UK National Screening Committee

UK National Screening Committee (UK NSC)

Newborn screening for congenital adrenal hyperplasia

Date: 4 November 2021

Contents

Aim

To ask the UK National Screening Committee (UK NSC) to make a recommendation, based on the evidence presented in this document, whether or not newborn screening for congenital adrenal hyperplasia (CAH) meets the UK NSC criteria for a systematic population screening programme.

Current Recommendation

The UK NSC currently does not recommend systematic population screening for CAH in newborns. The Committee based this recommendation on the evidence provided by the 2015 review which was carried out by Glen Wilson.

The 2015 review found that screening tests using 17-hydroxyprogesterone (17-OHP) immunoassay produce a high number of false positive results, and that the test performance is particularly poor in premature babies and those with low birth weight. Though the 2015 review acknowledged that second-tier testing by mass spectrometry could improve test performance, for example the positive predictive value (PPV), the evidence on this was very limited. The review did not completely clarify the uncertainties surrounding the question on incidence of the condition in the UK. There was also uncertainty on whether screening at day 5 might take place too late to detect patients presymptomatically and be of benefit to the patient.

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Evidence Summary

The 2021 evidence summary was undertaken by the School of Health and Related Research (ScHARR), University of Sheffield in accordance with the triennial review process: https://www.gov.uk/government/publications/uk-nsc-evidence-review-process/uk-nsc-evidence-review-process

The aim of the 2021 evidence summary was to address the gaps in the evidence from the 2015 review through the following questions:

- What is the incidence of congenital adrenal hyperplasia in the UK population, including discrete subgroups of the population?
- What is the median age of presentation of congenital adrenal hyperplasia?
- What is the accuracy of available screening tests using dried blood spots (DBS) to detect congenital adrenal hyperplasia?

The conclusion of the 2021 evidence summary is that the current recommendation should be retained and therefore whole population screening for CAH in newborns should not be introduced in the UK. This is for the following reasons:

- A total of 24 papers were included in the evidence summary, some of which were relevant to more than one question
- No new studies of UK incidence of CAH were identified since the 2015 review, however the 2 studies from Great Britain (GB) that featured in the previous review were also included in this evidence summary. All the included studies reported data collected from newborn screening programmes, apart from those from GB which collected data through an active surveillance programme. The average incidence rate across screening studies was calculated as 1:16,869. The incidence rate in Great Britain was around this international average, being reported as 1:18,248
- No study set out explicitly to determine the time to presentation of symptoms in newborns. Instead, age at diagnosis was most commonly reported, hence the relevance of these studies to appropriately address question 2 is limited. The included data suggest that a number of children present with symptoms before the results of their screening tests would be currently available in the UK, and therefore they may not benefit from screening
- Overall, the incidence of CAH in Great Britain has been found to be approximately 1 in 18,000 children. However, the evidence on median age of presentation in newborns is limited in terms of volume and quality and it is therefore difficult to draw definitive conclusions relating to the impact

screening would have on clinical outcomes. Therefore, criterion 1 overall is not met

- Several countries use fluoroimmunoassay of 17-OHP to screen for CAH, and some use an additional second-tier liquid chromatography tandem mass spectrometry (LC-MS/MS) test to reduce the number of false positives referred to specialist services. There was variation between studies on cut-offs and day of screening. The reference standards also varied across studies and generally, there was a lack of clarity about the reference standard used in each study. Across studies, those with positive tests were subjected to variable and often poorly described diagnostic work-up strategies, and identification of false negatives was problematic, with uncertainty around whether all false negatives were being recorded. Whilst there was a fair amount of evidence relating to fluoroimmunoassay from large scale studies, all studies had high or unclear risk of bias. The evidence relating to LC-MS/MS was limited in terms of study design, sample size and quality, but showed promise for reducing the number of false positives (but not false negatives) identified by fluoroimmunoassay. Whilst there was variation between studies on the cut-off used and about which parameters to vary cut-offs by, the review noted that included studies showed that it was possible to describe cut-off values that, within their own specific context, can deliver adequate test performance

- Further studies could clarify a number of variables including the optimum cut-off values to be used by fluoroimmunoassay and LC-MS/MS with respect to weight, gestational age, and age when sampled, and whether cut-offs defined with reference to population biomarker percentiles could be an appropriate method in the UK. However, at present based on the findings of this evidence summary, the criteria 4 and 5 are judged as not met

- In summary, due to the limitations of the evidence, the recommendation is that newborn screening for CAH is still not recommended and that further research is needed to address the evidence gaps

Consultation

A three-month consultation was hosted on the UK NSC website. Direct emails were sent to 15 stakeholders. (Appendix A)

The public consultation closed on 1 September 2021. Please note that a general extension until 1 September was granted after some stakeholders fed back that they could not locate the consultation document on the new UK NSC website.

