UK National Screening Committee

Newborn Screening for Biliary Atresia

External review against programme appraisal criteria for the UK National Screening Committee (UK NSC)

Version: Final

Solutions for Public Health

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The UK NSC advises Ministers and the NHS in all four UK countries about all aspects of screening policy. Its policies are reviewed on a 3 yearly cycle. Current policies can be found in the policy database at http://legacy.screening.nhs.uk/screening-recommendations.php and the policy review process is described in detail at https://www.gov.uk/guidance/evidence-and-recommendations-nhs-population-screening#evidence-review-process

Abbreviations List

CI	Confidence Interval
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPV	Negative Predictive Value
PPV	Positive Predictive Value
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies-2
RCT	Randomised Controlled Trial
UK	United Kingdom
UK NSC	UK National Screening Committee
US	United States of America

Competing Interest

All Solutions for Public Health (SPH) authors have completed the ICMJE uniform disclosure form (www.icmje.org/coi_disclosure.pdf) and declare: grants from Public Health England to SPH to undertake the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

Plain English Summary

Biliary atresia is a rare condition that causes the bile ducts to become blocked or inflamed. This prevents the secretion of bile into the digestive tract and, if not treated, can cause liver damage and death by 2 years of age. Bile is a digestive fluid necessary to digest fats and vitamins.

A surgical procedure to allow drainage of the bile ducts (the Kasai portoenterostomy procedure) can prevent or delay the need for liver transplant.

This document reviews new evidence about screening newborns for biliary atresia. It looks at evidence published between January 2012 and November 2016. The aim of a screening programme for biliary atresia would be to allow for earlier intervention, thereby reducing the extent of liver damage and potentially improving outcomes.

The UK National Screening Committee (UK NSC) published its last review in 2012. This recommended against introducing a newborn screening programme for biliary atresia in the UK. The current review looked at 2 key questions:

1. has a suitable method of screening for biliary atresia using newborn dried bloodspots been identified?
2. what is the reported mean age at surgery for biliary atresia (Kasai portoenterostomy) in the UK?

Some countries use stool (faeces) samples to screen for biliary atresia. This review is looking at the evidence for screening for biliary atresia using newborn dried bloodspots. This method was identified in previous UK NSC reviews as the best approach that could potentially detect disease very early, may fit with current screening practice and allow for earlier treatment.

Following a search of the literature no new evidence about screening using newborn dried bloodspot was identified and only limited information was available about a study exploring screening for biliary atresia using liquid blood (question 1).

No new evidence was identified about the mean age at surgery for biliary atresia in the UK (question 2). Age at surgery in countries that screen for biliary atresia using a stool colour card is comparable to the latest available information on age at surgery in the UK.

As there is no new evidence addressing the questions arising from the previous review, it is recommended that the current UK NSC policy remains in place and systematic population based newborn screening is not implemented in the UK.

Executive Summary

This document reviews new evidence published between January 2012 and November 2016 on population screening for biliary atresia in newborn babies.

Background

Biliary atresia is a rare, life-threatening condition which affects the liver and bile ducts. The presenting symptoms include jaundice, pale stools and dark urine. Without treatment biliary atresia can result in progressive liver disease and death by 2 years of age. A surgical procedure to allow drainage of the bile ducts (the Kasai portoenterostomy procedure) can prevent or delay the need for liver transplant. Native liver survival is improved when surgery is performed at an earlier age. At present the early detection of biliary atresia relies on the clinical recognition of prolonged jaundice which the National Institute for Health and Care Excellence (NICE) define as more than 14 days in term infants and more than 21 days in preterm infants. However jaundice is common in infancy and most of these infants will not have biliary atresia.

Previous studies have found that testing for biliary atresia by measuring conjugated bile acids in dried bloodspots is not reliable as a screening test. The 2012 UK NSC review sought to explore whether any progress had been made in developing screening tests using dried bloodspots or alternative screening tests.

Previous findings

The current UK NSC policy is that systematic population screening for biliary atresia in newborn babies is not recommended.

The previous UK NSC external review of newborn screening for biliary atresia was published in 2012. The 2012 review concluded that there was insufficient information to recommend a population screening programme. The gaps in the evidence related to:

- no studies exploring the value of measuring bile acid concentrations on dried bloodspots published between 1999 and 2012
- some promising results for identifying liver disease from measuring conjugated bilirubin in liquid blood samples, but the predictive value for biliary atresia had not been explored and the sampling procedure limited its value as a population screening tool
- the reported sensitivity and specificity for screening using stool colour cards were 89% and 99.9% respectively. Despite reasonable test performance values, the benefit of introducing this screening strategy in the UK is unclear because the median age of surgery in the UK was 54 days and was comparable to that achieved by pilot screening programmes using stool colour as a screening method.

The current review

The current review explores the volume, quality and direction of the literature published since 2012 and focuses on key questions relating to the conclusions of the previous review. This review assessed key questions to determine if new evidence published since 2012 suggests that the current recommendation for newborn screening for biliary atresia in the UK should be reconsidered.

The key questions considered in this review are:

- has a suitable method of screening for biliary atresia using newborn dried bloodspots been identified?
- what is the reported mean age at surgery for biliary atresia (Kasai portoenterostomy) in the UK?

Although some countries use stool (faeces) samples to screen for biliary atresia, this review is looking at the evidence for screening for biliary atresia using newborn dried bloodspots. This method was identified in previous UK NSC reviews as the main candidate approach that could potentially detect disease very early, may fit logistically with current screening practice and allow for earlier treatment.

