UK National Screening Committee

Newborn hearing screening programme modification to detect auditory neuropathy spectrum disorder

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

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Plain English summary

This review looks at whether there could be a change to the tests used in the UK to screen newborn babies for hearing problems.

Currently, healthy babies (those not needing special care) are screened using what is called an automated otoacoustic emission (AOAE) test. When a baby passes the AOAE test it means the baby has no suspected hearing problems. There is, however, a rare condition called Auditory Neuropathy Spectrum Disorder (ANSD) that the AOAE test does not find. ANSD means that there is a problem with the hearing nerve. Babies with ANSD would pass the AOAE test and seem to have no hearing problems. There is another test available called the automated auditory brainstem response (AABR) test. If a baby passes the AABR test, it shows that the whole ear is healthy, including the hearing nerve. A baby with ANSD would pass the AOAE test but would fail the AABR test.

Most babies with ANSD have other problems, such as being born early or of very low birthweight. This means they are more likely to spend time in the special care baby unit. Babies in the special care units are screened using both the AABR and AOAE tests, so ANSD would be found. However, it is possible that some healthy babies (the general 'well-baby' population) might have ANSD and would not be found. This review aimed to find out whether all babies should be tested using the AABR test, not just sick (special care) babies.

The main findings from the review were:

- Information from the screening programme in England shows that 1 out of 1000 special care babies have ANSD. The programme found that ANSD affects a much smaller number of 2 out of 100,000 well-babies. Because well-babies in England are not screened using AABR, it is possible that some babies with ANSD are missed. Some areas of Scotland already screen well-babies using AABR, and these show that ANSD may actually affect 6 out of 100,000 well-babies. So the current screening programme in England might miss 4 out of 6 well-babies with ANSD. The information available suggests that these missed babies might have ANSD that only affects one ear and so is less likely to affect their hearing and development. More work is needed to be sure that the current screening programme is not missing babies with more severe ANSD that could affect their hearing and development.
- One small study from the United States carried out screening using AABR in well-babies. The study found that around 1 in 100 newborns had ANSD when screened. A few weeks later when they were tested again, they no longer had ANSD. This happens sometimes because it can take a few weeks for hearing to develop properly. A similar study needs to be carried out in the UK to see if the findings are the same.

- Some studies from other countries find that the AABR test takes longer to perform than the AOAE, costs more and uses more staff time. No UK studies were found that could provide an estimate of resource use and costs in the UK.

Because there are still a lot of unanswered questions, there is not enough information to support a change to the newborn hearing screening programme at the current time.

Executive summary

Purpose of the review

This evidence summary aims to evaluate whether the evidence available supports the modification of the current newborn hearing screening programme (NHSP) to include screening for Auditory Neuropathy Spectrum Disorder (ANSD) using automated auditory brainstem response (AABR) screening in the well-baby population.

In the current well-baby protocol, the automated otoacoustic emission (AOAE) is used as the initial screening test with AABR performed as the second step only if the baby fails the AOAE in one or both ears. AABR is generally more resource intensive and takes longer to perform. Concurrent AABR and AOAE screening is only performed in the neonatal intensive care unit (NICU) or special care baby unit (SCBU) protocols, as babies in these settings are known to be at higher risk of hearing problems, including ANSD.

The AOAE test tends to have a high false positive rate for any hearing loss, with subsequently higher referral rates than AABR. However, another concern is that the AOAE test will miss well-babies who have ANSD because this condition cannot be detected using the AOAE alone. Therefore, this review assesses whether there is evidence for a programme modification to incorporate AABR testing into the first stage of the well-baby screening protocol to allow detection of such babies.

Background

Rather than being a specific diagnosis with specific aetiology, ANSD represents a range of possible disorders and prognoses that are defined by a pattern of test results.[1] Babies with ANSD have normal function of the outer sensory hair cells of the cochlear, which is demonstrated by present OAEs (or cochlear microphonics test). However, they have an abnormal transmission at some point from the inner hair cells of the cochlear along the auditory nerve pathway to the auditory

brainstem, which is demonstrated by an absent or grossly abnormal ABR. As such ANSD would be characterised by an 'AABR fail/AOAE pass' screening response.

ANSD is associated with a range of risk factors including extreme hyperbilirubinaemia, prematurity, low birthweight and respiratory distress. For these reasons most babies with ANSD are expected to have spent time in NICU/SCBU where they would receive both AABR and AOAE screening and be detected. However, any well-babies with ANSD would pass the single-stage OAE screening that is offered to the general population of newborns who are not admitted to NICU/SCBU. Such babies would be discharged from the screening system, leaving them undetected and at potential risk of hearing impairment and associated developmental delay.

However, it is important to note that even if ANSD is screen-detected in the newborn period (either among the NICU/SCBU or well-baby populations), it is not possible to predict the effect that this may have on the child's hearing, speech and language development. In some cases, the test profile is temporary and due to a delayed maturation of the auditory nerve, also known as 'Transient ANSD'.[1, 2] Therefore the British Society of Audiology recommends that repeat testing is performed at 8-10 weeks corrected age. A definitive diagnosis of ANSD with resulting hearing impairment also requires full audiological assessment including conventional (rather than automated) ABR, behavioural testing and middle ear reflexes.[1] Full assessment is usually conducted by around 6 months. Even then, the ABR response and behavioural assessments may fluctuate or change over time.

Recommendation under review

This independent evidence review was commissioned by the UK National Screening Committee (UK NSC) following the 2017 annual call for topics. The National Deaf Children's Society (NDCS) proposed that the current NHSP well-baby protocol is extended to include AABR screening, in addition to AOAE, in order to allow detection of ANSD among well-babies (alongside other causes of hearing impairment). This review therefore aimed to assess whether the evidence is available to support such a screening programme modification.

The current NHSP screening protocols were informed by a 1997 health technology assessment (HTA) which explored the role of newborn hearing screening in detecting congenital hearing impairment.[3] Pre-1997 studies among general newborn population samples demonstrated that AOAE had lower specificity than AABR for detection of permanent childhood hearing impairment (PCHI). This would mean that AOAE would result in more false positives. Sensitivity was rarely reported, though some studies in high-risk populations demonstrated that AOAE had lower sensitivity than AABR. Notably these assessments were for detection of PCHI, only. ANSD is not mentioned in the HTA, which is likely a reflection of the fact that ANSD was only first described in 1996.

There could be an argument that AABR would be preferable as an initial screening test in the well-baby population because of its higher specificity, which would reduce false positives. However, this evidence review is not assessing the inclusion of AABR in the first stage of NHSP well-baby protocol due to low specificity of the AOAE test. Rather, the review solely focuses on the issue that AABR should be included in the first-stage of the protocol because AOAE would not detect ANSD among the well-baby population as ANSD is characterised by an AOAE test pass.

Focus of the review

This evidence review assesses whether there is evidence that the current NHSP well-baby protocol could be modified to include AABR as a universal screening test to identify ANSD among well-babies.

This review addressed 3 key questions:

1. What is the incidence of ANSD in newborn babies in the UK? What proportion present in NICU/SCBU and what proportion present in the otherwise well-baby population –Criterion 1
2. What is the test performance of AABR screening to identify ANSD among the well-baby population? – Criterion 4
3. What are the practical implications of including AABR screening for well-babies? – Criteria 6, 14, 18

A rapid review search for each of these 3 questions was conducted in June 2019 for studies published from 1997 onwards (the date of the last HTA). The focus of this rapid review was on ANSD. However, recognising that studies may have been published around programme modifications and practical implications of AABR screening for detecting PCHI in general (where the same issues such as test time and resources would apply), a supplementary search was conducted for question 3, removing the ANSD search filter. In this case the search was conducted only from 2014 onwards. It was established that this rapid review into ANSD would never be able to give a comprehensive view of all literature evaluating the resource implications of AABR in newborn screening programmes. This supplementary search therefore aimed to capture just the most recent literature on this wider topic.

For question 1 on the incidence of ANSD in the UK, the decision was made *a priori* that the literature search would be supplemented by data obtained from the NHSP in England and from Universal Newborn Hearing Screening in Scotland (UNHS) on the number of cases of ANSD identified across the NICU and well-baby populations. In the UNHS, 7/14 health boards provide AOAE screening for well-babies, as the NHSP, while 7 boards already perform AABR well-baby screening. Therefore, this information could give a valid indication of the difference than AABR screening for well-babies could make.

Findings and gaps in the evidence of this review

Overall the evidence available on the incidence of ANSD among well-babies, and the potential test performance results from AABR screening of well-babies, leaves uncertainty. There is also a lack of information on the practical implications from screening programme modification.

Incidence of ANSD among well-babies in the UK

Data from both the NHSP in England and UNHS in Scotland find that the incidence of ANSD among babies from NICU/SCBU (who all receive AABR screening) is around 1 in 1000. The majority of these babies (>75%) appear to have bilateral ANSD. Bilateral hearing impairment is recognised to have the greatest effect on developmental outcomes.

Among well-babies, data from the NHSP and the 7 health boards in Scotland where AOAE screening is performed find a much lower incidence of ANSD of 2 in 100,000. Data from the other 7 health boards in Scotland that already perform AABR screening indicate that this is an underestimate, finding a slightly higher incidence of 6 in 100,000 well-babies. This suggests that around 4 in 100,000 well-babies with ANSD remain undetected within AOAE screening systems. Where AABR screening was used, 2/6 well-babies had bilateral ANSD while 4/6 had unilateral ANSD, thereby contrasting with the pattern seen for NICU/SCBU. Extrapolating this incidence to England and the rest of Scotland indicates that most well-babies expected to have had bilateral ANSD within AOAE-screening systems have still been identified, while unilateral ANSD appears to have been missed. However, this is a speculative conclusion based on small numbers.

The NHSP data shows that two-thirds of well-babies with bilateral ANSD failed AOAE screening. This is at odds with the typical ANSD profile (AABR fail/AOAE pass) but could be for several reasons including the high ‘false positive’ rate for the AOAE test. For those well-babies with bilateral ANSD who were missed by screening, neither the NHSP nor UNHS report how or when they were detected clinically. As such there is insufficient information to know whether well-babies with bilateral ANSD could be at risk of adverse outcomes as a result of delayed clinical detection rather than screen detection.

Of babies with unilateral ANSD, those with other hearing loss in the contralateral ear (that is, most at risk due to bilateral PCHI) should be detected through AOAE screening. The data suggests that it could be well-babies with isolated unilateral ANSD who remain undetected. Given that this has uncertain effect on developmental outcomes and there is no consensus on management, this could potentially avoid over-detection of such cases.

As these are all audiological diagnoses, the UK data is also unable to inform the incidence of transient ANSD at birth (due to delayed maturation of the auditory nerve) which then recovers. This could be another issue of potential over-detection within an AABR screening programme.

Further study of AABR screening in a larger sample of well-babies would be needed to confirm whether the incidence of 6 in 100,000 is correct, that unilateral ANSD predominates in this population, and to look at the incidence of transient ANSD at birth. There is also a need to address whether clinical diagnosis of bilateral ANSD affects the timing of audiological assessment, management and outcomes compared with screening detection. This would allow better understanding of the condition and whether AABR screening may need to be included in the newborn well-baby protocol.

Test performance of AABR screening to identify ANSD among well-babies

One small cohort study has trialled AABR screening in the well-baby population in one US region. This study found a 0.92% referral rate for ANSD (20/2167 with ABBR fail/OAE pass) of a total 1.0% referral rate (plus 2 babies with AABR fail/OAE fail). At repeat outpatient testing no babies had ANSD (0% PPV) giving no referrals for audiology diagnosis. These cases likely reflect transient ANSD at birth due to delayed neural maturation. In the context of screening programme, this could mean over-identification and further assessment of babies who may not be identified through standard AOAE screening, and who may have gone on to have normal speech and language development. Notably 85% had also demonstrated isolated unilateral ANSD, the management of which is unclear according to current guidance. The complete absence of any permanent cases in this study likely reflects the small sample size and low incidence of ANSD among well-babies. However, if AABR well-baby screening were introduced on a wider scale, a predominance of unilateral ANSD could lead to management uncertainties.

Sensitivity, specificity or NPV could not be assessed in this study due to the lack of audiology follow-up of babies who passed AABR, either at screening or repeat testing. There is also uncertain applicability to the UK due to the different automated devices used and the low socioeconomic status of this population (where the incidence of ANSD may be higher). This was also a sequential testing programme where AOAE was performed only if babies failed the AABR. This would not reflect the findings from a screening programme where AABR and AOAE were performed concurrently, with referral for failure on either/both tests. Such a programme would have a higher overall referral rate, and there would likely be more non-ANSD false positives (babies who fail only the AOAE test).

Overall, the current evidence provides an unreliable indication of the test performance of AABR screening of well-babies. A UK study is needed to assess the performance of AABR screening among well-babies using AABR and AOAE devices as used in the NHSP.

The practical implications of AABR screening of well-babies

No UK evidence was identified to inform the practical implications of including AABR in newborn hearing screening for well-babies. Two studies, from the US and from Iran, demonstrated that AABR screening takes longer to perform than AOAE, permits screening of fewer newborns per day, and is

associated with higher cost. However, there was uncertainty around the inputs used to estimate cost and timing, and the 2 studies gave inconsistent results. Neither study has accounted for changes to hospital infrastructure, personnel requirements or training. There is uncertainty whether the AABR and AOAE devices used are applicable to the UK. The studies also consider only single stage screening, rather than a programme where both screening tests are performed concurrently. There is no information on acceptability of well-baby AABR screening to either health professionals or parents, or whether this may affect screening uptake by parents.

The lack of applicable evidence means that further study is needed of the practical implications of AABR screening from the UK perspective.

Recommendations on screening

The evidence available does not indicate that the well-baby newborn hearing screening programme should be modified at the current time to included AABR as a universal screening test to detect ANSD among well-babies.

Evidence uncertainties

Further study of AABR screening in well-babies would be needed to address the outstanding questions of this evidence review. This may help:

- to confirm the incidence of ANSD among well-babies – both transient at birth and confirmed at audiology follow-up at 2 to 3 months of age
- to confirm whether unilateral ANSD does predominate, and whether this may result in unnecessary referral or management uncertainties
- to obtain information on the effect of diagnostic delay in well-babies with bilateral ANSD
- to obtain information on the practical implications including resources for staffing, training and other programme modifications, and the acceptability of ABBR testing in the well-baby population.

Limitations

The search strategy was built on a protocol developed *a priori* for each of the 3 key questions. Searching was limited to 3 literature databases and did not include grey literature resources (except for NHSP and UNHS data). Studies only available in non-English language, editorials, abstracts, conference reports or poster presentations were not included. The reviewers were also unable to contact study authors or review non-published material. For pragmatic reasons within the constraints of a rapid review, the literature search on the practical implications of AABR screening was limited to the previous 5 years. Literature was then only obtained for full text appraisal when

this was a clear aim of the study, as stated in the study abstract. As such there is the possibility that literature containing relevant information on the implications of AABR screening may have been missed.

Introduction and approach

Background

Auditory Neuropathy Spectrum Disorder (ANSD) is a term used for a pattern of test results that show normal function of the outer sensory hair cells of the cochlear, but abnormal transmission at some point from the inner hair cells of the cochlear along the auditory nerve pathway to the auditory brainstem.[1] It has been estimated that ANSD may account for around 1 in 10 children with permanent childhood hearing impairment (PCHI).[2]

The term 'auditory neuropathy' was first used in 1996 when Starr et al[4] described 10 children and adults who presented with hearing impairment characterised by:

- Present otoacoustic emissions (OAEs) and cochlear microphonics (CM) tests, demonstrating normal outer hair cell function
- Absent or severely abnormal auditory brainstem response (ABR), demonstrating a disrupted auditory pathway

(The tests and their interpretation are explained further below)

The condition was variably referred to as auditory dys-synchrony or de-synchrony, peri-synaptic audiopathy, auditory mismatch, neural hearing loss or persistent outer hair cell function, before ANSD was adopted by consensus in 2008. This term was considered to better reflect the fact that this is not a diagnosis with single aetiology, but a range of possible disorders and prognoses defined by a pattern of test results.[1]

Early studies indicated that around 40% of cases of ANSD may have genetic cause.[2] Several gene variants have been associated, including those of the *DFNB9* gene which codes for otoferlin protein involved in synaptic functioning at the inner cochlear hair cells.[1] Other possible causes may include neurodegenerative, metabolic and mitochondrial conditions, and structural conditions, such as hydrocephalus, tumours, auditory nerve or brainstem anomalies.[1] ANSD has also been associated with a number of risk factors:[1, 2]

- Hyperbilirubinaemia (particularly extreme requiring exchange transfusion)
- Prematurity (particularly extreme <28 weeks' gestation)
- Low birthweight
- Anoxia
- Respiratory distress
- Hypoxic ischaemic encephalopathy or intraventricular haemorrhage
- Receipt of artificial ventilation
- Ototoxic drugs

Due to the range of associated risk factors, most babies with ANSD are expected to have spent time on the neonatal intensive care unit (NICU) or special care baby unit (SCBU).