The total number of consultation responses received was 3.

Comments were received from the following 3 stakeholders (see Appendix B for comments):

- British Society for Paediatric Endocrinology and Diabetes (BSPED)
- Royal College of Paediatrics and Child Health (RCPCH)
- Lesley Tetlow, UK Newborn Screening Laboratories Network (UK NSLN)

The following themes were reflected across stakeholders' comments:

- The UK is an outlier in relation to the exclusion of CAH from a screening programme

    a. **Response**: the UK is often criticised because its newborn blood spot screening programme compares unfavourably to those of the majority of similar high-income countries, such as USA, Italy and the Netherlands in terms of the number of conditions included in the screening panel. However, this comparison, by itself, is too narrow. The UK NSC's rigorous approach towards evaluating the benefits and harms of screening often contrasts with evaluations of newborn blood spot tests done by policy makers in other countries. A 2018 systematic review by Taylor-Phillips *et al*. found that 42% of recommendations by national policy making organisations about whether to screen babies for diseases using the newborn blood spot test do not take account of the evidence on test accuracy, 36% do not review evidence about whether early treatment improves health outcomes, and 76% do not consider the evidence around potential harms of overdiagnosis (Taylor-Phillips *et al*. 2018)[1]. Not all countries appear to apply the same robust approach of conducting evidence reviews and health economic assessments before making a recommendation on newborn blood spot screening, as is standard in the UK. In the UK, newborn screening is also an intensively quality assured process which includes a full end to end pathway. This pathway is managed from the invitation to take part in screening (which is extended to every parent), testing, further testing as required, referral, diagnosis and treatment. It is uncertain whether other countries have such a robust service. This ultimately leads to safer programmes and better outcomes for children and their families in the UK.

[1] Taylor-Phillips S, Stinton C, Ferrante di Ruffano L, Seedat F, Clarke A, Deeks J J et al. Association between use of systematic reviews and national policy recommendations on screening newborn babies for rare diseases: systematic review and meta-analysis. BMJ 2018; 361:k1612. Available at: https://www.bmj.com/content/361/bmj.k1612.long

- The incidence of CAH is likely to be higher than reported in the evidence summary. Contrary to the conclusion of the review, criterion 1 is fully met as the incidence of CAH is common enough to justify screening and because serious events such as adrenal salt loss can be prevented if screening is conducted in the correct way

    a. **Response**: the active surveillance study reported by Knowles and Khalid involving the whole of Great Britain provides the most relevant data available in relation to incidence estimates of CAH in the UK. The studies were included in this evidence summary and it was noted that the incidence rate found in Great Britain, without screening, is broadly comparable with the included international studies, with screening. Therefore, the UK NSC is satisfied with the findings of this evidence summary in relation to the question on incidence, which is considered dealt with and met, and it will not need to be re-evaluated in future reviews of the topic. However, criterion 1 is very broad and covers many aspects of the condition, its epidemiology and natural history. The included studies provide a limited amount of evidence to indicate patterns of development and presentation of symptoms in children with CAH in their first month of life, suggesting that a number of children would present with symptoms before the results of their screening tests would be currently available in the UK, and therefore they may not benefit from screening. Hence, despite the availability of incidence data relevant to the UK, the criterion is not met overall because the current evidence on median age of presentation in newborns is too limited in terms of volume and quality to draw definitive conclusions relating to the impact screening would have on clinical outcomes

- The timing of blood spots in the UK newborn screening programme (5-8 days) poses a significant challenge for CAH screening and the detection of other inherited metabolic disease. A review of the day of screening should be undertaken to assess the impact of screening earlier on both current conditions and potential new candidates for newborn screening

    a. **Response**: A review of screening at day 5 is in the blood spot screening programme 5-year plan and the UK NSC would welcome the opportunity of taking part in the discussions on this complicated issue