The age at surgery in the UK is of interest to establish whether this has changed since the previous 2012 review. Should the average age at surgery in the UK increase, this may stimulate interest in the potential value of stool colour card screening.

The volume, quality and direction of new evidence published since January 2012 does not suggest that there have been any significant changes in the evidence base since the previous review. Several findings might be noted, including:

- no studies published between 2012 and 2016 considered testing for biliary atresia using newborn dried bloodspots in a general screening population
- a study exploring a 2-stage screening strategy for biliary atresia using liquid blood has been published as a letter with limited details available for appraisal at present
- case control studies have explored potential new targets for screening for biliary atresia using dried blood spots and liquid blood and may be developed further in the future
- no studies were published between 2012 and 2016 that provided the mean or median age at surgery for biliary atresia in the UK. It is therefore not possible to determine whether the age at surgery has changed from the median of 54 days reported in the 2012 UK NSC review
- two studies reported reductions in age at surgery after the introduction of screening programmes using stool colour cards (in Taiwan and Japan). Median age at surgery, reported by one of study, was 58.5 days (range 18 to 109). The other study reported a mean age at surgery of 46.0 ± 23.8 days. This is comparable with the median age of 54 days (range 7-209) at Kasai surgery in the UK, reported in the 2012 UK NSC review.

Recommendation

The review concluded that there has been no significant change in the evidence base since the previous UK NSC review. The current recommendation not to introduce a UK systematic population screening programme for biliary atresia in newborn babies should be retained.

Introduction

Biliary atresia is a life-threatening disorder affecting the liver and bile ducts[1]. Untreated, biliary atresia can result in progressive liver disease and death by 2 years of age[1]. The presenting symptoms of biliary atresia include jaundice, pale stools and dark urine which can appear at or soon after birth[1]. A surgical procedure to allow drainage of the bile ducts (the Kasai portoenterostomy procedure) can prevent or delay the need for liver transplant[2]. Native liver survival is improved when surgery is performed at an earlier age[3]. Biliary atresia is a rare condition with the incidence in England and Wales estimated at 0.58 per 10,000 live births[6].

At present, early detection of biliary atresia relies on clinical recognition of prolonged jaundice which the National Institute for Health and Care Excellence (NICE) define as more than 14 days in term infants and more than 21 days in preterm infants[6]. However, jaundice is common in infancy and few of these infants will have biliary atresia. NICE have not published clinical guidance on biliary atresia, however biliary atresia is mentioned as one of the potential causes of jaundice in NICE guidance on neonatal jaundice[4].

Basis for current recommendation

The current UK National Screening Committee (NSC) policy is that systematic newborn population screening for biliary atresia is not recommended. The previous UK NSC external review of screening for biliary atresia was produced in 2012[5]. The 2012 review concluded that[6]:

- no studies exploring the value of measuring bile acid concentrations on dried bloodspots published between 1999 and 2012
- some promising results for identifying liver disease from measuring conjugated bilirubin in liquid blood samples, but the predictive value for biliary atresia had not been explored and the sampling procedure limited its value as a population screening tool
- the reported sensitivity and specificity for screening using stool colour cards were 89% and 99.9% respectively. Despite reasonable test performance values, the benefit of introducing this screening strategy in the UK is unclear because the median age of surgery in the UK was 54 days and was comparable to that achieved by pilot screening programmes using stool colour as a screening method.

Current update review and approach taken

The current review considers newborn screening for biliary atresia and was prepared by Solutions for Public Health, in discussion with the UK NSC. The evidence summary was developed using a rapid review methodology and assessed using the UK NSC reporting checklist for evidence summaries. The key questions addressed in the current review were developed by the UK NSC and are based on the key areas where biliary atresia did not meet the criteria for a screening programme in the last, 2012, UK NSC review. The aim of the current review is to update the evidence in these key areas, namely around the screening test and the mean age at surgery. The key questions and the UK NSC criteria that they relate to are presented in Table 1 below.

A systematic literature search of 3 databases was conducted by the UK NSC in November 2016 for new evidence published since January 2012. The search was structured around the issues raised in the 2012 UK NSC external review. A total of 1,368 unique references were identified and sifted by title and abstract by the UK NSC for potential relevance to the review. Details of the databases searched, search terms and a flow diagram summarising the references identified are presented in the Search Strategy section at the end of this

report. One hundred and eighteen references were sent to Solutions for Public Health for further appraisal and possible inclusion in the final review. Selection and appraisal of studies was undertaken by one reviewer. Any queries were resolved through discussion with a second reviewer.

Overall, 29 studies were identified as potentially relevant during title and abstract sifting and further assessed at full text, including 9 relating to screening tests and 20 relating to mean age at surgery. This includes papers where relevance could not be determined from the title or abstract alone. Reasons for excluding studies at the abstract stage included:

- guideline about the management of cholestatic jaundice in the United States
- studies where the population was symptomatic babies eg with cholestasis or prolonged jaundice
- studies on diagnostic rather than screening tests
- a retrospective review revisiting Danish recommendations around using a percentage value as a cut-off level in the diagnosis of biliary atresia
- a study on testing for bilirubin levels in cord blood
- studies on the management of children with biliary atresia or prolonged jaundice
- studies of medications (antibiotics, steroids and cox-2 inhibitors) post Kasai portoenterostomy
- studies of revision Kasai portoenterostomy following failure of an earlier procedure
- studies focusing on native liver survival after Kasai portoenterostomy
- studies focusing on liver transplantation
- discussion or descriptive papers/ commentary

Each section below provides information on the evidence selection process and number of included studies for the given criterion.