Screening detection of ANSD

The auditory brainstem response (ABR)* test measures brain activity in response to sound. The test involves placing surface electrodes on the baby's head and playing click or tone pip stimuli through headphones. In ANSD, an absent or severely abnormal ABR (test fail) is defined by a grossly abnormal waveform (no wave V, which reflects brainstem auditory processing) in response to click stimuli at greater than 75 decibels.[1, 5, 6] The ABR can distinguish between conductive and sensorineural loss,† though an otoacoustic emission (OAE) or cochlear microphonic (CM) test is required to confirm the diagnosis of ANSD.

OAEs are vibrations produced by the outer hair cells of the cochlear in response to auditory stimulation. These can be detected by a small probe placed in the ear, which both emits sound and records the response.[5, 7‡] ANSD is indicated by an absent or grossly abnormal ABR (test fail) combined with present OAE (test pass), showing neuropathy combined with normal cochlear function. Cochlear microphonics (CM) is an alternative test of cochlear outer hair cell function. This is not normally required if the OAE is clearly present. However, the OAE has been observed to disappear over time in some cases of ANSD (possibly due to coexisting sensorineural hearing loss). If both ABR and OAE are absent (test fails), CM is also required. ANSD is, therefore, determined by an absent or grossly abnormal ABR in the presence of OAEs and/or CMs.[1]

Diagnostic follow-up and prognosis

Although many children with the ANSD profile of test results at diagnostic follow-up do turn out to have some form of permanent hearing impairment, the prognosis is variable. An absent or abnormal ABR cannot predict the level of hearing loss or the impact that this will have on the child.[1, 2] 'Transient ANSD' is also well recognised, where the test profile is temporary in the newborn period, resulting from delayed maturation of the auditory nerve (for example, in preterm

* The automated ABR system (AABR) is used in all screening programmes, but conventional ABR is required for diagnosis.
† Tone pip air conduction ABR (4kHz) is often be used as the initial test. If this is absent, a normal ABR with use of a bone conductor indicates conductive or mixed hearing loss. A normal waveform with air conduction tone pip ABR at lower frequency (0.5 or 1 kHz), or with click-evoked ABR, indicates sensorineural hearing loss. Click-evoked ABR is required in ANSD diagnosis.
‡ There are two 2 forms of OAE test, the distortion product (DPOAE) and transient evoked (TEOAE). The latter is preferable and used in most screening programmes (including UK) being considered easier to perform and more reliable than DPOAE as it differentiates from background noise. TEOAE delivers a series of clicks with the responses averaged to create a waveform.

babies) rather than from other causes. Therefore repeat ABR at around 8-10 weeks corrected age is recommended (along with testing of cochlear function) before a definitive diagnosis is made.[1§] Full audiological assessment would include behavioural audiometry, electrophysiological tests, tympanometry and middle ear reflex testing.[1, 2] These tests are usually carried out from around 6 months of age to assess the child's hearing and development, and are used as part of ongoing assessment and monitoring. The British Society of Audiology suggest that a repeat ABR at around 12-18 months is considered on an individual basis.[1] There is the issue of practicality in performing ABR at this age (the test requires the child to be still/asleep), but also questions of how informative it is compared with assessments of behavioural responses and speech development, and whether ongoing use of ANSD as a term is helpful.[1]

Management of children with the ANSD profile is multidisciplinary, centring upon support for the parents/carers and guided by the language and communication development and needs of the child. The prognostic course is known to be highly variable and both ABR and auditory behavioural thresholds may be stable, improve, fluctuate or deteriorate over time. Hearing aids may be indicated for children with clear behavioural hearing loss. However, due to the variable outlook, cochlear implants are usually only considered at a later stage when audiological assessments are stable and it is clear that there is permanent profound hearing loss.[1]

Current screening policy context and previous reviews

This independent evidence review was commissioned by the UK National Screening Committee (UK NSC) following the 2017 annual call for topics. The National Deaf Children's Society (NDCS) proposed that the current Newborn Hearing Screening Programme (NHSP) well-baby protocol is extended to include AABR screening, in addition to OAE, in order to detect ANSD among well-babies.

The NHSP in England currently has 2 screening pathways, one for well-babies and one for babies who spend time in NICU or SCBU.

Well-babies are screened first by the automated OAE (AOAE) test:[**]

- No response in one or both ears: repeat AOAE 0.5 hours after first AOAE
- Still no response in one or both ears: then screen by automated ABR (AABR)
- Clear response in both ears: discharge (unless there are risk factors indicating surveillance)

[§] As noted above, the automated ABR system (AABR) is used in all screening programmes, but conventional ABR is required for diagnosis in follow-up auditory assessment.

[**] As noted, TEOAE systems are used in the NHSP. As with ABR, automated OAE (AOAE) is used in screening programmes.

In NICU/SCBU, babies are screened by both AOAE and AABR:

- AABR no clear response (or inconclusive) in one or both ears: refer for audiology assessment (within 4 weeks)
- AABR clear response in both ears, but no AOAE response in both ears: refer for audiology assessment (at 7 to 9 months of age)
- AABR clear response in both ears and AOAE clear response in one or both ears: discharge (unless there are risk factors indicating the need for further audiology assessment at 7-9 months of age)

Therefore there is the potential that any well-babies with ANSD would be missed by the current NHSP, as by the definition of ANSD, they should have a clear pass response to OAE[††] testing and so would be discharged.

Northern Ireland endorses the standards of the NHSP and follows the same protocols as England. Wales differs slightly in that well-babies who fail the initial OAE may be referred either directly for diagnostic ABR or for repeat OAE. Babies who spend >48 hours in NICU/SCBU receive initial AABR screening. However, as only high-risk babies receive initial AABR screening, the Welsh well-baby protocol would similarly not detect ANSD.

In Scotland, Universal Newborn Hearing Screening (UNHS) is not nationally commissioned but is delivered at the regional health board level. There are 2 different protocols currently in operation, in both well-baby and NICU/SCBU populations. In 7 of 14 NHS boards, well-babies are screened using OAE only (with AABR only if the baby fails initial and repeat OAEs), while in the other 7 boards well-babies are screened using AABR (with repeat AABR for a fail response). Therefore, it is where this latter protocol is applied in Scotland that well-babies with the ANSD test profile could be screen-detected in the UK. NICU/SCBU babies in Scotland may be screened using AABR only (like Wales) or using both AOAE and AABR (like NHSP).

The current NHSP screening recommendations were informed by a 1997 health technology assessment (HTA) which explored the role of newborn hearing screening in detecting congenital hearing impairment.[3] The HTA reviewed studies that had looked at the test performance of OAE and AABR (either as individual tests or programmes using variable sequence) for the detection of permanent congenital hearing impairment (PCHI). Pre-1997 studies among general newborn population samples essentially demonstrated that the OAE screening test had specificity roughly between 70 and 90% for PCHI, while AABR would have very high specificity around 99% (compared

[††] NB. Most literature refers only to OAE, often specifying the type of test such as TEOAE or DPOAE, but not specifying that this as an automated test. For consistency, the remainder of this report uses the term OAE, which may be assumed to be an automated test.

with conventional ABR). Sensitivity was rarely reported for general population studies, though some studies in high-risk populations demonstrated lower sensitivity of OAE at around 80% compared with closer to 100% for AABR.

Notably these assessments are for detection of PCHI. ANSD is not mentioned in the HTA, which is likely a reflection of the fact that the HTA was published in 1997 and ANSD was only first described in 1996. It could be questioned whether AABR would be preferable as an initial screening test in the well-baby population as the higher specificity would reduce the number of false positives and referral rates for PCHI. However, this evidence review is not assessing whether there is a case for including AABR in the NHSP well-baby protocol due to the lower false positive rate compared with the OAE test. This review focuses solely on the fact that OAE does not allow detection of ANSD among the well-baby population (because ANSD is characterised by an OAE test pass‡‡) and therefore whether inclusion of AABR would improve detection.

The latest 2007 position statement from the US Joint Committee on Hearing Impairment (JCHI)[6] recommended different screening protocols for NICU and well-baby populations, stating that all babies admitted to NICU require ABR screening to ensure that neural hearing loss is not missed. The JCHI acknowledged that universal screening of well-babies by the OAE test may miss ANSD. However, they state that these disorders typically occur among children who spend time on NICU. They advise that all children should receive ongoing monitoring for age-appropriate auditory behaviours and communication, regardless of their screening outcome.[6] Therefore the UK NHSP is consistent with the current JCHI position.

Objectives

This review aims to assess whether there is evidence indicating that the current NHSP well-baby protocol could be modified to include AABR as a universal screening test to detect ANSD among well-babies.

Three questions have been assessed: the incidence of ANSD among well-babies (that is, how many are being missed), test performance of the AABR in detecting ANSD among well-babies, and the expected practical implications of such an extensive programme modification. These questions are outlined in Table 1.

‡‡ Excepting referrals for some newborns with ANSD where the OAE is absent (when CM is needed to confirm the diagnosis), or where there is additional conventional hearing loss.

Table 1. Key questions for the evidence summary, and relationship to UK NSC screening criteria

	Criterion	Key questions	Studies Included
	THE CONDITION		
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.	1. What is the incidence of ANSD in newborn babies in the UK? How many new cases are there each year? What proportion present in NICU/SCBU? What proportion present in the otherwise well-baby population? How are these babies identified?	2 studies, in addition to NHSP and UNHS programme data
	THE TEST		
4	There should be a simple, safe, precise and validated screening test.	2. What is the test performance of AABR screening to identify ANSD among the well-baby population?	1 study
	THE TEST, SCREENING PROGRAMME, IMPLEMENTATION		
6	The test, from sample collection to delivery of results, should be acceptable to the target population	3. What are the practical implications of including AABR in newborn hearing screening for well-babies?	2 studies
14	The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie. value for money). Assessment against this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.		
18	Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme.		

Methods

The current review was conducted by Bazian (part of the Economist Intelligence Healthcare Unit), in keeping with the UK National Screening Committee evidence review process. Database searches were conducted on 29th June 2019 to identify studies relevant to the questions detailed in

Table 1.

Eligibility for inclusion in the review

The systematic literature search of MEDLINE and Embase databases (Embase.com) and The Cochrane Library (Wiley Online) was performed for studies published between January 1997 and June 2019.

Individual searches were conducted for each of the 3 key questions. For question 3, the search from 1997 onwards looked for literature on the implications of programme modification to include AABR screening in relation to detection of ANSD, specifically. However, recognising that programme modification may have been considered for detection of PCHI in general (where the same issues such as test time and resources would apply) the decision was made *a priori* to conduct a supplementary search looking at the implications of AABR programme modification removing the ANSD filter. In this case the search was conducted only from 2014 onwards. It was established that this rapid review into ANSD would never be able to give a comprehensive view of all literature evaluating the resource implications of AABR in newborn screening programmes. This supplementary search therefore aimed to capture just the most recent literature on this wider topic.

For question 1 on the incidence of ANSD in the UK, the decision was also made *a priori* that the literature search would be supplemented by data from the NHSP in England and from UNHS in Scotland on the number of cases of ANSD identified across the NICU and well-baby populations.

Searches for each of the 3 questions retrieved a total of 845 citations, which included duplication across the questions. The full search strategy is presented in Appendix 1.

The following review process was followed:

1. Each of the 845 titles and abstract were reviewed against the inclusion/exclusion criteria for each question by one information specialist. Where the applicability was unclear, the article was included at this stage to ensure that all potentially relevant studies were captured. Duplicates across the key questions (for example, studies identified in both the search for Q2 and Q3) where not removed at the first sifting stage so that the main reviewer could see the full range of evidence retrieved for each question. In total 162 citations were included at first sift (125 unique articles when removing duplicates across questions).
2. At second sift the main reviewer reviewed each of the 125 abstracts for potential relevance to any of the 3 questions. Where the article content was unclear from the abstract, full text was obtained to ensure that potentially relevant literature was not missed.
3. A total of 40 articles were acquired for the full-text review stage. Each full-text article was reviewed against the inclusion/exclusion criteria by the main reviewer, who determined whether the article was relevant to one or more of the review questions. All inclusion/exclusion decisions were reviewed by a

second independent reviewer who provided input in cases of uncertainty. Any disagreements were resolved by discussion until a consensus was met.

Eligibility criteria for each question are presented in **Error! Reference source not found.** below.

Table 2. Inclusion and exclusion criteria for the key questions

Key question	Inclusion criteria							Exclusion criteria
	Population	Target condition	Intervention	Reference Standard	Comparator	Outcome	Study type	
1. What is the incidence of ANSD in newborn babies in the UK?	Newborn babies in the UK: in NICU and among the well-baby population	ANSD	NA	NA	NA	ANSD diagnosis or profile of test results	Surveillance reports/registry data. Cross-sectional or cohort studies. Systematic reviews (SRs) of these studies	Non-UK studies. Studies with population size <1000. Editorials, conference abstracts, opinion pieces, non-SRs, non-English language studies.
2. What is the test performance of AABR to detect ANSD?	Newborn well-babies	ANSD	AABR as an initial screen, alone or in combination with OAE	Diagnosis including any combination of ABR, OAE/CM test or other audiological tests	OAE alone, or none	Referral rate Test failure rate Sensitivity Specificity Positive and negative predicative value	Cohort studies in consecutively enrolled populations where all received the test and reference standard. SRs of these studies	Studies in high-risk samples such as babies with low birthweight, hyperbilirubinaemia, NICU/SCBU. Editorials, conference abstracts, opinion pieces, non-SRs, non-English language studies.
3. What are the practical implications of including	Newborn well-babies	ANSD	AABR as an initial screen, alone or in	NA	OAE alone, or no screening	Time to complete test Staffing	Comparative cohort studies, randomised controlled	Non-comparative studies, qualitative studies.

AABR in newborn hearing screening for well-babies?	PCHI (search 2014 to date)	combination with OAE	Acceptability or practicality Costs Screening equipment IT system change or other resources	trials, cost-effectiveness studies. SRs of these studies.	Studies where relevant information is not apparent from the study abstract. Editorials, conference abstracts, opinion pieces, non-SRs, non-English language studies.

In addition to the exclusions outlined in Table 2, the following exclusion criteria were applied at second sift, either at abstract level (if the content was clear from the abstract*) or at full-text appraisal. Although some of these exclusions were question specific, others were general topic exclusions that were not related to a specific question. Therefore, they have been listed here:

- Studies reporting cases of ANSD among babies/children with PCHI when this could not be related to population size to give incidence (Q1), or to screening test results to look at test performance (Q2)
- Studies reporting test performance of AABR (+/- OAE) for detection of PCHI, but not giving any data on ANSD
- Studies evaluating the current system of initial OAE screen, with AABR only included in the subsequent work-up of referred cases (several studies related to the issues of the high referral rate/false positives of OAE, as discussed above)
- Studies assessing selective high-risk samples, for example preterm babies, or those with hyperbilirubinaemia
- Studies assessing the risk factors associated with screening test response or with SNHL
- Studies looking at the genetic associations with PCHI or SNHL
- Studies assessing the relationship between ABR waveforms and behavioural audiometry thresholds
- Case-control studies assessing the validity of new automated systems
- Non-applicable screening scenarios, such as community screening of older babies or screening using conventional ABR (which would not be applied in practice)

*Of note there was one exception to this. For question 3 on the practical implications of AABR screening, it was recognised that information such as time or cost could be contained within the full-text of many articles of variable design. It may not be possible from the abstract to know that such information was covered within the publication at all. In the context of a rapid review, it would not be feasible to review all retrieved literature for potential content on implications. Therefore, the decision was made *a priori* that for this question such information would have to be reported in the abstract or be a clear aim of the study in order for the study to be eligible for full text review. Any other studies that may have discussed such issues would therefore have been excluded at abstract level.