- The assumption that “the results from the UK newborn screening programme would potentially be available at around 17 days” would render a CAH newborn screening programmes close to useless as the clinical presentation of a salt wasting crisis is usually in the second to third week of life. It remains unclear why such long turn-around times are estimated

a. **Response**: the point outlined by the stakeholder refers to the context of current English standards for the reporting of newborn screening results, which should be available on the child health information service system (CHISS) by 17 days of age or under (birth is day 0). This is part of the standards for newborn blood spot screening and the evidence summary simply made reference to it. In practice the day that the result is available on CHISS does not necessarily determine the day by which clinical action is taken for screen positive cases, with the majority of babies expected to be referred and on treatment by day 14 of life (personal communication). However, the issue of time to referral and intervention highlights the important practical, logistic, constraints within which cases for newborn screening must be considered. Further information on this would be a useful contribution to any subsequent discussion on screening for CAH.

- The two-tier testing approach is simple, safe and precise and can be conducted in such a way to meet criterion 4. The test values will depend on the used analytical platform, sample preparation and the specific analytic method. Thus, it would not be possible to extrapolate any values or specific ranges from the literature, which would render criterion 5 obsolete. No mention has been made of studies which use second tier molecular testing. Though at higher cost, this approach may result in fewer recalls, less clinical follow-up, and a reduction in unnecessary worry for families

    a. **Response**: the evidence included in the evidence summary about the screening test related to fluoroimmunoassays and liquid chromatography tandem mass spectrometry (LC-MS/MS) as first-tier and second-tier screening tests respectively. The inclusion criteria for the test question were not restricted to immunoassays and LC-MS/MS, and no studies using second-tier molecular testing were found within the search dates of the review. The evidence summary noted that both types of tests found (fluoroimmunoassays and LC-MS/MS) can be considered simple and safe since they require a dried blood spot, and can be used for mass screening, as is the case in other countries, though LC-MS/MS is somewhat more technical and, due to the constraints of processing large volumes of tests, it is more suited to a second-tier setting. Unfortunately, the quality of the studies assessing the performance of screening tests was generally poor. There was variation between studies on cut-offs and day of screening. The reference standards also varied across studies and generally, there was a lack of clarity about the reference standard used by each study. Across studies, those with positive tests were subjected to variable and often poorly described diagnostic work-up strategies, and identification of false negatives was problematic, with uncertainty around whether all

false negatives were being recorded. False negatives may be clinically significant in particular for those with classic salt-wasting CAH. A false negative may also hinder subsequent clinical diagnosis when presenting with symptoms. The evidence relating to LC-MS/MS was limited in terms of study design, sample size and quality, but showed promise for reducing the number of false positives (but not false negatives) identified by fluoroimmunoassay. Therefore, based on the findings of this evidence summary, the test criteria were judged as "not met". However, whilst there was variation between studies on the cut-off used and about which parameters to vary cut-offs by, the review noted that included studies showed that it was possible to describe cut-off values that, within their own specific context, can deliver adequate test performance. Hence, further studies (ideally UK-based) with better methodological quality and reporting clarity could help to improve the evidence base by clarifying a number of variables including the optimum cut-off values to be used by fluoroimmunoassay and LC-MS/MS with respect to weight, gestational age, and age when sampled, and whether cut-offs defined with reference to population biomarker percentiles could be an appropriate method in the UK

- It is unfortunate that there are so few studies using LC-MS/MS technology for first or second tier testing as the limited evidence suggests acceptable sensitivity, specificity and PPV. The time is right for an evaluation exploring this technology. A UK evaluation would also allow further evidence to be gathered regarding the impact screening would have on clinical outcomes

    a. **Response**: the UK NSC would welcome a UK-based study evaluating test accuracy for a screening strategy for CAH. As outlined by the evidence summary, studies conducted in a UK setting with better methodological quality and reporting clarity could help to improve the evidence base relating to the test accuracy. Some methodological considerations are suggested in the 2019 paper by Holtman *et al*. on test accuracy studies in low prevalence settings[2]. The UK NSC is also working with colleagues from the Netherlands to establish some principles for the design of test accuracy studies in rare conditions, in very low prevalence settings. The aim of this exercise is to provide helpful advice for those working in the field and ultimately improve the quality of the evidence base on which the UK NSC and other screening advisory bodies make their recommendations on the potential inclusion of rare conditions in the newborn blood spot screening programme. A