The review was quality assured by a second senior reviewer who was not involved with the writing of the review in accordance with Solutions for Public Health's quality assurance process.

Table 1: Key questions for current review of newborn screening for biliary atresia

Criterion*	Key Questions	# Studies Included
4. There should be a simple, safe, precise and validated screening test.	Has a suitable method of screening for biliary atresia using newborn dried bloodspots been identified?	1
15. Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme.	What is the reported mean age at surgery for biliary atresia (Kasai portoenterostomy) in the UK?	2

* UK NSC evidence review criteria (January 2016)

Appraisal against UK NSC Criteria[†]

Each of the key questions and their associated criteria are considered in turn below.

Each criterion was summarised as 'met', 'not met' or 'uncertain' by considering the results of the included studies in light of the volume, quality and consistency of the body of evidence. Several factors were considered in determining the quality of the identified evidence, including study design and methodology, risk of bias and applicability of the evidence.

Criterion 4: There should be a simple, safe, precise and validated screening test.

Key Question: Has a suitable method of screening for biliary atresia using newborn dried bloodspots been identified?

The UK NSC review protocol states that prospective studies of test accuracy in a consecutively enrolled population should be prioritised.

The 2012 UK NSC review did not identify any studies published between 1999 and 2012 that explored the value of measuring bile acid concentrations on dried bloodspots[5]. The 2012 review discussed various tests that have been proposed as screening tests for biliary atresia but concluded that none were ideal. The tests considered included measuring conjugated bile acids in newborn dried blood spots; measuring direct or conjugated bilirubin levels in liquid blood samples and assessing stool colour using a stool colour card.

Description of the evidence

In the current review, of the 29 studies identified as potentially relevant during title and abstract sifting, 9 related to this criterion. After review of the full texts 1 study was included (Hapavat et al 2016[7]). Four case control studies did not meet the criteria for full inclusion as they did not assess test performance in consecutively enrolled populations, however, they are briefly described for information on potential screening tests that may be further developed in the future.

The excluded studies were:

- a study describing a range of diagnostic tests in infants presenting with jaundice
- a study exploring metabolic profiles for potential biomarkers with no test performance (ie sensitivity and specificity) reported
- 2 discussion papers

No new studies assessing test performance using newborn dried bloodspots in a consecutively enrolled population were identified. One study did explore test performance in a consecutively enrolled population using blood serum (ie liquid) samples (Hapavat et al 2016[7]). This study was published as a letter and therefore contains limited information that can be used for critical appraisal. Hapavat et al assessed a 2-stage screening strategy using direct or conjugated serum bilirubin measurements in infants born at 4 hospitals in Texas over a 15-month period. In the first stage, serum samples from 11,636 infants ≤60 hours old were tested and were positive if they exceeded the 95% percentile reference interval of the laboratory. Infants who tested positive at stage 1 (n=121) were re-tested at or before the first well-child visit (≤2 to 3 weeks

[†]These criteria are available online at UK NSC evidence review criteria (January 2016)

old) and were considered positive if they had rising concentrations of direct or concentrated bilirubin concentration levels. Eleven infants tested positive on re-testing. Cases of biliary atresia were identified by tracking infants who were undergoing liver evaluation at the 2 sub-speciality care paediatric hospitals in Houston. The authors reported a sensitivity of 100% (95%CI 19.8% to 100%), a specificity of 99.9% (95%CI 99.8% to 99.9%) and a positive predictive value (PPV) of 18.2% (95% CI 3.2% to 52.2%).

The infants were born at 4 different hospitals so it is possible that the tests were assessed in different laboratories using different cut-off levels for a positive result. Information about the 11 infants who tested positive at the second stage of testing suggests that the 95% percentile cut-off level used for the first stage of testing did vary. Positive biliary atresia cases were identified by tracking infants at local specialist hospitals. It is possible that some infants could have been missed (eg moved from the area). The information provided by the authors appears to suggest that a diagnosis was not available for all of the 11 infants who tested positive at the second stage of testing. This study is currently published as a letter. Given the limited information available, the potential limitations in the study design and the wide confidence intervals around the sensitivity and PPV, the test performance results reported should be treated with caution.

Further details of this study, including an assessment of the quality of each study using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) framework, are provided in Appendix Table 1. The QUADAS-2 framework is used to assess the quality of primary test accuracy studies and includes 5 domains on patient selection, the index test, the reference standard, test strategy flow and timing and applicability[‡]. The QUADAS-2 assessment of Harpavat et al**Error! Bookmark not defined.** suggests that there are a number of areas in which the study is at high or unclear risk of bias, including uncertainties around the cut-off levels used and whether assessors were blinded to the other test results, and the limitations discussed relating to the process used to identify positive cases.

Four case control studies were identified exploring the performance of tests to distinguish between babies with known biliary atresia and healthy controls. As these studies did not include a consecutively enrolled population they do not meet the criteria for full inclusion in the review, however, they are briefly described here for information. Confidence intervals around the test performance results are provided where available. It should be noted that case control studies using a two gate design can exaggerate diagnostic accuracy especially if the sample size of either the control or those with the disorder is small as the range of values detected in the study may not reflect those in the general population.