Further description of the evidence selection for each key question is presented in the question level synthesis.

Appraisal for quality/risk of bias tool

Incidence studies for question 1 were assessed for quality and risk of bias using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Studies Reporting Prevalence Data. Diagnostic accuracy studies for question 2 were assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.

Formal quality appraisal tools were not used to appraise studies for question 3 on the implications of AABR screening. This is because, while relevant information on test time and cost was extracted from the studies, they were not being assessed according to their primary study design. The quality issues and limitations of the relevant information were therefore considered on an individual basis.

Results of the quality assessments for each study are presented in the Summary and appraisal of individual studies (Appendix 3).

Each criterion was summarised as ‘met’, ‘not met’ or ‘uncertain’ by considering the results of the included studies in light of the volume, quality, consistency and applicability of the body of evidence.

Question level synthesis

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.

Question 1 – What is the incidence of ANSD in newborn babies in the UK? What proportion present in NICU/SCBU? What proportion present in the otherwise well-baby population and how are these babies identified?

In the current NHSP in England, well-babies receive initial screening by the OAE test, with the AABR test used only if they have an absent OAE (test fail) in one or both ears. As ANSD is defined by a present OAE (normal cochlear function) combined with an absent or severely abnormal ABR, well-babies with ANSD would be expected to pass the OAE test[§§] and be discharged from screening (unless they had risk factors indicating further assessment).

Due to the range of associated risk factors, such as extreme hyperbilirubinaemia or extreme prematurity, it is expected that most babies with ANSD would spend time in NICU/SCBU where they would be screened initially with both ABR and OAE, and therefore be detected. For the proposed programme modification, it is of central importance to understand if this is true and to understand the proportion of well-babies with ANSD that could be missed with the current system, who may go on to have communication and development delays. Therefore, the UK NSC needed to review evidence on the proportions of babies with ANSD coming from the NICU/SCBU and well-baby populations.

Eligibility for inclusion in the review

The review aimed to look at UK cross sectional studies, cohort studies or surveillance data that contained information on the incidence of ANSD, either in the general population, in NICU/SCBU or well-baby populations. Where possible, information would be extracted on the method of identification and diagnosis. Eligible studies were required to contain data on both the number of cases and the sample population to calculate the incidence of ANSD among newborns. Such studies were required to include an initial sample size of >1000 newborns to give a reliable estimate. Studies that reported only the number of cases of ANSD among samples with PCHI, but provided no data on the baseline population, were excluded. This is because the aim was to review the

[§§] Excepting cases with ANSD where the OAE is absent (when CM is needed to confirm the diagnosis), or where there is additional conventional hearing loss resulting in OAE fail and a refer response.

frequency of ANSD among newborns, rather than the frequency among those with hearing impairment.

Description of the evidence

From the 125 unique articles at first sift, only 14 were specifically identified by the search for UK incidence of ANSD. Two of these studies were selected for full text review, with others not being relevant to topic and excluded at abstract level. Such exclusions included, for example, the prevalence of mutations associated with hearing loss, the prevalence of risk factors for PCHI, and the prevalence of auditory processing disorders among children and adults. Both studies met inclusion criteria for question 1 on the incidence of ANSD among newborns in the UK. These studies covered the incidence of ANSD among newborns screened as part of the NHSP in England, one locally (2002-07) and one nationally (2001-04).

The NHSP in England and Universal Newborn Hearing Screening in Scotland (UNHS) were able to supplement the literature identified by the search. The NHSP provided data on the number of infants from the well-baby and NICU/SCBU populations diagnosed with ANSD over an 11-year period (2007 to 16). This was as a proportion of all babies diagnosed with bilateral PCHI at audiology follow-up, so would include either bilateral ANSD, or unilateral ANSD in combination with non-ANSD hearing loss in the contralateral ear. Isolated unilateral ANSD would not be included. The UNHS provided comparative data on the number of babies diagnosed with ANSD (2014 to 17) in the health boards providing the 2 different well-baby protocols: OAE-first or AABR-first. This was, therefore, pertinent information as it provides some indication of the proportion of well-babies that might be missed though current OAE-first protocols. The data provided by the NHSP (Table 3) and UHNS (Tables 4) is addressed first in the following section, being considered to be the most comprehensive information available to address this key question. This is followed by summarised data (Table 5) from the 2 UK studies retrieved by the literature search.

Full data extraction from the retrieved studies, and the complete information provided by NHSP and UNHS, is presented in the 'Summary and appraisal of individual studies' in Appendix 3. This appendix also contains a table summarising the newborn incidence of ANSD as reported by 7 non-UK studies with baseline population >1000 (Table 20). The search for this key question was not targeted to retrieve non-UK evidence, but these studies were identified by the search for question 2 on AABR screening. They have therefore been summarised to provide contextual information of interest to compare against the UK incidence estimates, with the caveat that this may not be a comprehensive list.

Appendix 2 contains a full PRISMA flow diagram (Figure 1), a table of the included publications and details of the questions that these publications were relevant to, and a table of studies excluded at full text (Table 16).

Presentation and discussion of findings

Table 3. NHSP England, data across 11 annual birth cohorts (2006/07 to 2016/17)

Screen outcome	Babies identified with bilateral PCHI	ANSD in one or both ears (of cases with bilateral PCHI)	Incidence of unilateral/bilateral ANSD Calculated from total births across 11 annual birth cohorts
All babies			
Screen refer/fail	7577	576	
Screen incomplete	164	3	
Screen pass	944	41	
Total cases	8685 (of 7.2 million newborns screened)	620 Unilateral: 45 Bilateral: 575	0.086 per 1000 8.6 per 100,000 (Roughly 56 per year across England)
Well-babies			
Screen refer/fail	5117	82	(Roughly 7 per year still otherwise referred)
Screen incomplete	131	2	
Screen pass	178	37	(Roughly 3 per year potentially missed)
Total cases	5426 (of 6.8 million well-babies screened)	121 Unilateral: 16 Bilateral: 105	0.018 per 1000 1.8 per 100,000 (Roughly 11 per year in England)
NICU/SCBU			
Screen refer/fail	2460	494	
Screen incomplete	33	1	
Screen pass	166	4	
Total cases	2659 (of 435,039 screened in NICU)	499 Unilateral: 29 Bilateral: 470	1.1 per 1000 110 per 100,000 (Roughly 45 per year in England)

Table 4. UNHS Scotland, data for 14 heath boards over 3 years (2014 to 2017)

Screening protocol	Total screened in 3 years	Total proportion referred	PCHI (not limited to bilateral[***])	ANSD in one or both ears	Incidence of ANSD
Well-babies					
ABBR-first (7/14 boards)	101,250	1.4%	81	6 Unilateral: 4 Bilateral: 2	0.06 per 1000 6 per 100,000
OAE-first (7/14 boards)	54,503	NR	NR	1 Unilateral: 0 Bilateral: 1	0.02 per 1000 2 per 100,000
				Based on above incidence 0.06 per 1000	

[***] UNHS data gives the number of babies screened, referrals, PCHI, bilateral ANSD and unilateral ANSD. It does not specify that the total number with PCHI *includes* unilateral PCHI (unlike NHSP which specifies that it is limited to bilateral PCHI). However, the supplementary text provided appears to indicate this in that it gives the incidence of both bilateral PCHI (1.14 per 1000 screened) and unilateral PCHI (0.6 per 1000 screened). The inclusion of unilateral PCHI therefore suggests that unilateral ANSD may include cases of isolated unilateral ANSD, not limited to cases of unilateral ANSD only where there is other PCHI in the contralateral ear.

				expected 3.23 cases in 54,503: 2.15 unilateral 1.08 bilateral	
NICU/SCBU					
7/14 boards performing AABR-first for well-babies	6,423	3.8%	33	5 Unilateral: 1 Bilateral: 4	0.8 per 1000 80 per 100,000
7/14 boards performing OAE-first for well-babies	5,187	NR	NR	4 Unilateral: 1 Bilateral: 3	0.8 per 1000 80 per 100,000

The data provided by the NHSP (Table 3) and UNHS (Table 4) provide the most comprehensive information available on what is known of the newborn incidence of ANSD in England and Scotland, respectively. Both screening programmes cover 98% of all eligible newborns. The inherent limitation is that this central data collection is limited by the level of detail provided by each individual NHS programme (for example, whether there is information on the screening results or method of detection for babies with ANSD).

The NHSP data indicates an overall incidence of 8.6 cases per 100,000 newborns in England: 110 per 100,000 among babies in NICU/SCBU, and a much lower incidence of 1.8 per 100,000 among the well-baby population. As all babies in NICU receive AABR screening, this is expected to be a reliable indication of the incidence in this population. However, as well-babies receive OAE-first screening in the NHSP protocol, and ANSD is defined by an OAE test pass, it would be expected that well-babies with ANSD would be missed by the current screening system. In addition, as these audiological diagnoses cover bilateral PCHI only (this being the target of screening programmes as it has the greatest effect on speech, language and development) it covers bilateral ANSD, unilateral ANSD with contralateral other PCHI, but does not report on isolated unilateral ANSD. Therefore 1.8 in 100,000 could be an underestimate of the true incidence among well-babies.

The UNHS for Scotland provides a valuable dataset for comparison to indicate whether this could be the case. It covers all 14 health boards in Scotland, 7 of which provide OAE-first screening for well-babies while 7 provide AABR-first screening, as for special-care babies. Therefore these latter 7 boards would be expected to identify all cases of ANSD among well-babies. The UNHS data only covers a 3 year period (2014 to 2017) compared with 11 years of NHSP data (2006/07 to 2016/17), and therefore incidence estimates are based on only a small number of cases of ANSD. However, the comparability of estimates between countries/regions where the same screening protocols were performed gives some confidence in the findings and any inferences that can be made.

Looking firstly at NICU/SCBU, where babies in both countries receive AABR screening, the ANSD incidence is not dissimilar at 110 per 100,000 in England and 80 per 100,000 in Scotland. The Scottish regions that perform the 2 different well-baby protocols also show the same incidence of

80 per 100,000 NICU/SCBU babies. Both NHSP and UNHS data indicate that the majority of cases of ANSD among special care babies are bilateral. In England 94% of cases were bilateral, compared with 75 to 80% in Scotland. The higher proportion of unilateral ANSD in special care babies in Scotland could potentially be because the Scottish data appears to include cases of isolated unilateral ANSD, whereas the NHSP data only includes unilateral ANSD in the context of bilateral PCHI (where there is other hearing loss in the contralateral ear). However, if this were the case then it may be expected that the incidence of all ANSD among NICU/SCBU babies in England could have been even higher than 110 per 100,000. Similarly, the slightly lower overall NICU incidence and distribution of unilateral and bilateral ANSD in Scotland could be just chance variation due to the lower total number screened over 3 years compared with 11 for the NHSP. Despite this variation, the overall findings from the combined national data seem quite clear: the incidence of ANSD among NICU is roughly 1 in 1000 and it appears that the majority of those affected have bilateral ANSD.

For well-babies, the English estimate of 1.8 cases of ANSD per 100,000 well-babies is also comparable with the incidence of 2 per 100,000 in the 7 Scottish boards where well-babies received OAE-first screening. On the basis of this broad comparability, the well-baby ANSD incidence in the 7 Scottish health boards where AABR screening was used may similarly be expected to be generalisable had AABR screening been applied universally elsewhere. These 7 boards found an incidence of 6 per 100,000 well-babies. This suggests that the NHSP well-baby incidence of around 2 per 100,000 is an underestimate. It appears that the current OAE-first system could be missing 4 cases of ANSD per 100,000 well-babies. To try and discern the potential implications from this, it is worth looking in more detail at the proportion of bilateral and unilateral cases identified in Scotland – with the important caveat that the small number of cases over 3 years might not reflect the true pattern of ANSD among well-babies.

Where AABR screening was performed first, there were 6 in 100,000 well-babies with ANSD, two-thirds (4/6) had the condition unilaterally, while only one third (2/6) had bilateral ANSD. Therefore this seems to contrast with the findings for NICU/SCBU where most cases were bilateral. Again taking the cautious step of extrapolating this incidence to the 6.8 million well-babies screened in England over 11 years would indicate that there may have been 402 babies with ANSD: 268 unilateral and 134 bilateral. In reality 121 cases were identified, of which 16 were unilateral and 105 bilateral. Therefore it could be speculatively inferred that most well-babies with bilateral ANSD are still being detected within or despite the OAE screening system. It suggests that the majority of well-babies with ANSD who remain undetected in the current screening system may have unilateral ANSD.

The NHSP aims to identify babies with bilateral PCHI because there is most evidence on screening performance and outcomes in these babies.[3] The 16 babies with unilateral ANSD documented by the NHSP all had bilateral PCHI with non-ANSD hearing loss in the contralateral ear. All of these babies were referred through OAE screening, likely because they had a fail response in that

contralateral ear. Therefore it is expected that babies with unilateral ANSD who are most at risk of speech and language impairment because they have bilateral PCHI should still be detected through the current system. It may be inferred that isolated unilateral ANSD is most likely missed. However, the effect of isolated unilateral ANSD is poorly understood and there is currently no consensus on management.[1] Therefore the current OAE-first system may potentially avoid over-detection of these cases that could raise management uncertainties and not have affected language and development.

The main concern appears to be whether well-babies with bilateral ANSD are at risk of poor outcomes from being missed though OAE-first systems. Extrapolation of the incidence from the AABR-first health boards in Scotland indicates that most well-babies expected to have had bilateral ANSD in England and the rest of Scotland have been referred to audiology by some means. The UNHS data from Scotland does not provide information on individual screening results nor detail how the single case with bilateral ANSD in OAE-first boards was identified. The NHSP does provide individual screening results, which show that around two-thirds of well-babies with bilateral ANSD had in fact failed OAE screening, which is at odds with the expected ANSD test profile (OAE test pass). It is not possible to know the reason for this, but 2 potential reasons are:

- the NHSP report that 30% of babies fail the initial OAE screening test due to fluid or debris in the ear canal, therefore babies with ANSD may have been among this group (essentially 'false positives' for a failed OAE test, but in actual fact true positives for ANSD impairment)
- some babies with ANSD may genuinely have had an absent OAE response (where ANSD is then confirmed by an AABR fail and cochlear microphonic test pass)

Meanwhile a third of well-babies diagnosed with bilateral ANSD in England passed the OAE screening test (as would be expected with the usual ANSD test profile). Like the UNHS, the NHSP does not explain in detail how these screen-negative babies were detected clinically and it is not possible to be sure that ascertainment is 100%. They reported that 'all babies who passed screening were confirmed to have PCHI at mean 475 days, median 194 days, and range 20 to 1,779 days.' This suggests that bilateral ANSD among OAE screen-negatives may have been diagnosed at median 6 months or mean 15 months. However, it is difficult to know whether this has implications for child outcomes, particularly given that full audiological assessment is not usually completed until 6 months of age in any case, given that the ANSD test profile is known to fluctuate during infancy.

Overall it could be cautiously inferred from the available data that most well-babies expected to have had bilateral ANSD during these periods still appear to have been detected early at the time of OAE screening – albeit indirectly, non-systematically and often through false positive results. For those with bilateral ANSD missed by screening, it is not possible to know from the available information whether any could be adversely affected in the longer term as a result of delayed clinical detection.

One final important consideration, which neither the NHSP nor UNHS data can inform upon, is the rate of transient ANSD at birth. All diagnoses are at audiology follow-up, at several months of age. It is not possible to know how many newborns may have had a transient ANSD test profile at birth (because the auditory nerve had not fully matured) which then subsequently disappeared. The incidence of transient ANSD among well-babies may be far higher than the 6 in 100,000 incidence of ANSD at audiological diagnosis. Such babies would usually be missed by OAE screening but may otherwise be unnecessarily detected and referred in an AABR-screening system. This could raise the potential issue of over-diagnosis through a screening programme (this will be addressed further by question 2).