[2] Holtman GA, Berger MY, Burger H, Deeks JJ, Donner-Banzhoff N, Fanshawe TR, Koshiaris C, Leeflang MM, Oke JL, Perera R, Reitsma JB, Van den Bruel A. Development of practical recommendations for diagnostic accuracy studies in low-prevalence situations. J Clin Epidemiol. 2019 Oct; 114:38-48. Available at: https://www.sciencedirect.com/science/article/pii/S0895435618306619?via%3Dihub

study of reasonable size may also be able to explore issues relating to test turnaround time as highlighted as a concern by one response

- Additional considerations regarding the implementation of first tier and/or second tier tests were: a) if a test with high false positive rates is implemented, there will be implications on the paediatric endocrinology workforce, such as increased workload; b) two-tier approaches and application of algorithms of normative values according to gestational age are mainly driven by economical rationales rather than the highest standard methods available. Some European countries with health insurance-based reimbursement will only reimburse a first-tier immunoassay-based method, followed by a second tier LC/MSMS based methods; c) if mass spectrometry is used as second-tier test, the investment into several LC/MSMS machines is likely to be financially challenging (at least 2-3 needed per laboratory for back-up and method development and high sample throughput)

    a. **Response**: these are important points to consider. As previously mentioned, a UK-based study of test accuracy could help to clarify important measures of test performance in a UK setting. In relation to the points surrounding the costs, these would need to be considered in any potential future cost-effectiveness modelling exercises

Recommendation

The Committee is asked to approve the following recommendation:

A systematic population screening programme for congenital adrenal hyperplasia in newborns is not recommended in the UK.

Discussions with stakeholders indicate that this is an important topic and forthcoming work on the blood spot may provide a forum to explore this topic further.

Section 1 - Criteria for appraising the viability, effectiveness and appropriateness of a screening programme

This section looks at whether certain UK NSC criteria have been met when reviewing a given screening programme. Only the criteria evaluated by the current review have been included below.

The Condition

Criterion 1: The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.

- **Criterion 1 not met**

The Test

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

- **Criterion 4 not met**

Criterion 5: The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.

- **Criterion 5 not met**

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Appendix A: List of Organisations Contacted

1. ArchAngel MLD Trust
2. British Association of Perinatal Medicine
3. Clinical Genetics Society
4. Faculty of Public Health
5. Genetic Alliance UK
6. Metabolic Support UK
7. MetBio
8. PHE ANNB Screening Programmes
9. Rare Disease UK
10. Royal College of General Practitioners
11. Royal College of Midwives
12. Royal College of Paediatrics and Child Health
13. Royal College of Physicians
14. Royal College of Physicians and Surgeons of Glasgow
15. Royal College of Physicians of Edinburgh

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Appendix B: Consultation Responses

Note: Personally identifiable information has been redacted from certain comments, where individuals have chosen not to have personal details made public

1-British Society for Paediatric Endocrinology and Diabetes (BSPED).

After assessing the updated UK NSC CAH review from April 2021 in detail on behalf of the British Society for Paediatric Endocrinology and Diabetes (BSPED), we have come to the following conclusions.

Although the review seems to be formally correct when providing an external review against the programme appraisal criteria for the UK National Screening Committee, there seem to be major problems with the overall assessment and the recommendation to not screen for CAH.

This appears to be about screening for 21-hydroxylase deficiency the most common form of Congenital Adrenal Hyperplasia (CAH) and not all forms. Thus, from the start, a lack of precision appears to cause some confusion. Most screening programmes, particularly when using liquid chromatography tandem mass spectrometry (LC/MSMS) as first or second-tier test, detect other forms of CAH. This is commonly regarded as added benefit and should have been emphasised. Rather than defining strict criteria, it would have been useful to also define the aims and objectives of CAH (21-hydroxylase deficiency) newborn screening more clearly.

Criterion 1

Based on newborn screening programmes, the incidence of 21-hydroxylase deficiency in the literature has been established over the last 20-25 years in various similar populations to range between 1 in 10,000 to 1 in 18,000 life births. Other forms are rather rare and will not alter these numbers significantly. Of note whether the UK incidence is 1:16,000 or 1:18,000 does not appear to be relevant as conditions that are currently included in newborn screening are less common. In addition, the slightly lower incidence

compared to other European countries is highly suggestive that some cases in the UK remain undiagnosed. Furthermore, if the incidence data are not based on newborn screening it will depend on years of follow up (thereby including milder forms and increasing the incidence). Although this will not have a massive effect, one can estimate that the incidence in the UK is higher than 1 in 16,000, as cases (males and females) in the UK are still diagnosed later (aged 2-6 years) with moderate to severe forms of CAH, that consequently require a significantly higher degree of medical and psychological input than an early diagnosis with less favourable growth and puberty outcomes than in early diagnosed individuals as a result.