Peng et al (2016)[8] explored the performance of circulating microRNAs as a potential biomarker for biliary atresia using next-generation sequencing with 2ml whole blood samples. The study

[‡] The patient selection domain considers the study design, the population sample and the patient exclusions; the index test domain considers assessor blinding and the process for determining the threshold to be used; the reference standard domain considers test performance and assessor blinding; the test strategy and flow and timing domain considers the interval between the test and reference standard and whether all patients received the reference standard and were included in the analysis; the applicability domain considers applicability to a UK screening population and the relevance of the test and reference standard to the UK.

reported a sensitivity of 67% and a specificity of 79% for the microRNA 140-3p to distinguish 44 patients with biliary atresia from 20 controls with other cholestatic disease and 20 healthy controls.

Harpavat et al (2016b)[9] explored the test performance of direct or conjugated bilirubin levels using retrospective data obtained from medical records. The study included 35 infants with biliary atresia and 9,102 infants without biliary atresia that acted as controls. The authors reported a sensitivity of 100% (95%CI 88% to 100%) and a specificity of 98% (95%CI 97.9% to 98.4%).

Zhou et al (2012)[1] explored the test performance of bile acids using tandem mass spectrometry with dried bloodspot samples. The study included 8 infants with biliary atresia, 17 controls with neonatal jaundice and 292 controls (comparison group). The bile acid taurocholate was found to be elevated in patients with biliary atresia compared to infants with jaundice and healthy controls. Using a cut-off level of 0.63µmol/L, the test was able to distinguish infants with biliary atresia from the comparison group with a sensitivity of 79% (95%CI 74% to 83%) and a specificity of 63% (95% CI 25% to 88%).

Song et al (2012)[10] assessed the performance of protein biomarkers using serum samples. The study included 42 infants with biliary atresia, 38 infants with neonatal cholestasis and 36 healthy controls and identified 2 biomarkers (Apo C-II and Apo C-III) as potential protein biomarkers for biliary atresia. The authors reported a sensitivity of 94% and a specificity of 92% to distinguish biliary atresia from neonatal cholestasis with a PPV of 88%. Sensitivity and specificity for distinguishing biliary atresia from healthy controls was not reported.

Discussion

No new studies considering a suitable method of screening for biliary atresia using newborn dried bloodspots in a consecutively enrolled population were identified. The only study identified that used a consecutively enrolled population was published as a letter describing a 2-stage screening strategy measuring direct or conjugated bilirubin levels in serum (ie liquid blood). This study reported a sensitivity of 100% and a specificity of 99.9%, however the PPV was low at 18.2% and the confidence intervals around the sensitivity and PPV results were wide. As this study was published as a letter limited details were available and a number of areas of potential or unclear bias were identified reducing confidence in the test performance results.

Four case control studies exploring potential screening tests for biliary atresia were also briefly described. These studies explored the ability of tests to distinguish between babies with known biliary atresia and controls and included measures of potential biomarkers such as circulating microRNAs, Apo C-II and Apo C-III; direct or conjugated bilirubin levels and bile acids. One of these studies (measuring bile acids) used dried bloodspot samples.

Summary: Criterion 4 not met

No new studies were identified that establish a suitable method for screening for biliary atresia using newborn dried bloodspots. A number of studies were identified considering other potential screening tests which may be developed further in the future. At present this criterion is not met.

Criterion 15: Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme.

Key Question: What is the reported mean age at surgery for biliary atresia (Kasai portoenterostomy) in the UK?

Additional sub-questions relating to this question include:

- is there any data to suggest that age at surgery has changed since 2012?
- what proportion of affected infants have late (>90 days[§]) Kasai portoenterostomy in the UK?
- how does this compare with areas which have introduced stool colour screening programmes?

The 2012 UK NSC review identified 1 UK study that reviewed all infants with confirmed biliary atresia born in England and Wales between January 1999 and December 2009. The study found that the median age at surgery was 54 days (range 7 to 209), and 10% of infants (n=44) were ≥90 days of age at time of the procedure. There was variation in age at procedure between centres. The 2012 review found that this was the best operative age reported of all national series in Europe and North America. Performance in England and Wales was also comparable with before-after analyses from Taiwan, where screening using stool colour cards was introduced nationwide in 2004[5].

Description of the evidence

In the current review, of the 29 studies identified as potentially relevant during title and abstract sifting, 20 related to this criterion. After review of the full texts no studies addressing the key question were identified. However, 2 studies described the age at surgery in Taiwan[11] and Japan[12] following the introduction of screening programmes using a stool colour card, therefore addressing 1 of the sub-questions.

Excluded studies at this stage included:

- 3 studies from non UK countries that do not have screening programmes
- 2 studies of service provision for Kasai portoenterostomy
- 2 descriptions of surgical techniques
- 2 studies focused on liver preservation and liver transplantation respectively
- 1 study focused on preterm babies only
- 1 study comparing open and laparoscopic surgery
- 1 study focused on the use of steroids after Kasai portoenterostomy
- 1 study looking at international incidence and outcomes of biliary atresia
- 4 commentaries or discussion papers

No studies were published between 2012 and 2016 that provided the mean or median age at surgery for biliary atresia in the UK. It is therefore not possible to determine whether the age at surgery has changed from the median of 54 days reported in the previous 2012 UK NSC review. No studies published between 2012 and 2016 provided details of the proportion of affected infants that have late (>90 days) Kasai portoenterostomy in the UK.