Table 5. Newborn incidence of ANSD in the UK, as reported in the published literature

Study	Design	Sample	Level of ANSD diagnosis	Incidence of ANSD across birth cohorts
Dowley et al 2009[8]	Clinical audit of ANSD using NHSP programme data. Nottingham University Hospital NHS Trust, 2002 to 2007.	n=45,050 screened n=12 with ANSD (of n=30 with hearing loss ≥60dB) All 12/12 admitted to NICU	Audiological assessment including behavioural audiogram and repeat OAE and ABR tests at 3, 9 and 12 months. Diagnosis at mean 4 months. No detail on initial screening response. (NB: in mean 2.5 year follow-up, 2/12 had hearing maturation after 7 months)	0.27 per 1000 27 per 100,000 Roughly 2 per year in this trust Incidence by well-baby and NICU setting unknown.
Uus et al 2006[9]	Clinical audit of bilateral PCHI using NHSP programme data. 23 first phase NHSP sites in England, 2001 to 2004.	N=169,487 screened N=17 with ANSD (of N=169 with bilateral PCHI ≥40dB) All 17/17 admitted to NICU	Audiological assessment including ABR + OAE (no further detail). Diagnosis at mean 5 weeks. No detail on initial screening response.	0.1 per 1000 10 per 100,000 Roughly 4 per year across the 23 first sites. Incidence by well-baby and NICU setting unknown.

The 2 UK studies retrieved by the literature search contain information of very limited scope compared with the data provided by the NHSP and UNHS Scotland. Uus et al (2006)[9] conducted a clinical audit of babies with bilateral PCHI identified across the first 23 sites of the NHSP (2001 to 04). This study shows an incidence of ANSD of 10 per 100,000 newborns, which is broadly compatible with the 8.5 per 100,000 estimated from the later NHSP data. Dowley et al (2009)[8] by comparison conducted a smaller audit of babies with severe hearing loss (not specified bilateral)

identified at one NHS trust (2002 to 07). This study finds a much higher incidence for ANSD of 27 per 100,000 newborns, but it is difficult to know whether this may be due to the smaller size of this study and the inclusion of unilateral ANSD. The main limitation with both of these studies is that they provide only an overall incidence estimate with no distinction by NICU or well-baby populations. Both studies report that all babies with ANSD presented through NICU, but the total screened in NICU is not given so it is not possible to calculate incidence for this specific population. It is also unknown whether there may have been some well-babies with ANSD during these study periods who have remained undetected because they were not screened using AABR. Like the later NHSP and UNHS data, these studies also cover only the number of diagnoses at audiological assessment, with the frequency of transient ANSD at birth unknown.

Appendix 3 provides a summary table of incidence data from non-UK studies to set the UK figures in context. In countries where all newborns received both AABR and OAE screening, the incidence of ANSD (at audiology assessment) was around 2 to 6 per 10,000 newborns. Two studies reporting the incidence for well-babies, specifically, gave a similar figure of 3 to 4 per 10,000 well-babies. Therefore, both these estimates are about 10 times higher than that indicated by the UK data. However, differences in population demographics, screening uptake level, the AABR and OAE devices used, thresholds used to define hearing loss, and whether unilateral ANSD was included, make it difficult to know how applicable these incidence estimates are to the UK. Therefore, it is not possible to infer that the UK incidence figures are underestimates.

Summary of Findings Relevant to Criterion 1: Criterion not met[†††]

Published literature on the incidence of ANSD among the NICU and well-baby populations in the UK was limited in volume. The available studies were not designed to address this question and prevented conclusions from being drawn. Unpublished data submitted from the NHSP in England (2006 to 2017) and UNHS is Scotland (2014 to 2017) provided the best information for this question. NHSP gave the number of ANSD diagnoses at audiology follow-up, among all diagnoses of bilateral PCHI (therefore bilateral ANSD or unilateral ANSD combined with unilateral non-ANSD hearing loss). Screening results were given, but the method of clinical detection among screen-negatives was unavailable. UNHS gave the number diagnosed with ANSD (apparently not limited to bilateral PCHI) but did not give screening results or method of clinical detection.

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††† **Met** -for example, this should be applied in circumstances in which there is a sufficient volume of evidence of sufficient quality to judge an outcome or effect which is unlikely to be changed by further research or systematic review.
Not Met - for example, this should be applied in circumstances where there is insufficient evidence to clearly judge an outcome or effect or where there is sufficient evidence of poor performance.
Uncertain -for example, this should be applied in circumstances in which the constraints of an evidence summary prevent a reliable answer to the question. An example of this may be when the need for a systematic review and meta-analysis is identified by the rapid review.

The combined data suggests that the incidence of ANSD among babies presenting from NICU/SCBU is around 1 in 1000, with the majority of cases being bilateral. Among the well-baby population, OAE screening protocols from England and Scotland found a much lower incidence 2 per 100,000. Regions in Scotland that already perform AABR well-baby screening indicate that this may be an underestimate, finding a slightly higher incidence of 6 in 100,000. Two-thirds of these cases were unilateral ANSD. Extrapolation of this expected incidence to the rest of Scotland and England suggests that most cases of bilateral ANSD among well-babies have still been detected, while it is predominantly unilateral ANSD that has been missed.

Two-thirds of well-babies diagnosed with bilateral ANSD in England had failed OAE screening for uncertain reasons. The remainder were clinically diagnosed sometime between 6 and 18 months of age. However, there is no further information on presentation, it is unclear whether there may have been clinical consequences from late detection, and there may be under-ascertainment of cases. Babies with unilateral ANSD combined with conductive or SNHL in the contralateral ear were detected through AOAE screening. If it is predominantly isolated unilateral ANSD that is missed, this could potentially avoid over-detection of a condition that has uncertain effect on outcomes and where there is no consensus on management.

However, these are speculative conclusions based on extrapolation from a small number of cases detected during 3 years of AABR screening in 7 health boards in Scotland. Further study of AABR screening of well-babies would be needed to confirm whether the incidence of 6 in 100,000 is correct, and that unilateral ANSD predominates in this population. There is a need to address whether clinical diagnosis of bilateral ANSD affects the timing of audiological assessment, management and outcomes compared with screen detection. It would also be beneficial to look at the incidence of transient ANSD at birth (due to delayed maturation of the auditory nerve), which has no effect on long-term outcomes. OAE screening currently avoids detection of such cases but this could be a relevant issue if there was a change to universal AABR screening. Addressing these uncertainties would allow better understanding of the condition and whether AABR screening may need to be included in the newborn well-baby protocol.

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

Question 2 – What is the test performance of AABR screening to identify ANSD among the well-baby population?

ANSD is defined by a test profile of an ABR that is absent or of grossly abnormal morphology (test fail), in combination with present OAE and/or CM (test pass) indicating normal cochlear function. It may, therefore, seem unsuitable to assess the test performance of AABR to detect ANSD, given that ABR forms part of the diagnostic criteria, and this is not a condition diagnosed by a separate reference standard. However, there are several considerations. Firstly, ANSD is not a condition that can be definitely diagnosed at the time of screening. Due to the possibility for delayed maturation of the auditory nerve, the BSA recommends that ABR and cochlear testing is repeated at 8 to 10 weeks of age. Secondly, conventional, rather than automated ABR needs to be used for diagnosis. But even then, the test profile of ABR fail/OAE pass alone does not necessarily indicate a child with hearing impairment. A confirmed diagnosis of ANSD with resulting hearing loss requires full audiological assessment including behavioural audiometry, electrophysiological tests, tympanometry and middle ear reflexes. The baby will then need ongoing follow up to see that hearing loss is permanent (the BSA reports that the auditory nerve can still mature up to 18 months of age).[1]

Therefore, this question aimed to assess the reliability of the newborn screening test of AABR (combined with OAE) for predicting confirmed, diagnosed ANSD several months after birth. However, studies looking at the performance of screening AABR for predicting later testing stages leading towards diagnostic confirmation, for example comparing against repeat AABR days/weeks after birth, or against conventional ABR, would also be reviewed.

Eligibility for inclusion in the review

The review aimed to look at any studies that had assessed the performance of AABR screening (with sequential or concurrent OAE) for the detection of ANSD among the newborn well-baby population. Eligible studies would be required to have assessed the performance of the initial screening tests against later re-testing, against conventional ABR or against final audiological confirmation of ANSD and related hearing loss. Outcomes of interest were referral rate, positive predictive value and sensitivity, specificity, and negative predictive value. Studies were required to include consecutively enrolled or randomly selected newborns who would be representative of the general well-baby population. Studies could be either from the UK or from representative Western countries.

Description of the evidence

Of the 40 articles retrieved at full text, 20 were specifically identified by the search for question 2 on the test performance of initial AABR screening against later diagnostic assessment of ANSD

among newborn well-babies. However, there was considerable duplication with the search for question 3, and all full texts were reviewed for assessment against this question.

A single US study (Berg et al, 2011)[10] met inclusion criteria for this question. This study had trialled AABR screening for detection of ANSD. This was a sequential screening system where OAE was performed only if babies failed the AABR test (screen positive). Screen-positives who failed AABR screening (whether or not they also failed the OAE) then received repeat AABR/OAE testing as outpatients. This allowed assessment of referral rates for ANSD (at first and repeat testing) and positive predictive value of the initial screening test for outpatient repeat. This study is summarised in Table 6 with full data extraction in the 'Summary and appraisal of individual studies' in Appendix 3, Table 21.

No studies assessed the performance of AABR (plus OAE) screening for the predication of ANSD at full audiological assessment, including conventional ABR and other assessments. Several non-UK incidence studies (as summarised in Criterion 1) had performed AABR as an initial screening test for well-babies and assessed the rate of ANSD at further audiological assessment at age 3-6 months.[11-14] However, these studies did not relate the audiological diagnoses to the test response at initial newborn screening, and so could not provide evidence for this question.

No studies followed up screen-negatives (who passed AABR screening) preventing assessment of sensitivity, specificity or negative predictive value against any of the reference standards.

Studies assessing the sensitivity and specificity of AABR (+/- OAE) screening for the diagnosis of PCHI in general were excluded as they were not specific to ANSD, as were studies assessing high risk populations, such hyperbilirubinaemia or preterm babies, and case-control studies assessing the validity of new systems.

Appendix 2 contains a full PRISMA flow diagram (Figure 1) along with a table of the included publications and details of the questions that these publications were relevant to, and a table of studies excluded at full text (Table 16).

Presentation and discussion of findings

Table 6. Screening performance of AABR (plus sequential OAE) for ANSD at repeat test

Study and design	Population	Index test	Reference standard	Test performance
Berg et al 2011[10] Prospective cohort 2 US hospitals	N=2167 well-babies (random sample of N=20,259 total newborns)	AABR followed by DPOAE if fail Newborn inpatient (age unclear)	Screen positives: repeat AABR and DPOAE as outpatient (age unclear)	ANSD at screening (AABR fail plus OAE pass): N=20/2167 N=17/20 (85%) unilateral ANSD Referral rate for ANSD: 0.92%, 95% CI 0.52 to 1.32

Study and design	Population	Index test	Reference standard	Test performance
2006-09			Repeat positives: audiology referral Screen negatives and repeat-test negatives: no further follow-up	Any hearing loss at screening (AABR fail plus OAE pass/fail): N=22/2167 Referral rate for hearing loss: 1.0% 91% of referrals for ANSD ANSD at repeat testing: N=0/20 Positive predictive value (PPV)=0% N=1/20 failed OAE at repeat Any hearing loss at repeat testing: N=1/20 with ANSD at screening failed both AABR and OAE at re-testing N=2/2 failing both AABR and OAE at screening also failed both at re-testing Final audiology referral rate: N=3/2167 0.14% referral rate for hearing loss 0% referral rate for ANSD N=2 diagnosed with SNHL and N=1 with conductive hearing loss PPV of AABR fail for hearing loss =3/22=13.6% PPV of AABR fail/OAE pass for hearing loss =1/20=5%

This prospective cohort demonstrates a 0.92% screen positive rate/referral rate (n=20 of 2167) for the ANSD test profile (AABR fail/OAE pass) at well-baby screening. At repeat outpatient testing, none of these 20 babies demonstrated this test profile. This gives a 0% PPV of ANSD at initial screening for ANSD at repeat testing, and 0% final audiology referral rate for ANSD.

One of the 20 babies failed both AABR and OAE at re-testing and was found at audiological follow-up to have non-ANSD PCHI. The remaining 19/20 cases likely demonstrate the occurrence of transient ANSD. This has been observed in other studies among the NICU population[15] and is recognised by the BSA.[1] This study did not specify the ages when repeat outpatient testing was performed, though it is expected that there would have been at least a few weeks between screening and re-testing. This delay may have allowed for maturation of the auditory nerve. Therefore, although these 19 babies had ANSD at birth (which is defined by ABR fail/OAE pass alone) they were false positives for a confirmed diagnosis of ANSD with resulting hearing impairment. In the context of a screening programme, this could mean over- detection and unnecessary referral (with associated parental/carer anxiety) of babies who would have gone on to have normal speech and language development. It is, however, important to acknowledge that it cannot be known with complete certainty that all 19 were false positives because they did not receive full audiological assessment at 3 to 6 months of age. It seems unlikely that any would have had fluctuating ABR results, but without audiological follow-up it is not possible to exclude the

potential that some may have had ANSD and PCHI (that is, the scenario where the re-test was a false negative rather than the screen test being a false positive). Similarly, the lack of follow-up of those who passed AABR at initial screening means it is not possible to calculate sensitivity, specificity or NPV or screening for ANSD with resulting hearing loss.

Another notable point is that most of the well-babies with ANSD at screening had isolated unilateral ANSD (17 of 20, 85%), albeit transient in this case. Berg et al had observed the same in their earlier study of a NICU population.[16] As noted in question 1, screening programmes focus upon identifying bilateral hearing loss as this is known to have greatest effect on outcomes. The effect of unilateral ANSD is poorly understood and there is currently no consensus on management.[1] If AABR screening of well-babies were introduced on a wider scale, a predominance of unilateral ANSD could lead to uncertain management. The total absence of any permanent cases (0% PPV) in this study is likely a reflection of the small study sample size and low incidence of ANSD among well-babies.

There are further applicability concerns with the findings of this study. Firstly, the study used a US-manufactured AABR device and the distortion product OAE (DPOAE) rather than transient evoked (TEOAE) test which is preferably used in most screening programmes, including the UK. It is not known whether these various devices and the thresholds used may have different test performance. Secondly, although this was a randomly-selected sample of a Western, well-baby population, the study was conducted in only 2 New York hospitals where most patients were of low socioeconomic status. This could have potentially increased the incidence of ANSD in this sample as the risk factors for ANSD are associated with low socioeconomic status. In theory this would mean a higher referral rate and PPV than would be expected in the general population. However, as the PPV was zero, little further can be inferred from this. Thirdly, the screening programme in this study was sequential, with AABR first followed by OAE only if the baby failed the AABR. Therefore, it would not represent the findings from a well-baby protocol where AABR and OAE were performed concurrently, with referrals if a baby failed both/either test. Concurrent testing would not have affected the number of babies with ANSD identified, but it would have increased the overall referral rate for all hearing loss. This is because a number of babies in this study who passed the AABR and were discharged might have failed OAE screening (Berg et al report a 3% referral rate with the standard OAE-first protocol vs 1% with AABR-first). As such, concurrent testing would be expected to have decreased the proportion of referrals that were specifically due to ANSD (AABR fail/OAE pass) and increased the number of false positives for any hearing loss, including those who failed only the OAE test.