Importantly, it is not clear what the primary aim of prevention in the UK CAH newborn screening will be. Is this avoidance of critical illness due to salt losing crisis as consequence of mineralocorticoid deficiency and cardiovascular shock due to glucocorticoid deficiency? Early diagnosis of 46XX girls with atypical genitalia? Diagnosis of milder forms to avoid future complications such as androgen excess, precocious pseudopuberty, psychological distress etc.? Aim to diagnose and manage patients with severe and moderate forms as early as possible?

It is important to realise that as long as these questions remain unanswered, the UK will remain a significant outlier in the developed world in not relying on CAH newborn screening to diagnose infants with CAH earlier and provide the optimal care.

We recognised that the timing of blood spots in the UK newborn screening programme (5-8 days) poses a significant challenge for CAH screening and further studies or systematic data analysis would need to be performed if this timing is maintained in the UK over the long-term. As far as logistics go and communication of results, the recent Sydney experience (Neonatal Screen. 2020 Aug 12;6(3):63. doi: 10.3390/ijns6030063. eCollection 2020 Sep) shows that samples collected between 48-72 hrs and analysed by Day 8 in the first tier can still achieve the desired results. Thus, CAH newborn screening in the UK could be conducted in a meaningful way.

In the Sydney experience, the majority of cases were started on hydrocortisone (HC) in Week 2 or Week 3. This is in line with most other international screening programmes (personal communications). Thus, the current UK system, despite screening later than most other Western countries, could still be delivering significant improvements to patients' care as long as the processes were streamlined. We recognised that this will require service evaluation; however, the assumption that "the results from the UK newborn screening programme would potentially be available at around 17 days." would indeed render a CAH newborn screening

programmes close to useless as the clinical presentation of a salt wasting crisis is usually in the second to third week of life. Importantly, it remains unclear why such long turn-around times are estimated, when other newborn screening programmes, even when using LC/MSMS as second tier test, can turn around results significantly faster and even precisely diagnose CAH forms other than 21-hydroxylase deficiency. An introduction of LC/MSMS based testing would most likely reduce time until results are available significantly.

In contrast to the draft review, we suggest that criterion 1 is in fact fully met, as the incidence of CAH is common enough to justify screening and because serious events such as adrenal salt loss can be prevented if the screening is conducted in the correct way.

Criteria 4 and 5

There are indeed various approaches employed in newborn screening programmes around the world. A pure focus on the literature without assessing the wider context of different screening programmes appears to be of limited use to reach a decision if CAH newborn screening can be and should be implemented in the UK.

Nowadays two-tier approaches and application of algorithms of normative values according to gestational age are mainly driven by economical rationales rather than the highest standard methods available. Some European countries with health insurance-based reimbursement will only reimburse a first-tier immunoassay-based method, followed by a second tier LC/MSMS based methods. Another problem in several countries, and possibly also in the UK, is that the number of regional screening laboratories is very high, which makes the investment into several LC/MSMS machines (at least 2-3 needed per laboratory for back-up and method development and high sample throughput) financially challenging.

All biomarkers measured in different newborn screening programmes are steroid hormones. It is widely accepted and well established that liquid chromatography tandem mass spectrometry represents the gold standard with regards to sensitivity and specificity in the analysis of steroid hormones independent of the matrix. It is, however, also well-established in other analytical areas os steroid endocrinology that even with using LC/MSMS platforms different normative reference are required. This is particularly relevant in ranges very close to the cut-off concentrations.

It is well-established that the positive predictive value (PPV) when using immunoassays is poor. This is caused by lack of specificity of these assays and the high degree of cross-reactivity of fetal steroid hormones during the neonatal phase. This is a well-established analytical phenomenon that applies to steroid hormones in general and can only be overcome by using LC/MSMS based technologies. Thus, a critical and thorough appraisal is required of the wide-ranging strategies that have been employed till now by CAH newborn screening programmes. One of the most robust approaches published in 2007 (J Clin Endocrinol Metab. 2007 Jul;92(7):2581-9) has been a two-tier approach, measuring the first sample by an immunoassay followed by a second tier LC/MSMS approach. To our knowledge this strategy has been validated, is simple, safe and precise and this approach presents a long-standing example that CAH newborn screening can be conducted in a way meeting criterion 4. There are multiple other strategies employed by other screening laboratories globally. To suggest that criterion 4 is not met by such providers who need to operate in a competitive market often partially regulated by health insurance providers is not accurate.