[§] Time to surgery is used as a proxy for clinical outcome with 90 days representing the upper limit considered acceptable

One study (Lin et al 2015[11]) was identified which described age at diagnosis and surgery and incidence over a 15-year period in Taiwan for 540 infants with biliary atresia. Taiwan introduced a screening programme using a stool colour card in 2004. In this study, Lin et al compared age at diagnosis, age at receiving Kasai surgery and age at receiving liver transplantation among 3 birth cohorts: (1) 1997 to 2001; (2) 2002 to 2006; and (3) 2007 to 2011. The authors reported that the mean age at diagnosis for the 3 cohorts were 57.9 ± 70.0 days, 55.6 ± 55.4 days and 52.6 ± 36.4 days respectively. The mean age at receiving Kasai surgery were 58.2 ± 42.0 days, 50.5 ± 30.8 days and 46.0 ± 23.8 days respectively. They also found that the proportion of biliary atresia cases that received the Kasai surgery within 60 days of age increased from 76.6% to 81.1%; however this increase was not statistically significant. A summary of these results are provided in Appendix Table 2.

Although the mean age at Kasai surgery decreased significantly, the standard deviation around the mean is quite large. This reduces confidence in these results particularly as the increase in proportion of biliary atresia cases operated on before 60 days of age was not significant. The authors did not report on the number of procedures that took place before 90 days of age.

Another study (Gu et al 2015[12]) investigated the age at Kasai surgery and the long-term probabilities of native liver survival as well as evaluating the sensitivity and specificity of a stool colour card used for a mass screening of biliary atresia conducted over 19 years in a Prefecture[**] in Japan. From 1994 to 2011, the stool colour card was distributed to all pregnant women in Tochigi Prefecture. Before or during the postnatal 1-month health check-up, the mothers returned the completed stool colour card to the attending paediatrician or obstetrician and 264,071 stool colour cards were collected out of 313,230 live births (a return rate of 84%). Of these, 26 were diagnosed with biliary atresia. Overall 34 patients were diagnosed with biliary atresia during the study period (ie 8 were not identified by the screening programme). All suspected cases of biliary atresia were referred for further examination. Gu et al reported a mean age at the time of surgery of 59.7 ± 19.4 days, an improvement from 70.3 days (before the implementation of the screening programme). They also reported that the median age at surgery was 58.5 days (range 18 to 109) compared to 65.5 days before the implementation of the screening programme. The proportion of biliary atresia cases that underwent surgery after 90 days of age was 5.9%. A summary of these results are provided in Appendix Table 3.

It should be noted that no confidence intervals or standard deviations were reported for the pre implementation figures. Out of 34 biliary atresia cases diagnosed during the study period, 26 (76.5%) were detected by the screening programme. Of the 8 cases not identified, 2 were in intensive care for more than 1 month after birth, 3 reported pale-pigmented coloured stool but did not present with visible jaundice and 1 patient did not show abnormality at the 1-month checkup. The guardian of 1 patient failed to use the stool colour card and 1 patient was not on the list but was later identified through the medical aid list.

Discussion

Both Lin et al[11] and Gu et al[12] observed a reduction in mean age at the time of Kasai surgery in Taiwan and Japan after the implementation of the stool colour card programme.

Lin et al[11] did not set out to assess the effectiveness of the stool colour card screening programme, which was introduced in Taiwan in 2004. The study compared different time

[**] a district under the authority of a prefect or governor

periods but these overlap with when the screening programme was implemented. The authors note that the reducing trend of the age at diagnosis started before the national stool colour card screening programme was implemented. Therefore they argue that the decrease in ages at biliary atresia diagnosis and subsequent surgery could not have been entirely due to the stool colour card screening program alone. They attribute it to other factors such as medical resource availability and better accessibility to surgical interventions which may also have contributed to these changes. However, Gu et al[12] concluded that the improvement in the time to Kasai surgery observed in their study were benefits of the stool colour card screening programme.

The most recent figure for the median age at surgery in the UK is the 54 days (range 7-209) cited in the 2012 UK NSC review which is less than that the median age at surgery reported in Japan (58.5 days) after the introduction of the screening programme. The mean age at Kasai surgery was 46 days in Taiwan but this was not thought to be just as a result of the screening programme. However, the median age at surgery was not reported so it is not possible to directly compare this with the latest available UK figure.

The proportion of biliary atresia cases that underwent surgery after 90 days of age in Japan reported by Gu et al[12] is lower at 5.9% than the 10% reported in the previous UK NSC review but it is not clear if this difference is clinically significant. Lin et al did not report the proportion of patients that underwent surgery at more than 90 days.

Summary: Criterion 15 met

The previous 2012 UK NSC review stated that biliary atresia care in England and Wales has been optimised through centralisation of care since 1999. No studies were published between 2012 and 2016 that provide an updated figure for the mean or median age at surgery for biliary atresia in the UK. It is therefore not possible to determine whether the age at surgery has changed from the median of 54 days reported in the previous 2012 UK NSC review. In the absence of new evidence to the contrary this criterion is met.

Conclusions and implications for policy

This report is an update review on systematic population screening for biliary atresia in newborn babies against select UK NSC criteria for appraising the viability, effectiveness and appropriateness of a screening programme. This review assessed key questions to determine if new evidence published since 2012 suggests that reconsideration of the current recommendation for newborn screening for biliary atresia in the UK is required.