Summary of Findings Relevant to Criterion 4: Criterion not met‡‡‡

One small cohort has trialled AABR screening in the well-baby population in one US region, where OAE was performed sequentially for those who failed the AABR. This study found a 0.92% referral rate for ANSD (20/2167 with ABBR fail/OAE pass) of a total 1.0% referral rate (plus 2 babies failing both tests). At repeat outpatient testing no babies had ANSD (0% PPV) giving no ANSD referrals for audiology diagnosis. One of the 20 babies failed both tests at re-testing and was subsequently diagnosed with non-ANSD PCHI. The remaining 19/20 likely reflect transient ANSD at birth due to delayed neural maturation. In the context of screening programme, this could mean over-identification and further assessment of babies who may not be identified through standard OAE screening, and who may have gone on to have normal speech and language development. Notably 85% of these screen-positives had demonstrated isolated unilateral ANSD, for which there is currently no agreed management approach. The complete absence of any permanent cases in this study likely reflects the small sample size and low incidence of ANSD among well-babies. However, if AABR well-baby screening were introduced on a wider scale, a predominance of unilateral ANSD could also lead to management uncertainties.

Sensitivity, specificity or NPV could not be assessed in this study due to the lack of audiology follow-up of babies who passed AABR, either at screening or repeat testing. There were also applicability concerns. This study used automatic ABR and OAE devices that are not used in UK programmes, and represented a population of low socioeconomic status where the incidence of ANSD may be higher. Additionally, this study would not reflect the findings from a screening programme where AABR and OAE were performed concurrently, with referral for failure on either/both tests. In a concurrent screening programme, the referral rate would likely be higher than 1%, a smaller proportion of all referrals would be due to ANSD, and there would likely be more non-ANSD false positives (babies who fail only the OAE test).

Overall, the current evidence provides an unreliable indication of the test performance of AABR screening of well-babies. A UK study is needed to assess the performance of AABR screening among well-babies using AABR and OAE devices as used in the NHSP.

‡‡‡ **Met** -for example, this should be applied in circumstances in which there is a sufficient volume of evidence of sufficient quality to judge an outcome or effect which is unlikely to be changed by further research or systematic review.
Not Met - for example, this should be applied in circumstances where there is insufficient evidence to clearly judge an outcome or effect or where there is sufficient evidence of poor performance.
Uncertain -for example, this should be applied in circumstances in which the constraints of an evidence summary prevent a reliable answer to the question. An example of this may be when the need for a systematic review and meta-analysis is identified by the rapid review.

Criterion 6 – The test, from sample collection to delivery of results, should be acceptable to the target population.

Criterion 14 – The opportunity cost of the screening programme should be economically balanced.

Criterion 18 – Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available.

Question 3 – What are the practical implications of including AABR in newborn hearing screening for well-babies?

A change in the NHSP to include AABR as the initial screening test for well-babies could have considerable practical implications. OAE is known to be a brief and simple test that involves placing a small probe in each ear that both transmits and receives sound. It can be completed in a few minutes. AABR is known to be a longer test, involving placing several electrodes on the head, nape of the neck and shoulder, with sounds played through earphones. A change to protocol could have various effects including:

- staffing, for example number of staff, time and additional training
- equipment change, such as needing additional AABR equipment and compatibility changes on information technology software
- increased costs for equipment, consumables, staffing requirements
- patient acceptability and uptake
- potential increased referral rate to audiology for incomplete AABR tests

This question therefore potentially touches on several criteria, all of which are assessed in this section.

Eligibility for inclusion in the review

The review aimed to look for randomised controlled studies, cohort studies, cost-effectiveness studies or systematic reviews that had assessed these various implications from changing to a well-baby screening protocol that included AABR. At the scoping stage it was recognised that studies of various design and aim could include such content as part of the general reporting of the study, for example in the write-up of results or discussion. In the context of a pragmatic rapid evidence review, it would not be possible to review such literature on AABR screening of well-babies if it were available. Therefore, it was decided *a priori* that studies would need to state this as an objective of the study or include such information in the study abstract to be eligible for inclusion. Furthermore, it was recognised that studies with relevant information may have reviewed the implications of including AABR in newborn hearing screening programmes in general, not just in relation to detection of ANSD. Therefore, the main ANSD search for this question was conducted

from 1997 to date, but an additional supplementary search was conducted from 2014 to date to look for studies assessing any implications of well-baby AABR screening, not specific to ANSD.

UK studies would be prioritised, followed by studies from representative OECD (Organisation for Economic Co-operation and Development) Western countries if no or few UK studies were retrieved. Non-UK OECD studies would be considered on a case-by-case basis.

Description of the evidence

Of the 40 articles retrieved at full text, 19 were specifically identified by the search for question 3 on the implications AABR screening in relation to ANSD (8 of which were also identified for question 2) and 8 from the supplementary search.

No UK evidence was identified. Two studies were included for this question. One was the Berg et al study included for question 2 which included brief information on the AABR timing and personnel costs compared with OAE. The second was an Iranian cost-effectiveness study that had compared AABR and OAE screening for the detection of hearing loss in general. The cost effectiveness assessment relates to the wider question of detection of PCHI which was beyond the scope of this rapid review on ANSD. However, the specific inputs into the decision models, such as costs, test time and the screening rate per day were of relevance. Iran is a non-OECD country, but due to the limited body of evidence identified by this rapid review search, this study was considered for inclusion. Nevertheless, both this and the US study were recognised to have limited applicability to newborn hearing screening in the UK. These studies are summarised in Table 7 with full data extraction in the 'Summary and appraisal of individual studies' in Appendix 3, tables 21 and 22.

Studies assessing non-applicable screening scenarios were excluded; for example, studies assessing community screening of older babies or studies assessing conventional ABR which would not be used in a screening programme.

Appendix 2 contains a full PRISMA flow diagram (Figure 1) along with a table of the included publications and details of the questions that these publications were relevant to, and a table of studies excluded at full text (Table 16).

Presentation and discussion of findings

Table 7. Screening performance of AABR (plus sequential OAE) for ANSD at repeat test

Study and design	Index test	Inputs into resource use	Resource use
Berg et al 2011[10] Prospective cohort, 2 US hospitals 2006-09.	Click stimulus AABR (Bio-logic, Mundelein, IL) single-stage newborn screen	The costs for preparation and test time reportedly based on a screener salary of US $16/hour	Median time to prepare newborn for test): AABR 4min vs OAE 1min (p not reported)

Study and design	Index test	Inputs into resource use	Resource use
Trialling AABR screening of n=2167 well-babies (Random sample of N=20,259 who received standard OAE screening)	vs DPOAE single-stage screen	No further detail reported.	Median test times for both ears: AABR 4.23mins vs OAE 1.63mins (p<0.0005) Less than 1 min test time: 7% AABR vs 41% OAE Screening cost per newborn: AABR $2.19 vs OAE $0.70
Heidari et al 2017[17] Iran Cost-effectiveness analysis of AABR vs OAE for a newborn hearing screening programme Theoretical population of 1 million newborns (not specified well-baby/NICU) (model inputs analysed only) Iran	AABR single-stage screening within 24 hours of birth vs OAE single-stage screen No further detail on devices used.	Costs per newborn were informed by cost for device purchase, repair and maintenance, annual depreciation, consumer products, employees' salaries, overhead costs, taxes and other direct costs. Reports that location, overhead and infrastructure and costs for training were not taken into account Costs based on Iranian currency converted to US$ at exchange rate of 36,350 Iranian Rial. Test time informed by average duration of device per day, number screened per day, and average 288 days worked per year.	Device purchase: AABR $5,503 to 7,153 vs OAE $4,127 to 5,777 Annual repair & maintenance: AABR $165 to 220 vs OAE $110 to165 Testing & supplies cost per newborn: AABR $0.58 to 0.72 vs $0.33 to 0.47 Mean test time per newborn: AABR 17mins vs OAE 12mins Newborns screened per day: AABR 11 vs OAE 15 Newborns screened per year: AABR 3,168 vs OAE 4,320 Overall cost per newborn: AABR $2.3 to 2.9 and OAE $1.6 to 2.2

As expected, the studies found that AABR takes longer to perform than AOAE, permitting screening of fewer newborns per day, and is associated with higher costs. However, it is not possible to give clear estimates on these parameters because of the inconsistent results between studies and various uncertainties around the devices and inputs used. For example, the US study found AABR to take around 8.2 minutes for preparation and testing time versus 2.6 minutes with AOAE whereas the Iranian study reported a longer 17 versus 12 minutes. However, it is unclear what processes were taken into account for calculating this time, particularly in the Iranian study. For example, there could be differences in protocols between the US and Iranian programmes, increasing time spent with each newborn in the latter.

The US study took procedure time and screener salary into account when considering cost per newborn, but did not mention costs for device acquisition or other consumables. By contrast, the

Iranian study accounted for device purchase, maintenance, annual depreciation, screener salary, consumables and other direct costs. Despite the apparent differences and uncertainties of input, the screening costs per newborn were broadly similar, estimated at 2.19 US dollars for AABR and 0.70 for OAE compared, respectively, with 2.3 to 2.9 and 1.6 to 2.2 US dollars in the Iranian study. However, neither study considered changes to hospital infrastructure, personnel requirements or training.

There is also uncertainty about the AABR and OAE devices used and whether there may be differences to those used in the UK. As mentioned in question 2, the AABR device used in the US study is not manufactured in the UK, and the programme used DPOAE rather than TEOAE testing as used in the UK NHSP. In the Iranian study, the devices used were not specified. Similarly, the estimates for screening time and costs in these studies did not consider a screening programme where both AABR and OAE tests are performed concurrently, rather than only sequentially if the baby failed the first screening test.

No studies considered acceptability of well-baby AABR screening to either health professionals or parents, or whether this may affect screening uptake by parents.

Summary of Findings Relevant to Criterion 6/14/18: Criteria not met[§§§]

No UK evidence was identified to inform the practical implications of including AABR in newborn hearing screening for well-babies.

The 2 studies identified, from the US and from Iran, both demonstrated that AABR screening takes longer to perform than OAE, permits screening of fewer newborns per day, and is associated with higher costs. However, there was uncertainty around the inputs used to estimate cost and timing, and the 2 studies gave inconsistent results. Neither study accounted for changes to hospital infrastructure, personnel requirements or training. There was uncertainty whether the AABR and OAE devices used were applicable to the UK. The studies also consider only single stage screening, rather than a programme where both screening tests are performed concurrently. There was no information on the acceptability of well-baby AABR screening to either health professionals or parents, or whether this may affect screening uptake by parents.

The lack of applicable evidence means that further study of the practical implications of AABR screening would be needed to understand the implications for the UK.

[§§§] **Met** -for example, this should be applied in circumstances in which there is a sufficient volume of evidence of sufficient quality to judge an outcome or effect which is unlikely to be changed by further research or systematic review.
Not Met - for example, this should be applied in circumstances where there is insufficient evidence to clearly judge an outcome or effect or where there is sufficient evidence of poor performance.
Uncertain -for example, this should be applied in circumstances in which the constraints of an evidence summary prevent a reliable answer to the question. An example of this may be when the need for a systematic review and meta-analysis is identified by the rapid review.

Review summary

Conclusions and implications for policy

The evidence available does not indicate that the well-baby newborn hearing screening programme should be modified at the current time to included AABR as an initial screening test to detect ANSD among well-babies.

The evidence available on the incidence of ANSD among well-babies and the potential test performance results from AABR screening of well-babies leaves outstanding questions. There is also a lack of information on the practical implications from screening programme modification.

Incidence of ANSD among well-babies in the UK
Published literature on the incidence of ANSD among the NICU and well-baby populations in the UK was limited in volume. The available studies were not designed to address this question and prevented conclusions from being drawn. Unpublished data submitted from the NHSP in England (2006 to 2017) and UNHS is Scotland (2014 to 2017) provided the best information for this question. NHSP gave the number of ANSD diagnoses at audiology follow-up, among all diagnoses of bilateral PCHI (therefore bilateral ANSD or unilateral ANSD combined with unilateral non-ANSD hearing loss). Screening results were given, but the method of clinical detection among screen-negatives was unavailable. UNHS gave the number diagnosed with ANSD (apparently not limited to bilateral PCHI) but did not give screening results or method of clinical detection.

The combined data suggests that the incidence of ANSD among babies presenting from NICU/SCBU is around 1 in 1000, with the majority of cases being bilateral. Among the well-baby population, OAE screening protocols from England and Scotland found a much lower incidence 2 per 100,000. Regions in Scotland that already perform AABR well-baby screening indicate that this may be an underestimate, finding a slightly higher incidence of 6 in 100,000. Two-thirds of these cases were unilateral ANSD. Extrapolation of this expected incidence to the rest of Scotland and England suggests that most cases of bilateral ANSD among well-babies have still been detected, while it is predominantly unilateral ANSD that has been missed.

Two-thirds of well-babies diagnosed with bilateral ANSD in England had failed OAE screening for uncertain reasons. The remainder were clinically diagnosed sometime between 6 and 18 months of age. However, there is no further information on presentation, it is unclear whether there may have been clinical consequences from late detection, and there may be under-ascertainment of cases. Babies with unilateral ANSD combined with conductive or SNHL in the contralateral ear were detected through OAE screening. If it is predominantly isolated unilateral ANSD that is missed, this

could potentially avoid over-detection of a condition that has uncertain effect on outcomes and where there is no consensus on management.

However, these are speculative conclusions based on extrapolation from a small number of cases detected during 3 years of AABR screening in 7 health boards in Scotland. Further study of AABR screening of well-babies would be needed to confirm whether the incidence of 6 in 100,000 is correct, and that unilateral ANSD predominates in this population. There is a need to address whether clinical diagnosis of bilateral ANSD affects the timing of audiological assessment, management and outcomes compared with screen detection. It would also be beneficial to look at the incidence of transient ANSD at birth (due to delayed maturation of the auditory nerve), which has no effect on long-term outcomes. OAE screening currently avoids detection of such cases but this could be a relevant issue if there was a change to universal AABR screening. Addressing these uncertainties would allow better understanding of the condition and whether AABR screening may need to be included in the newborn well-baby protocol.

Test performance of AABR screening to identify ANSD

One small cohort study has trialled AABR screening in the well-baby population in one US region. This study found a 0.92% referral rate for ANSD (20/2167 with ABBR fail/OAE pass) of a total 1.0% referral rate (plus 2 babies with ABBR fail/OAE fail). At repeat outpatient testing no babies had ANSD (0% PPV) giving no referrals for audiology diagnosis. These cases likely reflect transient ANSD at birth due to delayed neural maturation. In the context of screening programme, this could mean over-identification and further assessment of babies who may not be identified through standard OAE screening, and who may have gone on to have normal speech and language development. Notably 85% had also demonstrated isolated unilateral ANSD, which has no agreed management approach. The complete absence of any permanent cases in this study likely reflects the small sample size and low incidence of ANSD among well-babies. However, if AABR well-baby screening were introduced on a wider scale, a predominance of unilateral ANSD could also lead to management uncertainties.

Sensitivity, specificity or NPV could not be assessed in this study due to the lack of audiology follow-up of babies who passed AABR, either at screening or repeat testing. There were also applicability concerns to the UK including the different automated devices used and the low socioeconomic status of this population. This was also a sequential testing programme were OAE was performed only if babies failed AABR. This would not reflect the findings from a screening programme where AABR and OAE were performed concurrently, with referral for failure on either/both tests. Such a programme would have a higher overall referral rate, and there would likely be more non-ANSD false positives.

Overall, the current evidence provides an unreliable indication of the test performance of AABR screening of well-babies. A UK study is needed to assess the performance of AABR screening among well-babies using AABR and OAE devices as used in the NHSP.

The practical implications of AABR screening of well-babies
No UK evidence was identified to inform the practical implications of including AABR in newborn hearing screening for well-babies.

The 2 studies identified, from the US and from Iran, both demonstrated that AABR screening takes longer to perform than OAE, permits screening of fewer newborns per day, and is associated with higher costs. However, there was uncertainty around the inputs used to estimate cost and timing, and the 2 studies gave inconsistent results. Neither study accounted for changes to hospital infrastructure, personnel requirements or training. There was uncertainty whether the AABR and OAE devices used were applicable to the UK. The studies also consider only single stage screening, rather than a programme where both screening tests are performed concurrently. There was no information on the acceptability of well-baby AABR screening to either health professionals or parents, or whether this may affect screening uptake by parents.

The lack of applicable evidence means that further study of the practical implications of AABR screening would be needed to understand the implications for the UK.

