortality. The clinical parameters used in the model are given Table xx.3.

Table xx.3  Clinical parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Range (Sensitivity analysis)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNT Rh disease</td>
<td>2</td>
<td>2 to 3</td>
<td>See Chapter 7</td>
</tr>
<tr>
<td>NNT ABO Disease</td>
<td>5</td>
<td>5 to 13</td>
<td>See Chapter 7</td>
</tr>
<tr>
<td>Exchange transfusion</td>
<td>2%</td>
<td>0.3% to 2%</td>
<td>Jackson (1997) ¹</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td>Ip et al. (2004) ¹</td>
</tr>
</tbody>
</table>

Finally, there are a range of cost benefit inputs which reflect NICE methodology. These inputs are shown in Table xx.4. The QALY gain of an averted exchange transfusion death is an approximation of the discounted QALY gain from a life lived in perfect health and for an average life expectancy.

Table xx.4  Cost benefit parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Source</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>QALY gain from averted</td>
<td>25</td>
<td>Approximately 75 to 80 years of life lived in full health</td>
<td></td>
</tr>
<tr>
<td>exchange transfusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results

The results with base-case values are shown in Table xx.5 and Table xx.6 for Rhesus haemolytic disease and ABO haemolytic disease respectively.

Table xx.5 Cost effectiveness of IVIG for babies with rhesus haemolytic disease with base case model values

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost</th>
<th>Mortality</th>
<th>QALY loss</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>No IVIG</td>
<td>£2,108</td>
<td>0.02</td>
<td>0.5</td>
<td>-</td>
</tr>
<tr>
<td>IVIG</td>
<td>£2,584</td>
<td>0.01</td>
<td>0.25</td>
<td>£1,904 per QALY</td>
</tr>
</tbody>
</table>

Table xx.6 Cost effectiveness of IVIG for babies with ABO haemolytic disease with base case model values

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost</th>
<th>Mortality</th>
<th>QALY loss</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>No IVIG</td>
<td>£2,108</td>
<td>0.02</td>
<td>0.5</td>
<td>-</td>
</tr>
<tr>
<td>IVIG</td>
<td>£3,216</td>
<td>0.016</td>
<td>0.4</td>
<td>£11,084 per QALY</td>
</tr>
</tbody>
</table>

With base case values IVIG appears cost effective in babies with rhesus and ABO haemolytic disease with incremental cost effectiveness ratios (ICER) of less than £20,000 per QALY. The treatment appears most cost-effective in babies with rhesus haemolytic disease which is because the data suggests a lower NNT to avoid an exchange transfusion. If more exchange transfusions are avoided that has a beneficial effect on both ‘downstream’ costs and averted mortality.

Sensitivity analysis

The results for the base case analysis are only as reliable as the base case inputs which produce them. There is important uncertainty in some of these inputs especially with respect to exchange transfusion.
mortality and the NNT to avoid exchange transfusion. The 95% confidence intervals for the NNT were as follows:

- Rhesus haemolytic disease: 1.6 to 3
- ABO haemolytic disease: 3 to 13

In exploring this uncertainty there is limited value in exploring scenarios where exchange transfusion mortality is higher than the base case, the NNT is lower than the base case and the cost differential between exchange transfusion and IVIG is bigger than the base case. That is not to say that such scenarios are implausible but rather they would simply reinforce the observed cost-effectiveness of treatment. Rather we are more interested in subjecting the cost-effectiveness finding to scrutiny by observing the extent to which the cost-effectiveness would still hold with the least propitious but still plausible scenarios. Therefore, the sensitivity analyses take a ‘worst case’ scenario with respect to clinical parameters and a threshold approach to costs.

*Analysis 1 – varying clinical parameters*

In this analysis it was assumed that the mortality rate for an exchange transfusion was 3 per 1,000. Furthermore, we took the upper limit of the 95% confidence intervals for the NNT. In this analysis the ICER for rhesus haemolytic disease was £31,053. For ABO haemolytic disease the ICER was £228,933.

*Analysis 2 – varying treatment costs*

In this sensitivity analysis the clinical parameters were maintained at their base case value. The costs of IVIG were then increased to determine the value at which IVIG treatment would no longer be cost-effective. For ABO haemolytic diseases IVIG treatment remained cost-effective for all IVIG treatment costs less than £2,421. For rhesus haemolytic disease IVIG treatment would have to exceed £6,054 for it to no longer be considered cost-effective.

**Discussion**
This analysis strongly suggests that IVIG is a cost-effective treatment in babies with rhesus haemolytic disease as an adjunct to phototherapy where bilirubin levels are still rising. This finding seems reasonably robust with respect to uncertainty in model inputs. Even when the NNT was taken from the upper limit of the 95% confidence interval and much lower exchange transfusion mortality than the base case was assumed, the ICER was only just outside what would be considered cost-effective by NICE criteria. Also, with base case clinical inputs the cost-effectiveness of IVIG in rhesus disease babies was not sensitive to the costs of IVIG.

For patients with ABO haemolytic disease the cost-effectiveness of IVIG is less certain because of the higher NNT. The cost-effectiveness in this group is very sensitive to exchange transfusion mortality and the NNT within plausible ranges. Whilst cost-effective in the base case analysis, the ICER in the ‘worst case’ scenario would not be considered to be a cost-effective use of scarce NHS resources.

Whilst the sensitivity analysis did not suggest that the results were particularly sensitive to changes in IVIG cost, it should be remembered that if the true clinical inputs conferred a lower benefit with IVIG treatment then the importance of treatment costs as a determinant of cost-effectiveness would increase.

**Conclusion**

The model seems to provide good evidence that IVIG treatment in babies with rhesus haemolytic disease can be considered cost-effective and it therefore supports the GDG recommendation. IVIG treatment in babies with ABO haemolytic disease may also be cost-effective as indicated by the base case results. However, sensitivity analysis suggested this finding was subject to considerable uncertainty. Nevertheless, IVIG treatment in this group of patients is consistent with recent Department of Health guidance and is also likely to have a relatively small cost impact given the number of babies affected and therefore the GDG recommendation seems reasonable. Further, research to ascertain the cost-effectiveness of IVIG especially in babies with ABO haemolytic disease could be useful given the current evidence base.
Reference List