The volume, quality and direction of new evidence published since January 2012 does not suggest that there have been any significant changes in the evidence base since the previous review. Several findings might be noted, including:

- no studies published between 2012 and 2016 considered testing for biliary atresia using newborn dried bloodspots in a general screening population
- a study exploring a 2-stage screening strategy for biliary atresia using liquid blood has been published as a letter with limited details available for appraisal at present
- case control studies have explored potential new targets for screening for biliary atresia using dried blood spots and liquid blood and may be developed further in the future
- no studies were published between 2012 and 2016 that provided the mean or median age at surgery for biliary atresia in the UK. It is therefore not possible to determine whether

the age at surgery has changed from the median of 54 days reported in the previous 2012 UK NSC review

- two studies reported reductions in age at surgery after the introduction of screening programmes using stool colour cards (in Taiwan and Japan). Median age at surgery, reported by one of study, was 58.5 days (range 18 to 109). The other study reported a mean age at surgery of 46.0 ± 23.8 days. This is comparable with the median age of 54 days (range 7-209) at Kasai surgery in the UK, reported in the 2012 UK NSC review.

Recommendation

The review concluded that there has been no significant change in the evidence base since the previous UK NSC review. The current recommendation not to introduce a UK systematic population screening programme for biliary atresia in newborn babies should be retained.

Limitations

Limited new evidence was identified to address the key questions in this review.

Search strategy

A literature search on newborn screening for biliary atresia was performed by Paula Coles, UK NSC Information Scientist on 23rd November 2016.

SOURCES SEARCHED: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present, Embase 1996-Present, Cochrane Library

DATES OF SEARCH: January 2012 to 23rd November 2016

SEARCH STRATEGY

Medline (OVID interface). Similar searches were carried out in the other databases.

1 Infant, Newborn/ 572735
2 (newborn or infan$ or neonat$).tw. 631082
3 1 or 2 (930036)
4 Biliary Atresia/ 2769
5 biliary atresia.tw. 3876
6 ((bile or hepatic) adj duct).tw. 36226
7 hepatobiliary disease.tw. 857
8 (conjugated adj (bilirubin or bile acid$)).tw. (1624)
9 4 or 5 or 6 or 7 or 8 (42276)
10 Neonatal Screening/ (9007)
11 (screen$3 or detect$3 or test or tests or testing or assess$).tw. (5719057)
12 10 or 11 (5720449)
13 3 and 9 and 12 (886)
14 limit 13 to yr="2012 -Current" (243)
15 Portoenterostomy, Hepatic/ (595)
16 kasai portoenterostomy.tw. (203)
17 Kasai procedure.tw. (195)
18 hepatoportoenterostomy.tw. (112)
19 bile drainage.tw. (454)
20 Liver Transplantation/ (51104)
21 liver transplant$.tw. (51267)
22 15 or 16 or 17 or 18 or 19 or 20 or 21 (65347)
23 Infant/ (749770)
24 Child/ (1593386)
25 child$.tw. (1241165)
26 3 or 23 or 24 or 25 (2798096)
27 9 and 22 and 26 (2096)
28 limit 27 to yr="2012 -Current" (447)
29 14 or 28 (602)

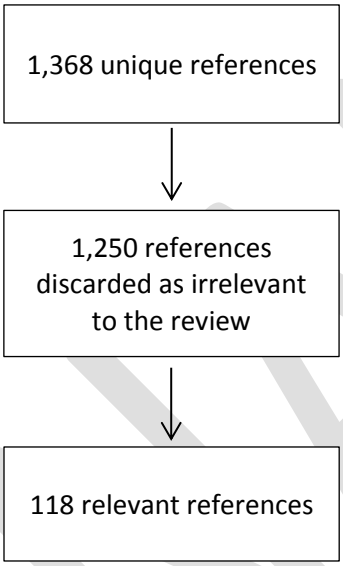
Table 2: Results of the literature search

Database	No. of citations retrieved
Medline	602
Embase	1,382

Cochrane Library	23
Total	**2,007**

After duplicates were removed, 1,368 unique references were sifted by title and abstract, and where necessary and available the full text, for potential relevance to the review. One hundred and eighteen papers remained and were passed to the SPH reviewer for further consideration.

Figure 1: Flow diagram summarising the results of the reference sifting process



These 118 references were classified as presented in Table 3.

Table 3: Summary of the relevant references by category

Category	No. of citations
Screening/ test: • guidelines (1) • screening or the test (20) • non-systematic reviews (6)	27
Surgery: • systematic reviews (3) • guidelines (2) • Kasai portoenterostomy (73) • non-systematic reviews (13)	91
Total	**118**

Key question PICOS[††]

Question	Has a suitable method of screening for biliary atresia using newborn dried bloodspots been identified?
Sub-questions/comments	Prospective studies of test accuracy in a consecutively enrolled population should be prioritised.
Population	Newborn
Intervention	Any testing process using newborn dried bloodspot eg TMS
Comparator	N/A
Outcomes	Sensitivity / Specificity. Positive / Negative predictive values
Inclusion criteria	4. There should be a simple, safe, precise and validated screening test