Limitations

The search strategy was built on a protocol developed *a priori* for each of the 3 key questions. Searching was limited to 3 literature databases and did not include grey literature resources (except for NHSP and UNHS data). Studies only available in non-English language, editorials, abstracts, conference reports or poster presentations were not included. The reviewers were also unable to contact study authors or review non-published material. For pragmatic reasons within the constraints of a rapid review, the literature search on the practical implications of AABR screening was limited to the previous 5 years. Literature was then only obtained for full text appraisal when this was a clear aim of the study, as stated in the study abstract. As such there is the possibility that literature containing relevant information on the implications of AABR screening may have been missed.

Appendix 1 — Search strategy

Electronic databases

The search strategy included searches of the databases shown in Table 8: MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print and Embase.

Table 8. Summary of electronic database searches and dates

Database	Platform	Searched on date	Date range of search
MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print	Embase.com	21/06/19	Dependent on question – see individual search tables below
Embase	Embase.com	21/06/19	Dependent on question – see individual search tables below
The Cochrane Library, including: - Cochrane Database of Systematic Reviews (CDSR) - Cochrane Central Register of Controlled Trials (CENTRAL) - Database of Abstracts of Reviews of Effects (DARE)	Wiley Online	21/06/19	Dependent on question – see individual search tables below

Search Terms

Search terms included combinations of free text and subject headings (Medical Subject Headings [MeSH] for MEDLINE, and Emtree terms for Embase), grouped into the following categories:

- disease area: ANSD
- population: newborn
- geography (selected questions): United Kingdom
- question specific terms: e.g. incidence/prevalence

Search terms for MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print and Embase, and search terms for the Cochrane Library databases are shown in the tables below.

Table 9. Search strategy for Question 1 MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print and Embase

Term Group	#	Search terms	Total results
Disease area	1	'auditory neuropathy spectrum disorder':ti,ab OR ansd:ti,ab OR 'auditory neuropathy':ti,ab OR 'auditory dys-synchrony':ti,ab OR 'auditory de-synchrony':ti,ab OR 'auditory mismatch':ti,ab OR 'peri-synaptic	

		audiopathy':ti,ab OR 'persistent outer hair cell function':ti,ab OR 'neural hearing loss':ti,ab	
Disease area	2	'perception deafness'/exp OR 'auditory neuropathy spectrum disorder'/exp	
Question specific terms	3	incidence:ti,ab OR prevalence:ti,ab OR epidemiolog*:ti,ab OR 'new case*':ti,ab OR 'annual rate':ti,ab	
Question specific terms	4	'incidence'/exp OR 'prevalence'/exp	
Geography	5	'united kingdom':ti,ab OR uk:ti,ab OR britain:ti,ab OR gb:ti,ab OR england:ti,ab OR scotland:ti,ab OR wales:ti,ab OR 'northern ireland':ti,ab	
Geography	6	'united kingdom'/exp	
	7	#1 OR #2	
	8	#3 OR #4	
	9	#5 OR #6	
	10	#7 AND #8 AND #9	
	11	#7 AND #8 AND #9 AND [english]/lim AND [1997-2019]/py	67

Table 10. Search strategy for Question 2 MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print and Embase

Term Group	#	Search terms	Total results
Disease area	1	'auditory neuropathy spectrum disorder':ti,ab OR ansd:ti,ab OR 'auditory neuropathy':ti,ab OR 'auditory dys-synchrony':ti,ab OR 'auditory de-synchrony':ti,ab OR 'auditory mismatch':ti,ab OR 'peri-synaptic audiopathy':ti,ab OR 'persistent outer hair cell function':ti,ab OR 'neural hearing loss':ti,ab	
Disease area	2	'perception deafness'/exp OR 'auditory neuropathy spectrum disorder'/exp	
Population	3	newborn*:ti,ab OR 'new born':ti,ab OR 'new-born':ti,ab OR neonat*:ti,ab	
Population	4	'newborn'/exp	
Question specific terms	5	'auditory brainstem response':ti,ab OR abr:ti,ab OR aabr:ti,ab	
Question specific terms	6	'evoked brain stem auditory response'/exp OR 'evoked response audiometry'/exp	
Question specific terms	7	sensitiv*:ti,ab OR specific*:ti,ab OR precis*:ti,ab OR 'diagnostic test accuracy':ti,ab OR ((test NEAR/3 accuracy):ti,ab) OR ((diagnostic NEAR/3 accuracy):ti,ab) OR 'test failure rate':ti,ab OR 'referral rate':ti,ab OR 'false negative*':ti,ab OR 'false positive*':ti,ab OR ppv:ti,ab OR npv:ti,ab	
Question specific terms	8	'sensitivity and specificity'/exp OR 'diagnostic accuracy'/exp OR 'diagnostic error'/exp	
	9	#1 OR #2	
	10	#3 OR #4	
	11	#5 OR #6	
	12	#7 OR #8	
	13	#9 AND #10 AND #11 AND #12	76

Table 11. Search strategy for Question 3 MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print and Embase

Term Group	#	Search terms	Total results
Disease area	1	'auditory neuropathy spectrum disorder':ti,ab OR ansd:ti,ab OR 'auditory neuropathy':ti,ab OR 'auditory dys-synchrony':ti,ab OR 'auditory de-synchrony':ti,ab OR 'auditory mismatch':ti,ab OR 'peri-synaptic audiopathy':ti,ab OR 'persistent outer hair cell function':ti,ab OR 'neural hearing loss':ti,ab	
Disease area	2	'perception deafness'/exp OR 'auditory neuropathy spectrum disorder'/exp	
Population	3	newborn*:ti,ab OR 'new born':ti,ab OR 'new-born':ti,ab OR neonat*:ti,ab	
Population	4	'newborn'/exp	
Question specific terms	5	'auditory brainstem response':ti,ab OR abr:ti,ab OR aabr:ti,ab	
Question specific terms	6	'evoked brain stem auditory response'/exp OR 'evoked response audiometry'/exp	
Question specific terms	7	screen*:ti,ab OR 'mass population':ti,ab	
Question specific terms	8	'screening'/exp	
Question specific terms	9	impact*:ti,ab OR implement*:ti,ab OR workforce*:ti,ab OR workload*:ti,ab OR staff*:ti,ab OR train*:ti,ab OR personnel:ti,ab OR practical*:ti,ab OR acceptab*:ti,ab OR cost*:ti,ab OR it:ti,ab OR 'information technology':ti,ab OR ict:ti,ab OR 'information and communications technology':ti,ab OR system*:ti,ab OR software:ti,ab OR equipment:ti,ab	
Question specific terms	10	'economic evaluation'/exp OR 'performance measurement system'/exp OR 'software'/exp OR 'implementation science'/exp	
	11	#1 OR #2	
	12	#3 OR #4	
	13	#5 OR #6	
	14	#7 OR #8	
	15	#9 OR #10	
	16	#11 AND #12 AND #13 AND #14 AND #15	
	17	#11 AND #12 AND #13 AND #14 AND #15 AND [english]/lim AND [1997-2019]/py	95

Table 12. Search strategy for the Cochrane Library Databases (Searched via the Wiley Online platform)

Term Group	#	Search terms	Total results
	#1	MeSH descriptor: [Hearing Loss, Sensorineural] explode all trees	
	#2	("auditory neuropathy spectrum disorder" OR ansd OR "auditory neuropathy" OR "auditory dys-synchrony" OR "auditory de-synchrony" OR "auditory mismatch" OR "peri-synaptic audiopathy" OR "persistent outer hair cell function" OR "neural hearing loss"):ti,ab	
	#3	#1 OR #2 with Cochrane Library publication date Between Jan 1997 and Jan 2019	443

Table 13. Search strategy for Question 3 supplement MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print and Embase

Term Group	#	Search terms	Total results
Disease area	1	'permanent childhood hearing impairment':ti,ab OR pchi:ti,ab OR ((hearing NEAR/3 loss):ti,ab) OR ((hearing NEAR/3 impairment):ti,ab)	
Disease area	2	'hearing impairment'/exp	
Population	3	newborn*:ti,ab OR 'new born':ti,ab OR 'new-born':ti,ab OR neonat*:ti,ab	
Population	4	'newborn'/exp	
Question specific terms	5	'auditory brainstem response':ti,ab OR abr:ti,ab OR aabr:ti,ab OR 'otoacoustic emission':ti,ab OR oae:ti,ab	
Question specific terms	6	'evoked brain stem auditory response'/exp OR 'evoked response audiometry'/exp OR 'otoacoustic emission'/exp	
Question specific terms	7	screen*:ti,ab OR 'mass population':ti,ab	
Question specific terms	8	'screening'/exp	
Question specific terms	9	impact*:ti,ab OR implement*:ti,ab OR workforce*:ti,ab OR workload*:ti,ab OR staff*:ti,ab OR train*:ti,ab OR personnel:ti,ab OR practical*:ti,ab OR acceptab*:ti,ab OR cost*:ti,ab OR it:ti,ab OR 'information technology':ti,ab OR ict:ti,ab OR 'information and communications technology':ti,ab OR system*:ti,ab OR software:ti,ab OR equipment:ti,ab	
Question specific terms	10	impact*:ti,ab OR implement*:ti,ab OR workforce*:ti,ab OR workload*:ti,ab OR staff*:ti,ab OR train*:ti,ab OR personnel:ti,ab OR practical*:ti,ab OR acceptab*:ti,ab OR cost*:ti,ab OR system*:ti,ab OR software:ti,ab OR equipment:ti,ab	
	11	'economic evaluation'/exp OR 'performance measurement system'/exp OR 'software'/exp OR 'implementation science'/exp	
	12	'economic evaluation'/exp OR 'performance measurement system'/exp OR 'implementation science'/exp	
	13	#1 OR #2	
	14	#3 OR #4	
	15	#5 OR #6 OR #7 OR #8	
	16	#9 OR #11	
	17	#10 OR #12	
	18	#13 AND #14 AND #15 AND #16	
	19	#13 AND #14 AND #15 AND #16 AND [english]/lim AND [2014-2019]/py	164

Table 14. Search strategy for Question 3 supplement for the Cochrane Library Databases (Searched via the Wiley Online platform)

Term Group	#	Search terms	Total results
Disease area	#1	("permanent childhood hearing impairment" OR pchi OR (hearing NEAR/3 loss) OR (hearing NEAR/3 impairment)):ti,ab	
Disease area	#2	MeSH descriptor: [Hearing Loss, Sensorineural] explode all trees	
Population	#3	#1 OR #2	
Population	#4	(newborn* OR "new born" OR "new-born" OR neonat*):ti,ab	
Question specific terms	#5	MeSH descriptor: [Infant, Newborn] explode all trees	
Question specific terms	#6	#4 OR #5	

Question specific terms	#7	("auditory brainstem response" OR abr OR aabr OR "otoacoustic emission" OR oae):ti,ab	
Question specific terms	#8	MeSH descriptor: [Evoked Potentials, Auditory, Brain Stem] explode all trees	
Question specific terms	#9	MeSH descriptor: [Audiometry, Evoked Response] explode all trees	
Question specific terms	#10	MeSH descriptor: [Otoacoustic Emissions, Spontaneous] explode all trees	
	#11	#7 OR #8 OR #9 OR #10	
	#12	#3 AND #6 AND #11 with Cochrane Library publication date Between Jan 2014 and Jan 2019	7

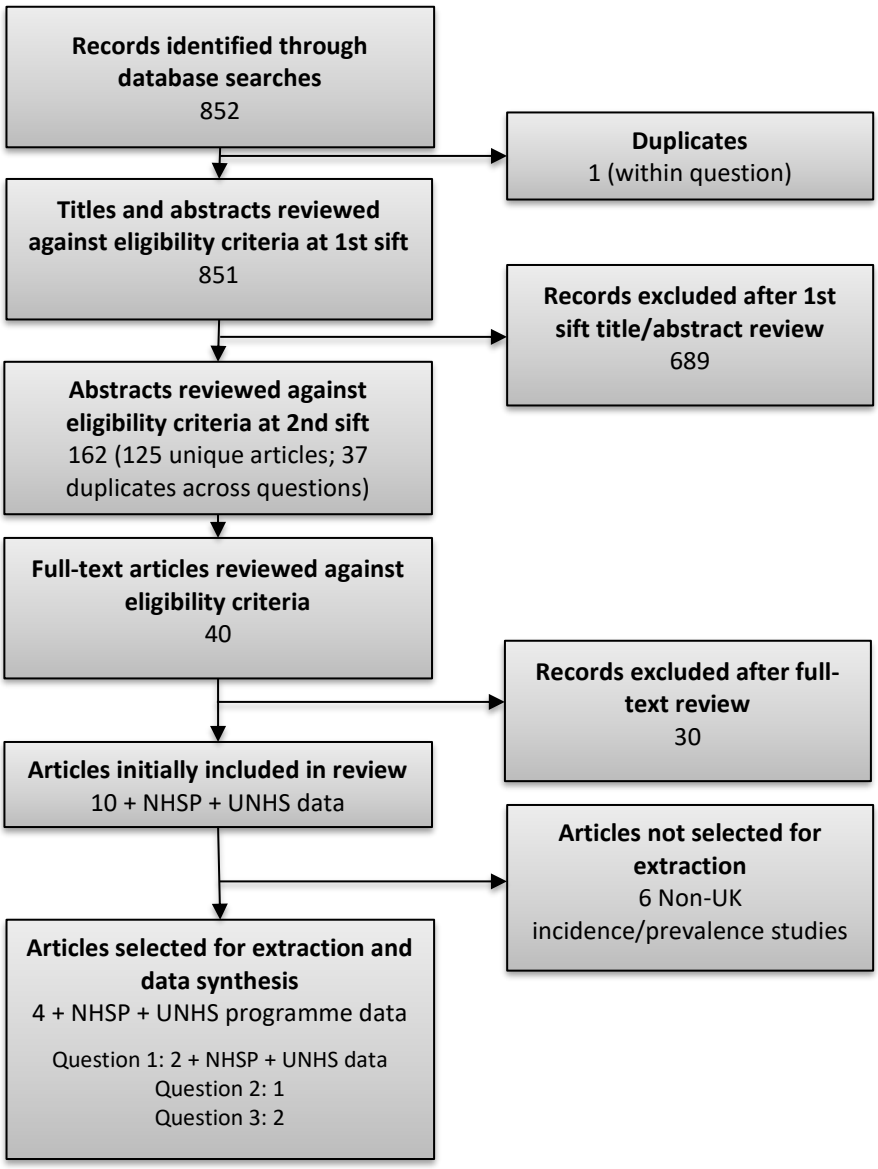
Results were imported into EndNote and de-duplicated within questions, but not between questions.

Appendix 2 — Included and excluded studies

PRISMA flowchart

Figure 1 summarises the volume of publications included and excluded at each stage of the review. Four publications were ultimately judged to be relevant to one or more review questions and were considered for extraction. Publications that were included or excluded after the review of full-text articles are detailed below.

Figure 1. Summary of publications included and excluded at each stage of the review



Publications included after review of full-text articles

The publications included after review of full-texts are summarised in
Table 15. Summary o15 below.
Studies were prioritised for extraction and data synthesis. It was planned *a priori* that the following approach would be taken to prioritise studies for extraction:

1. Systematic reviews and meta-analyses would be considered the highest quality of evidence if any were found. Following this, study designs would be prioritised for each question as listed in Table 2.
2. Studies considering a UK population would be prioritised, followed by studies from Western populations analogous to the UK.
3. For question 3, it would need to be apparent from the abstract that the study contained information or had assessed any potential implications of AABR screening.

Publications not selected for extraction and data synthesis are clearly detailed in
Table 15. Summary o16 below.

Table 15. Summary of publications included after review of full-text articles, and the question(s) each publication was identified as being relevant to

Study	The condition	The test	The intervention	The screening programme	Implementation criteria	Comments
Dowley 2009[8]	Q1	-	-	-	1	-
Uus 2006[9]	Q1	-	-	-	1	
Berg 2011[10]		Q2		Q3	4	
Heidari 2017[17]	-	-	-	Q3	4, 6, 14, 18	-

Publications excluded after review of full-text articles

Of the 40 publications included after the review of titles and abstracts, 30 were ultimately judged not to be relevant to this review. These publications, along with reasons for exclusion, are listed in Table 16.