The test values will depend on the laboratory delivering the screening programme and in particular the employed method. Even similar methods will require the implementation of provided specific normative values, which again will heavily depend on the used analytical platform, sample preparation and the specific analytic method. Thus, it will not be possible to extrapolate any values or specific ranges from the literature and renders criterion 5 obsolete.

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2-Royal College of Paediatrics and Child Health

Name:	Comments received on behalf of Dr Ali Aljumaili, the British Society of Paediatric Endocrinology and Diabetes and Dr Ranveer Sanghera.	**Email address:**	xxxx xxxx
Organisation (if appropriate):	Royal College of Paediatrics and Child Health		
Role:			

Do you consent to your name being published on the UK NSC website alongside your response?

Yes

Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*
General	General	CAH screening is a part of many national newborn screening programs for many countries that aim to detect congenital diseases as congenital hypothyroidism, congenital adrenal hyperplasia and inborn error of metabolism. It allows the diseases to be diagnosed as early as possible so that therapy can be stated at the optimal time to prevent complications. If the neonatal screening program for CAH is excluded, then other diseases may be missed or have a delayed diagnosis resulting in fatal outcomes.
General	General	CAH may be symptomatic, or asymptomatic without any apparent signs or symptoms that attract the attention of

		clinicians, because of this, congenital neonatal screening for C AH is important.
General	General	As the last assessment was in 2015, the reviewer was not sure if the accuracy of tests has improved. If you are implementing a test with high false positive rates, there will be implications on the paediatric endocrinology workforce, such as increased workload. If two tests are used (as per suggestion using mass spec), there can be a significant logistic burden. However, if most other countries in the EU are doing this, then this could work.
General	General	The reviewer was happy with this document.

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3-UK Newborn Screening Laboratories Network

Name:	Lesley Tetlow	**Email address:**	xxxx xxxx
Organisation (if appropriate):	UKNSLN (UK Newborn Screening Laboratories Network)		
Role:			

Do you consent to your name being published on the UK NSC website alongside your response?

Yes

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
P8	Median age of presentation	Benefit of screening for CAH is lower than in most other countries due to the current practice of screening on Day 5 of life. Detection of IMDs is similarly disadvantaged. It would seem appropriate that the NSC should undertake a review of the day of screening and assess the impact of screening earlier on both current conditions and potential candidates.
P8/9	Simple safe and validated screening test	It is unfortunate that there are so few studies using LC-MS/MS technology for first or second tier testing as the limited evidence suggests acceptable sensitivity, specificity and PPV. This suggests that the time is right for an evaluation exploring this technology.
P8/9	Simple safe and validated screening test	No mention has been made of studies which use second tier molecular testing. Notwithstanding the higher cost of this

		approach and problems associated with high sequence homology between the functional CVP21A2 gene and its non-functional pseudogene and in discriminating deleterious mutations from variants of unknown significance there are studies, some of which pre-date this review (e.g. Kosel et al Clin Chem 2005) which suggest that this approach may result in fewer recalls, less clinical follow-up, and a reduction in unnecessary worry for families.
P30	Incidence of CAH	Despite the short duration of the BPSU surveillance study and the high proportion of CAH cases of Asian ethnicity the study established an incidence rate of 1:18,248 and acknowledged that this may be an underestimate (due to only including children that had been brought to clinical attention and potentially missing those who may have died before diagnosis). The true incidence rate may therefore actually be higher. The study by xxxx xxxx shows clearly the benefits of screening in circumventing salt-wasting crises in boys. Hence these studies confirm that CAH is "an important health problem as judged by its frequency and/or severity". A UK evaluation would allow further evidence to be gathered regarding the impact screening would have on clinical outcomes.
P60	Summary of findings related to Criterion 4 & 5	It was deemed beyond the scope of the review to contact authors of international studies for clarification. Whilst appreciating time constraints of the reviewers, the UK is very much an outlier as regards the non-inclusion of CAH screening in our programme so it's important to gather all the evidence available, support studies to gather more evidence and revisit the decision in the light of further evidence.