Question	What is the reported mean age at surgery for biliary atresia (Kasai portoenterostomy) in the UK?
Sub-questions/comments	Is there any data to suggest that age at surgery has changed since 2012? What proportion of affected infants have late (>90 days) Kasai portoenterostomy in the UK? How does this compare with areas which have introduced stool colour screening programmes?
Population	Infants with biliary atresia
Intervention	Kasai portoenterostomy
Comparator	Reported mean age at procedure in screening programmes internationally
Outcomes	Reported mean age at procedure by country
Inclusion criteria	15. Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme

Question	What is the accuracy of stool colour card screening in the detection of biliary atresia?
Sub-questions/comments	This question should only be addressed if indicated by answer to question 2 eg if there have been changes to the time to surgery reported since the previous review. Prospective studies of test accuracy in a consecutively enrolled population should be prioritised.
Population	Newborn
Intervention	Stool colour card screening
Comparator	N/A
Outcomes	Sensitivity / Specificity. Positive / Negative predictive values
Inclusion criteria	4. There should be a simple, safe, precise and validated screening test

[††] Population, Intervention, Comparator, Outcomes

Appendix Tables

Appendix number	1
Relevant criteria	4. There should be a simple, safe, precise and validated screening test
Relevant key question	Has a suitable method of screening for biliary atresia using newborn dried bloodspots been identified?
Publication details	Harpavat S. Garcia-Prats JA. Shneider BL. Newborn screening for biliary atresia. New England Journal of Medicine 375(6): 605-606
Study details	Prospective study of test performance
Study objectives	To assess the performance of a 2-stage screening strategy for detecting biliary atresia using serum bilirubin measurements
Inclusions	Infants born at 4 hospitals in Houston, Texas over a 15-month period
Exclusions	None stated. 98.8% of newborns were tested. 137 were not tested due to early death (55), early transfer (22), physician oversight (60) or parental refusal (1)
Population	11,636 infants born at 4 hospitals over a 15-month period
Test	Test 1: Direct or conjugated bilirubin levels in serum collected from all newborns at ≤60 hours old. Infants were considered positive if their direct or concentrated bilirubin concentration level exceeded the 95% percentile reference interval of their laboratory Test 2: Direct or conjugated bilirubin levels in serum collected from infants who tested positive to Test 1 at or before the first well-child visit (≤2 to 3 weeks old). Infants were considered positive if they had rising concentrations of direct or concentrated bilirubin concentration levels at re-testing
Comparator / reference standard	Cases of biliary atresia were identified by tracking infants who were undergoing liver evaluation at the 2 sub-speciality care paediatric hospitals in Houston
Results	Test 1: 121/ 11,636 infants tested positive Test 2: 11/ 114 infants tested positive NB: Only infants who tested positive in Test 1 received Test 2. 7 eligible infants did not receive Test 2 due to early death (3), withdrawal by clinician (2) or missed appointment (2) Information on diagnosis was provided in an online supplementary appendix. This was available for 5 of the 11 infants who tested positive for Test 2. Two of the infants were described as having biliary atresia The authors reported a sensitivity of 100% (95%CI 19.8% to 100%) and a specificity of 99.9% (95%CI 99.8% to 99.9) and a PPV of 18.2% (95% CI 3.2% to 52.2%)

Quality appraisal

Question	Assessment (Y, N, unclear)	Risk of Bias (low, high, unclear)	Supporting info
Domain I: Patient selection			
Consecutive or random sample of population enrolled?	Y	Low	Babies born at 4 hospitals in a 15-month period
Case-control design avoided?	Y	Low	
Inappropriate exclusions avoided?	Y	Low	No exclusion criteria
Domain II: Index Test			
Index test results interpreted without knowledge of reference standard results?	Unclear	Unclear	Information not provided
Threshold pre-specified?	Unclear	Unclear	Laboratory 95% percentile used as the reference interval, however it is not clearly specified if more than one laboratory was used and whether they used the same 95% percentile
Domain II: Reference standard			
Reference standard likely to correctly classify condition?	N	High	Positive biliary atresia cases identified by tracking infants at local specialist hospitals. It is possible that some infants with biliary atresia could have been missed
Reference standard results interpreted without knowledge of index test results?	Unclear	Unclear	Information not provided
Domain IV: Test strategy flow and timing			
Appropriate interval between index test and reference standard?	Unclear	Unclear	Time period between index test and follow-up tracking and length of follow-up tracking not specified
Did all participants receive same reference standard?	N	High	Positive biliary atresia cases identified by tracking infants at local specialist hospitals. It is possible that some infants could have been missed
All patients included in analysis?	N	High	Only infants testing positive in Test 1 received Test 2 Positive biliary atresia cases identified by

			tracking infants at local specialist hospitals. It is possible that some infants could have been missed
Applicability			
Applicable to UK screening population of interest?	Y	Low	Population included all babies born at 4 hospitals in the USA
Applicable to UK screening test of interest?	Y	Low	Test used liquid blood samples
Target condition measured by reference test applicable to UK screening condition of interest?	N	High	It is possible that the method used to identify biliary atresia cases could result in missed cases

Other comments

A test was positive if the direct or concentrated bilirubin concentration level exceeded the 95% percentile reference interval of their laboratory. The infants were born at 4 different hospitals so it is possible, but not clear, that the tests were assessed in different laboratories. Information about the 11 infants who tested positive for Test 2 provided as a supplementary appendix suggests that the 95% percentile used for Test 1 did vary with ranges of 0.0 to 0.2; 0.0 to 0.3 and 0.0 to 0.4 cited for different infants.