Table 16. Publications excluded after review of full-text articles

Reference	Reason for exclusion
Abdul Wahid SNH, Md Daud MK, Sidek D, et al. The performance of distortion product otoacoustic emissions and automated auditory brainstem response in the same ear of the babies in neonatal unit. International Journal of Pediatric Otorhinolaryngology. 2012;76(9):1366-9.	Malaysia. Random sample of N=73 in the neonatal unit (reportedly mostly NICU discharge) receiving both AABR/DPOAE. Reports frequency of ABR fail/OAE pass response (n=8) and gives associated risk factors but excluded due to being a small sample of unclear representation to give prevalence.
Barsky-Firkser L, Sun S. Universal newborn hearing screenings: a three-year experience. Pediatrics. 1997;99(6):E4.	Incompatibility with UK system. Single US centre screening n=15,749 1993-95 but using conventional ABR rather than AABR. Gives test time and cost per baby for equipment nut no test performance data for ANSD diagnosis. Time and costs not considered applicable as AABR is likely to be used in initial screen.
Berg AL, Spitzer JB, Towers HM, et al. Newborn hearing screening in the NICU: Profile of failed auditory brainstem response/passed otoacoustic emission. Pediatrics. 2005;116(4):933-8.	US n=477 NICE sample receiving both test. Gives 25% prevalence of the ABR fail/OAE pass response at first screen, mentioned in background but excluded as prevalence evidence due to sample size <1000 and non-UK.
Berninger E, Westling B. Outcome of a universal newborn hearing-screening programme based on multiple transient-evoked otoacoustic emissions and clinical brainstem response audiometry. Acta Oto-Laryngologica. 2011;131(7):728-39.	Sweden n=31,092 in NHSP. Current system of AABR only if OAE fail, but testing system of multiple TEOAE tests to try and reduce referral rate for ABR. Assessing diagnosis of SNHL in general (acknowledging would miss ANSD cases)
Chen X, Yuan M, Lu J, et al. Assessment of universal newborn hearing screening and intervention in Shanghai, China. International Journal of Technology Assessment in Health Care. 2017;33(2):206-14.	China, assessing cost at each stage of screening and management for system with OAE as the initial screening test and ABR only for babies with 2 fail responses.
Chiou ST, Lung HL, Chen LS, et al. Economic evaluation of long-term impacts of universal newborn hearing screening. International Journal of Audiology. 2017;56(1):46-52.	Taiwan, cost effectiveness model for detection of hearing loss in general. Most inputs into the model are unclear therefore cannot be extracted for question 3. Furthermore the evaluation compares AABR vs TOAE vs no screening. It describes dividing the sample into 'normal and diseased newborns' but gives no further

	information on this making it difficult to know who they are considering in these categories, and whether they are considering one test or another for well-baby and NICU (e.g. as current system).
Colella-Santos MF, Hein TAD, De Souza GL, et al. Newborn hearing screening and early diagnostic in the NICU. BioMed Research International. 2014;2014.	Brazil n=929 NICU sample tested with AABR. Reports that n=1 diagnosed with ANSD. Excluded as prevalence evidence due to sample size <1000 and non-UK.
Colella-Santos MF, Sartorato EL, Tazinazzio TG, et al. An auditory health program for neonates in ICU and/or intermediate care settings. Brazilian Journal of Otorhinolaryngology. 2013;79(6):709-15.	NICU sample of n=526 at Brazil centre, 2011-12, screened by AABR, finding 1 case of ANSD. Subsequent study by the same authors from the same centre covering 2011-13 and including n=929, finding 1 case, which was reviewed in preference.
de Kock T, Swanepoel D, Hall JW. Newborn hearing screening at a community-based obstetric unit: Screening and diagnostic outcomes. International Journal of Pediatric Otorhinolaryngology. 2016;84:124-31.	Incompatibility with the UK system. Primarily assessing community screening of babies (range up to 190 days of age) by trained non-specialists, half with DPOAE, half with AABR. Refer for bilateral fail on either test, looking at prevalence of SNHL in referred cases from either group. No assessment ANSD.
Eden D, Ford RP, Hunter MF, et al. Audiological screening of neonatal intensive care unit graduates at high risk of sensorineural hearing loss. The New Zealand medical journal. 2000;113(1110):182-3.	New Zealand n=564 discharged from single NICU, looks at prevalence of risk factors and how many received ABR screening. Number with SNHL given, no information on ANSD.
Gökdoğan Ç, Altınyay Ş, Gündüz B, et al. Management of children with auditory neuropathy spectrum disorder (ANSD). Brazilian Journal of Otorhinolaryngology. 2016;82(5):493-9.	Turkey n=9520 (age <16 years) assessed in the audiology department. Looks at how many had SNHL and ANSD specifically (n=40). Can only inform frequency of ANSD among those assessed but this isn't related to screening/method of detection to give overall incidence, prevalence or referral rates
Hall AJ, Midgley E, Steer C, et al. Prevalence and risk factors for mild and high-frequency bilateral sensorineural hearing loss at age 11 years old: A UK prospective cohort study. International Journal of Audiology. 2011;50(11):809-14.	Prevalence of SNHL among the ALSPAC cohort.
Hall 3rd JW, Smith SD, Popelka GR. Newborn hearing screening with combined otoacoustic emissions and auditory brainstem responses. Journal of the American Academy of Audiology. 2004;15(6):414-25.	US random sample of n=300 well-babies receiving both AABR and OAE, compares referral rate between the two, but only for diagnosis of PCHI in general. Does report 1/5 were diagnosed with ANSD but sample considered too small to give reliable prevalence.

Karzon RK, Cho Lieu JE. Initial audiologic assessment of infants referred from well baby, special care, and neonatal intensive care unit nurseries. American Journal of Audiology. 2006;15(1):14-24.	Not fit to question. Assessing the effect of a restricted 2 hour audiology appointment and the range of ABR thresholds that can be achieved for babies referred following screening. No assessment of test performance of the screening test performed.
Kemaloğlu YK, Gökdoğan Ç, Gündüz B, et al. Newborn hearing screening outcomes during the first decade of the program in a reference hospital from Turkey. European Archives of Oto-Rhino-Laryngology. 2016;273(5):1143-9.	Turkey n=18,470 well-baby population assessing current system where ABR is performed only for failed OAE.
Korres SG, Balatsouras DG, Lyra C, et al. A comparison of automated auditory brainstem responses and transiently evoked otoacoustic emissions for universal newborn hearing screening. Medical Science Monitor. 2006;12(6):CR260-CR3.	No relevant content. Two samples of 50 children, performs same 3 tests of TEOAE, ATOAE and AABR in different order and comparing pass/fail responses each time. No further analysis of hearing loss.
Korver AMH, van Zanten GA, Meuwese-Jongejeugd A, et al. Auditory neuropathy in a low-risk population: A review of the literature. International Journal of Pediatric Otorhinolaryngology. 2012;76(12):1708-11.	Systematic review of literature 1996-2010 to assess the frequency of ANSD in the general population. Dowley, Ngo and Kirkim studies identified; our review found additional later studies, therefore the individual studies were analysed.
Li PC, Chen WI, Huang CM, et al. Comparison of newborn hearing screening in well-baby nursery and NICU: A study applied to reduce referral rate in NICU. PLoS ONE. 2016;11(3).	Taiwan n=13,676 well-babies and n=1948 NICU both given AABR. Compares referral rates (test fail) for the 2 populations and overall diagnosis in terms of non-specified hearing loss. No detail on OAE results or ANSD diagnosis so cannot give information on prevalence/incidence or test performance for ANSD.
Lin CY, Huang CY, Lin CY, et al. Community-based newborn hearing screening program in Taiwan. International Journal of Pediatric Otorhinolaryngology. 2004;68(2):185-9.	Taiwan n=5938 well-babies tested using the system where OAE is given at the first and second screen and ABR is performed only for 2 fails (unclear from the abstract).
Maris M, Venstermans C, Boudewyns AN. Auditory neuropathy/dyssynchrony as a cause of failed neonatal hearing screening. International Journal of Pediatric Otorhinolaryngology. 2011;75(7):973-5.	Belgium n=135 who failed AABR screening at 4 weeks of age assessed in the audiology clinic, n=4 with ANSD. Gives diagnostic ABR, TEOAE and MRI findings for this sample. Cannot relate to prevalence or test performance as no detail on the total number screened or the screen response. Also first screening at 4 weeks not considered applicable to UK.
Martines F, Salvago P, Bentivegna D, et al. Audiologic profile of infants at risk: Experience of a Western Sicily tertiary care centre. International Journal of Pediatric Otorhinolaryngology. 2012;76(9):1285-91.	Study aim to identify risk factors for SNHL among sample of n=412 transferred to the audiology department from birth centres of Western Sicily. Full audiological assessment performed. 58% of referred sample had risk factors. SNHL identified in n=41, n=4 had ANSD. Cannot relate to prevalence or

	test performance as no information on who the referred sample represent, how they were identified, or the size of the non-referred/non-screened population.
Mason S, Davis A, Wood S, et al. Field sensitivity of targeted neonatal hearing screening using the Nottingham ABR Screener. Ear and hearing. 1998;19(2):91-102.	NICU, UK, multicentre, 1988-93. Reviews audiological records of n=201 with hearing loss, n=51 had been screened of whom 8 had passed and 3 had ambiguous results. Essentially shows that ABR may miss cases later identified to have SNHL, but nothing on ANSD specifically.
Patel H, Feldman M, Amit M, et al. Universal newborn hearing screening. Paediatrics and Child Health. 2011;16(5):301-5.	Providing background only, no content of question applicability
Ricalde RR, Chiong CM, Labra PJP. Current assessment of newborn hearing screening protocols. Current Opinion in Otolaryngology and Head and Neck Surgery. 2017;25(5):370-7.	Providing background only, no content of question applicability
Sininger YS. Audiologic assessment in infants. Current Opinion in Otolaryngology and Head and Neck Surgery. 2003;11(5):378-82.	Providing background only, no content of question applicability
Suppiej A, Rizzardi E, Zanardo V, et al. Reliability of hearing screening in high-risk neonates: Comparative study of otoacoustic emission, automated and conventional auditory brainstem response. Clinical Neurophysiology. 2007;118(4):869-76.	Italy n=151 from NICU all tested by AABR, OAE and conventional ABR. N=6 diagnosed with hearing loss. No cases of ANSD detected, though does report that the ABR fail/OAE pass response was present for 40/290 ears at screening but recovered at subsequent assessment. Shows response may be transient. Covered in contextual information but excluded as evidence for test performance as the question focus is to assess this in the target well baby population.
Unlu I, Guclu E, Yaman H. When should automatic auditory brainstem response test be used for newborn hearing screening? Auris Nasus Larynx. 2015;42(3):199-202.	Turkey n=2933. Current system of AABR only if OAE fail. Looking at the frequency of OAE fail and referral for ABR and the frequency of hearing loss in general among the well-baby population.
Wroblewska-Seniuk KE, Dabrowski P, Szyfter W, et al. Universal newborn hearing screening: Methods and results, obstacles, and benefits. Pediatric Research. 2017;81(3):415-22.	Providing background only, no content of question applicability
Xu ZM, Cheng WX, Yang XL. Performance of two hearing screening protocols in NICU in Shanghai. International Journal of Pediatric Otorhinolaryngology. 2011;75(10):1225-9.	China, single centre. N=3000 high risk babies divided into 4 groups: preterm, very low birthweight, hyperbilirubinaemia, asphyxia (the latter 3 only said to come from NICU). Shows proportion/referral rates with 'ABR fail/OAE pass' response in

	each of the 4 groups and that n=22 were ultimately diagnosed with ANSD among the latter 2 groups but doesn't give further detail in terms of their screen response or whether others were false positives. Overall uncertain of applicability of the study and whether all such babies would typically present though NICU.
Yee-Arellano HM, Leal-Garza F, Pauli-Müller K. Universal newborn hearing screening in Mexico: Results of the first 2 years. International Journal of Pediatric Otorhinolaryngology. 2006;70(11):1863-70.	Mexico, general population sample n=3066 (including 2% with risk factors). Conducting first and repeat AABR, gives referral rate and overall incidence/prevalence, PPV and false positives for SNHL in general but no detail on ANSD.

Appendix 3 — Summary and appraisal of individual studies

Data Extraction

Table 17. Studies relevant to Criterion 1

Study reference, review questions	Study design and setting	Screening context	Population characteristics	Assessment of ANSD	Prevalence, incidence of ANSD
Dowley et al 2009[8] Question 1	Clinical audit of babies diagnosed with ANSD as part of the NHSP in one NHS Trust. Nottingham University Hospital NHS Trust, NHSP 2002 to 2007. Prospective data collection. Mean follow-up: 2 years 5 months.	OAE for the routine newborn population OAE plus ABR for babies admitted to NICU or with family history of hearing problems (as described)	N=45,050 screened (no breakdown of number by setting) N=12 diagnosed with ANSD of N=30 with severe to profound hearing loss (thresholds ≥60dB) All 12/12 admitted to NICU (vs 7/18 with non-ANSD, p=0.001) Other characteristics significantly different from non-ANSD hearing loss (p=0.02): • 4/12 hyperbilirubinaemia (vs 0/18) • 8/12 sepsis (vs 4/18) • 9/12 gentamicin (vs 5/18)	Diagnosed at mean 3 months, 25 days. Audiological assessment described to include behavioural audiogram and repeat OAE and ABR tests at 3, 9 and 12 months. No detail on initial screening response (for example, whether any had initial ANSD test profile at screening then recovered). 2/12 described to have evidence of hearing maturation at 7 and 10 months, respectively.	Incidence: 0.27 per 1000 (0.027% of total screened) All came from NICU: not possible to know the incidence by well-baby and NICU setting ANSD cases with moderate to severe hearing loss ≥60dB (no specification bilateral only)
Uus et al 2006[9] Question 1	Clinical audit of babies with bilateral hearing	TOAE for well-babies with AABR only if OAE fail in either ear	N=169,487 screened (no breakdown of number by setting)	First audiology follow-up of newborns referred following screening (median age 5 weeks),	Incidence: 0.10 per 1000 (0.010% of total screened)

Study reference, review questions	Study design and setting	Screening context	Population characteristics	Assessment of ANSD	Prevalence, incidence of ANSD
	impairment of moderate or greater severity detected across the first 23 sites in England to introduce the NHSP, from programme start (2001) to Jan 2004. Prospective data collection.	TOAE plus AABR for babies admitted to NICU ≥48 hours (as described)	N=169 diagnosed with permanent bilateral moderate or hearing loss (thresholds ≥40dB in the best ear) Broken down into: • n=17 with ANSD (10%) • n=140 SNHL (83%) • n=5 permanent conductive (3%) • n=7 mixed (4%) Those with ANSD specifically excluded by the study authors when analysing further characteristics. All ANSD cases stated in the conclusion to have presented through NICU.	with information collected by proforma sent to local audiology departments. No detail on assessment of ANSD, other than stating that 17 cases of auditory dyssynchrony were identified 'characterised by the absence or severe abnormality of ABR in the presence of OAEs' No detail on initial screening response, number of tests performed or whether there may be evidence of maturation.	All 17 cases came from NICU: not possible to know the incidence by well-baby and NICU setting ANSD with moderate hearing loss ≥40dB from bilateral PCHI cases only

NB: all information is as termed in the publication (for example, ABR written if the study does not specify AABR even if practice can be known or assumed by the authors)

Table 18. NHSP data on the cases of ANSD identified in England in 11 birth cohorts 2006/07 to 2016/17

Screen outcome	Bilateral PCHI	ANSD in one or both ears	Bilateral ANSD	Unilateral ANSD	Total babies in 11 annual birth cohorts	Screens completed in 11 annual birth cohorts	Incidence ANSD (one or both ears) by total babies (reviewer calculated)	Incidence ANSD (one or both ears) by screens**** (reviewer calculated)
All babies								
Screen refer/fail	7577	576	532	44	-	-	-	-
Screen incomplete	164	3	3	0	-	-	-	-
Screen pass	944	41	40	1	-	-	-	-
Total cases	8685	620	575	45	7,386,825	7,218,804	0.0084% 0.084 per 1000 8.4 in 100,000	0.0086% 0.086 per 1000 8.6 in 100,000 56 per year (over 11 annual birth cohorts)
Well-baby								
Screen refer/fail	5117	82	66	16	-	-	-	7 per year otherwise still referred

**** Though only screen outcomes are reported, it is unclear whether 'screen incomplete' may have been included in the total babies screened (where the screen was unsuccessful) or among total babies (where the baby has not been screened). However, the denominator makes minimal difference in terms of incidence.