Positive biliary atresia cases were identified by tracking infants at local specialist hospitals. It is possible that some infants could have been missed (eg moved from the area). The supplementary appendix appears to suggest that a diagnosis was not available for all of the 11 infants who tested positive for Test 2.

This study is currently published as a letter. Given the limited information provided in the letter and potential limitations in the study design the test performance results should be treated with caution.

Appendix number	2
Relevant criteria	15. Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme
Relevant Key question	What is the reported mean age at surgery for biliary atresia (Kasai portoenterostomy) in the UK? • is there any data to suggest that age at surgery has changed since 2012? • what proportion of affected infants have late (>90 days) Kasai portoenterostomy in the UK? • how does this compare with areas which have introduced stool colour screening programmes?
Publication details	Lin JS, Chen SC, Lu CL, et al. Reduction of the ages at diagnosis and operation of biliary atresia in Taiwan: a 15-year population-based cohort study. World J Gastroenterology

	2015; 21:13080–13086
Study details	15-year population-based retrospective cohort study
Study objectives	To describe the ages at diagnosis and operation of biliary atresia (BA) and its incidence over a 15-year period in Taiwan
Inclusions	All inpatient records of patients diagnosed with biliary atresia between 1997 and 2011 from the Taiwan National Health Insurance Research Database
Exclusions	None reported
Population	540 infants with biliary atresia
Intervention/ test	Kasai portoenterostomy
Comparator	N/A
Results	Patients' characteristics, including sex, age at diagnosis, age at receiving Kasai surgery and age at receiving liver transplant were compared among 3 birth cohorts: (1) 1997 to 2001; (2) 2002 to 2006; and (3) 2007 to 2011. Screening was introduced in 2004 540 biliary atresia cases identified (265 males and 275 females) with an incidence of 1.62 per 10,000 live births **Mean age at diagnosis:** Cohort 1: 57.9 ± 70 days Cohort 2: 55.6 ± 55.4 days Cohort 3: 52.6 ± 36.4 days in the third cohort The decrease in mean age at diagnosis was statistically significant (p = 0.035) **Mean age at Kasai surgery:** Cohort 1: 58.2 ± 42 days Cohort 2: 50.5 ± 30.8 days Cohort 3: 46 ± 23.8 days The decrease in mean age at surgery was statistically significant (p = 0.006) The average proportion of BA cases that received Kasai surgery at <60 days of age increased from 76.6% to 81.1% over the study period; however, these changes were not statistically significant (p = 0.285)
Comments	The study did not set out to assess the effectiveness of the stool colour card screening programme, which was introduced in 2004. The study compared time periods but these overlap with when the programme was implemented Although the mean age at Kasai surgery decreased significantly, the standard deviation around the mean is quite large. This reduces confidence in these results particularly as the increase in proportion of biliary atresia cases receiving surgery before 60 days of age was not significant. The authors did not report data on surgery that took place before 90 days of age

Appendix number	3
Relevant criteria	15. Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme
Relevant Key question	What is the reported mean age at surgery for biliary atresia (Kasai portoenterostomy) in the UK? • Is there any data to suggest that age at surgery has changed since 2012? • What proportion of affected infants have late (>90 days) Kasai portoenterostomy in the UK? • How does this compare with areas which have introduced stool colour screening programmes?
Publication details	Gu YH, Yokoyama K, Mizuta K, et al. Stool color card screening for early detection of biliary atresia and long-term native liver survival: a 19-year cohort study in Japan. J Pediatr. 2015; 166:897–902
Study details	19-year cohort study
Study objectives	To evaluate the sensitivity and specificity of a stool colour card used for mass screening of biliary atresia conducted over 19 years in Japan. In addition, the age at Kasai procedure and the long-term probabilities of native liver survival were investigated
Inclusions	Live newborn infants from August 1994 to March 2011 to mothers living in Tochigi Prefecture, Japan
Exclusions	Infants born in Tochigi Prefecture to mothers who lived outside the Prefecture before giving birth were excluded
Population	313,130 newborns
Intervention/ test	Kasai portoenterostomy
Comparator	N/A
Results	313,230 live born infants were screened; 34 patients were diagnosed with biliary atresia. The sensitivity and specificity of stool colour card screening at the 1-month check-up were: • Sensitivity: 76.5% (95% CI 62.2% to 90.7%) • Specificity: 99.9% (95% CI 99.9% to 100%) **Age at surgery** The mean age at Kasai surgery was 59.7 ± 19.4 days for all 34 patients compared with 70.3 days prior to the introduction of the stool colour card screening programme (p=0.02). The mean age at time of surgery was 54.3 ± 15.8 days in those referred promptly and 77.5 ± 20.4 days in those missed at the agreed 1-month check-up (p=0.002)

	The median age at the time of Kasai surgery was 58.5 (18 to 109) days for all 34 patients compared with 65.5 days prior to the introduction of the stool colour card screening programme (p value not reported) **Percentage of biliary atresia cases who had surgery at less than 60 days of age** 34% before implementation of stool colour card programme versus 56% (95% CI 39.2% to 72.6%) after implementation **Percentage of biliary atresia cases who had surgery at more than 90 days of age** 13% before implementation of stool colour card programme versus 5.9% (95% CI 2% to 13.8%) after implementation
Comments	No confidence intervals or standard deviations were reported for the pre implementation figures

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