Screen outcome	Bilateral PCHI	ANSD in one or both ears	Bilateral ANSD	Unilateral ANSD	Total babies in 11 annual birth cohorts	Screens completed in 11 annual birth cohorts	Incidence ANSD (one or both ears) by total babies (reviewer calculated)	Incidence ANSD (one or both ears) by screens**** (reviewer calculated)
Screen incomplete	131	2	2	0	-	-	-	-
Screen pass	178	37	37	0	-	-	0.00053% 0.0053 per 1000 0.53 in 100,000 possibly missed (OAE pass)	0.00055% 0.0055 per 1000 0.55 per 100,000 3 per year possibly could have been detected
Total cases	5426	121	105	16	6,935,137	6,783,765	0.0017% 0.017 per 1000 1.7 per 100,000	0.0018% 0.018 per 1000 1.8 per 100,000 11 per year
NICU								
Screen refer/fail	2460	494	466	28	-	-	-	-
Screen incomplete	33	1	1	0	-	-	-	-
Screen pass	166	4	3	1	-	-	-	-
Total cases	2659	499	470	29	451,688	435,039	0.11% 1.1 per 1000 110 per 100,000	0.11% 1.1 per 1000 110 per 100,000 45 per year

Supplementary information provided by NHSP (*ver batim*)

1. This summary is derived from data present in the NHSP national IT system for birth cohorts 2006/07 through to 2016/17 (i.e. 11 annual birth cohorts) and extracted from the system at March 2018

2. There are 3 possible outcomes from the screen. (i) screen fail or other outcome for which an immediate referral to audiology is mandatory (ii) screen not completed in spite of all efforts (iii) Screen pass. The rows in the table show these outcomes together with the total.

3. Data are presented for all babies and separately for babies screened under the Well baby protocol and the NICU protocol.

4. Prevalence/incidence of ANSD. 7.1 % of bilateral PCHI cases have ANSD in one or both ears. This translates to about 56 cases per birth cohort. This is somewhat lower than the 1 in 10 estimate of Sininger. For Well babies this figure is 2.2% and for NICU it is 18.7%.

5. We ask all programmes to notify cases of PCHI identified in childhood to the information system-hence the data for babies that pass the screen or have an incomplete screen. However we do not know how complete this notification is hence estimates for children with these screen outcomes must be treated with caution.

6. It is often not possible to confirm whether a PCHI was present at the time of the screen. Thus cases in the screen pass groups may or may not have been present at birth. They may have been acquired post screen. These cases may take time to emerge and further cases may emerge especially for more recent birth cohorts.

7. Cases in the screen refer group will mostly have been identified as a result of the screen but some may not. E.g. a baby may fail the screen, be referred to audiology and found to have satisfactory hearing and then be referred back into the system and found to have a PCHI at a later date.

8. All babies who passed screening were confirmed to have PCHI at mean 475 days, median 194 days, and range 20 to 1,779 days.

Retrospective review of audiological assessment outcomes following audiology referral from UNHS Scotland: 1st April 2014 to 31st March 2017

Table 19. UHNS data on the cases of ANSD identified across health boards in Scotland from 2014 to 2017

	Number screened	Referrals	PCHI	ANSD in one or both ears	Unilateral ANSD	Bilateral ANSD	Incidence
AABR-first protocol (7 health boards)							
Well-baby	101,250	1.4%	81	6	4	2	0.06 per 1000 6 per 100,000
NICU	6,423	3.8%	33	5	1	4	0.8 per 1000 80 per 100,000
OAE-first protocol (assumed 7 health boards, based on report that half of sites in Scotland perform each protocol)							
Well-baby	54,503	NR	NR	NR	NR	1*	0.02 per 1000[x] 2 per 100,000
NICU	5,187	NR	NR	4	1	3	0.8 per 1000 80 per 100,000

***Method of detection (e.g. screening status is unclear). The information from UNHS states '1 well baby was found, following diagnostics, to have bilateral ANSD'**

[x] **reviewer-calculated based on 1 in 54,503; all other incidence figures are given in the UNHS report**

UNHS additionally provided summary Statistics from the 2017/18 Annual Report Screening (*ver batim*):

Screening

- coverage rates are excellent with screening being offered to over 99.9% of eligible babies
- 98.9% of eligible babies completed the screening process
- 99.3% of babies have a screening outcome set within 10 weeks of birth and 95.1% within 4 weeks
- 20 families (0.04%) declined the screen and a further 4 (0.01%) withdrew consent after commencing screening
- 398 babies (0.78% of eligible babies) did not complete screening due to non-attendance

Assessment

- 4.7% of NICU babies screened were referred for assessment
- 1.6% of Well babies screened were referred for assessment

Timeliness of Diagnostic Audiology Assessment

- 90.4% of babies referred for diagnostic audiology assessment were offered an initial appointment either within 4 weeks of screen completion or by 44 weeks gestational age
- 72.2% of babies referred for diagnostic audiology assessment attended an initial appointment either within 4 weeks of screen completion or by 44 weeks gestational age

Outcome

- The prevalence of confirmed bilateral permanent hearing loss greater than 40dBHL was 1.14 per 1000 for those babies completing the screen
- The prevalence of confirmed unilateral permanent hearing loss greater than 40dBHL was 0.60 per 1000 for those babies completing the screen

Table 20. Non-UK studies reporting the incidence of ANSD (sample size n>1000)

Study	Setting	Population	Initial screening test	Level of ANSD diagnosis	Incidence of ANSD
All babies					
Kirkim et al 2008[12]	Turkey, 10 hospitals NHSP, 2005-07	N=23,786 screened N=10 ANSD	AABR + OAE (click-evoked) both well-baby and NICU	Audiology within 3 months ANSD bilateral >85dB Diagnosis mean 6 months Referred following fail at first screen (2-3 days) and repeat (1week)	4.2 per 10,000 screened By well-baby and NICU, unknown. Unable to relate to screen response.
Ngo et al 2005[13]	Singapore, single hospital NHSP 2002-03	N=14,807 N=9 with ANSD	AABR both well-baby and NICU	Audiology (no detail on screens) N=3/9 cases noted as unilateral N=2 reported to have no risk factors	6.1 per 10,000 screened By well-baby and NICU, unknown. Unable to relate to screen response.
Kim et al 2017[11]	South Korea, single hospital NHSP 2005-14	N=7,403 total screened: N=5,312 well-baby, N=2,091 NICU N=2 with ANSD (both well-baby)	AABR both well-baby and NICU	Audiology within 3 months Referred following fail at first screen (1-2 days) and repeat (2-4 weeks)	2.7 per 10,000 screened 3.8 per 10,000 well-babies NB low sample screened Unable to relate to screen response.

Study	Setting	Population	Initial screening test	Level of ANSD diagnosis	Incidence of ANSD
		54% screened of N=13,805 births (N=10,578 well-baby, N=3,227 NICU)			
Bieleki 2012[18]	Poland, single hospital, review of referrals NHSP, 2002-11	N=9419 screened N=18 with ANSD	All babies: OAE (ABR for repeat fails). Babies with one or more listed risk factors (including NICU): OAE plus ABR	Audiology Diagnosis mean 4.8 months N=4/18 cases noted as unilateral N=4 reported to have no risk factors	19 per 10,000 screened Unable to relate to screen response or know how many would presented through NICU.
Well-baby only					
Saki et al 2017[14]	Southeast Iran NHSP 2013-16	N=92,521 healthy newborns N=27 with ANSD	AABR +TEOAE both well-baby and NICU	Audiology assessment within 3 months N=16/27 unilateral Referred following fail at first screen (2 days) and repeat (unclear timing)	2.9 per 10,000 screened well-babies Unable to relate to screen response.
Berg et al 2011[10] (study include for Q2)	US, 2 hospitals Experimental screening protocol, 2006-09	N=2167 (random sample of n=20,259 well newborns) N=20 with ANSD at first screen N=0 of 20 at repeat screen	AABR followed by DPOAE if AABR fail	First (inpatient) and repeat screen (outpatient) Unilateral or bilateral (audiology follow-up not reported)	9.2 per 1000 at first screen 0 per 1000 at repeat screen Full audiology assessment not reported
NICU/SCBU only					
Psarommatis et al 2006[15]	Greece, single hospital NHSP, 1995-2004	N=1,150 screened in NICU N=25 with ANSD at first screen	AABR + OAE (click-evoked)	First (inpatient) and repeat screen (4-6 months) Unilateral or bilateral >75dBHL (audiology follow-up not reported)	2.2 per 100 at first screen 6.1 per 1,000 at repeat screen Full audiology assessment not reported

Study	Setting	Population	Initial screening test	Level of ANSD diagnosis	Incidence of ANSD
		N=7 of 20 at repeat screen			

Table 21. Study relevant to criteria 4, 6, 14, 18

Study reference, review questions	Study design and setting	Population	Screening context/index test	Reference standard	Test performance: detection and referral rates
Berg et al 2011[10] Question 2 and 3	Prospective cohort study of AABR screening of well-babies Aim 1: to assess the frequency of the ANSD test profile (ABR fail, OAE pass) Aim 2: to compare costs with OAE-only screening Setting: Morgan Stanley Children's Hospital of New York Presbyterian Hospital and the Allen Hospital, New York, US. 2006 to 2009.	N=2167 well-babies randomly sampled (every 9th or 10th newborn) to receive the experimental screening system from total newborn population n=20,259. The remaining N=18,362 received standard screening (comparative timing of OAE was assessed in a random sample n=281 of this group) 65% and 90% of births at the 2 respective hospitals were of low socioeconomic status (reimbursed by Medicaid)	Experimental screening: Click stimulus AABR (Bio-logic, Mundelein, IL) followed by DPOAE if AABR fail (discharge if AABR pass). Standard screening: DPOAE followed by AABR if DPOAE fail (discharge if OAE pass). Infants failing either 2-stage protocol returned for outpatient rescreening (timing unclear). Repeat fail at outpatient rescreening resulted in audiology referral. AABR click stimuli were 100 microseconds in duration and presented at a rate of 37.1 per sec. Low-pass filtered at 1500 Hz and high-pass filtered at 100 Hz	Screen positives: Repeat AABR and DPOAE at outpatient rescreening (timing unclear). Later audiological follow-up (e.g. including behavioural audiometry) is not performed for those passing the repeat screen. Screen negatives (initial AABR or OAE pass): received neither rescreening nor audiology follow-up.	N=20/2167 demonstrated initial ABR fail, OAE pass outcome (0.92%, 95% CI 0.52 to 1.32%). 17/20 (85%) were unilateral only. Notably only N=2/2167 failed both ABR and OAE (0.092%). Therefore the initial well-baby referral rate with AABR screening was 1% (compared with roughly 3% referral rate with OAE screening), though 91% of referrals appear to have ANSD. At outpatient rescreening N=0/20 had the ANSD profile (PPV 0%). N=1/20 failed both ABR and OAE at rescreening The N=2 initially referred due to failing both OAE and AABR also failed both tests at rescreening.

Study reference, review questions	Study design and setting	Population	Screening context/index test	Reference standard	Test performance: detection and referral rates
					Therefore N=3/2167 (0.14%) were referred to audiology: N=1 conductive and N=2 SNHL **Question 3** Median time to prepare newborn for test (min): OAE: 1 AABR: 4 (p not reported) Median test times for both ears (min): OAE: 1.63 AABR: 4.23 (p<0.0005) Less than 1 min test time: 41% of OAE and 7% AABR The costs for preparation and testing time based on a screener salary of $16/hour, costs: OAE: $0.70 per infant AABR: S2.19 per infant Costs assume that equipment, maintenance and consumable costs are equivalent.

Table 22. Additional study relevant to question 3 (criteria 6, 14, 18)

<table>
<tr><th>Study reference, review questions</th><th>Study design and setting</th><th>Method</th><th>Devices</th><th>Cost inputs reported</th><th>Relevant data (cost effectiveness analysis not reported)</th></tr>
<tr>
<td>Heidari et al 2017[17]

Question 3</td>
<td>Cost-effectiveness analysis of AABR and OAE in NHSPs

Iran</td>
<td>Decision tree model with one year time horizon from the perspective of the healthcare system, considering only direct costs.

Theoretical 1 million cohort of all newborns screened using either device in a single screening stage, within 24 hours of birth.

Effectiveness defined as number of neonates with hearing loss detected through either device.

Main model inputs:
• Annual birth rate statistics
• The prevalence of hearing loss in Iran
• Device sensitivity and specificity (informed by prior meta-analysis)
• Cost of screening
• Definite diagnosis of each newborn

NB cost-effectiveness analysis is not analysed for this question</td>
<td>AABR and OAE

(ABR gold standard)

No further detail on devices used.

Hearing loss defined as hearing loss exceeding 35dB</td>
<td>The unit cost of the devices for screening and of diagnostic ABR was determined.

The costs include that of device purchase, repair and maintenance, annual depreciation, location, consumer products, required infrastructures, employees' salaries and wages, human resources training, overhead costs, taxes and other direct costs. These were assessed to give cost per newborn.

Costs were also reported to include that of audiologist/technician salary (without need for training). In this case reporting 'location, overhead and infrastructure costs were not taken into account because the devices are portable.' Therefore some lack of clarity how this differs from the above description of cost considerations.

Salvage value of devices was assigned as zero.</td>
<td>Cost estimates
<table>
<tr><th>Parameter</th><th colspan="2">Baseline cost US $</th></tr>
<tr><th></th><th>AABR</th><th>OAE</th></tr>
<tr><td>Device purchase</td><td>5,503 to 7,153</td><td>4,127 to 5,777</td></tr>
<tr><td>Annual repair & maintenance</td><td>165 to 220</td><td>110 to165</td></tr>
<tr><td>Testing & supplies cost per newborn</td><td>0.58 to 0.72</td><td>0.33 to 0.47</td></tr>
<tr><td>Monthly salary personnel</td><td colspan="2">771 to 881</td></tr>
<tr><td>Infrastructure</td><td colspan="2">0</td></tr>
<tr><td>Monthly rent</td><td colspan="2">0</td></tr>
<tr><td>Monthly overhead</td><td colspan="2">0</td></tr>
</table>
Variables used to estimate costs
<table>
<tr><th>Variable</th><th>AABR</th><th>OAE</th></tr>
<tr><td>Device lifespan</td><td colspan="2">6 years</td></tr>
<tr><td>Test duration per newborn</td><td>17min</td><td>12min</td></tr>
<tr><td>Duration of device function per day</td><td>3 hours</td><td>2 hours</td></tr>
</table>
</td>
</tr>
</table>

Study reference, review questions	Study design and setting	Method	Devices	Cost inputs reported	Relevant data (cost effectiveness analysis not reported)
				Costs were calculated based on Iranian currency with the exchange rate of 36,350 Iranian Rial (IRR) used to convert the costs into the US dollars.	<table><tr><td>Newborns screened per day</td><td>11</td><td>15</td></tr><tr><td>Working days per year</td><td colspan="2">288 days</td></tr><tr><td>Newborns screened per year</td><td>3,168</td><td>4,320</td></tr></table> Overall cost per newborn: $2.3 to 2.9 for AABR and $1.6 to 2.2

Appraisal for quality and risk of bias

The Joanna Briggs Institute (JBI) Checklist for Prevalence Studies

Table 23. Quality assessment of Dowley et al (2009)[8]

Assessment	Yes, no, unclear, not applicable	Comment
Was the sample frame appropriate to address the target population?	Unclear	Representative of all those screened in the trust during the period, though unclear whether there could be regional variation
Were study participants sampled in an appropriate way?	Yes	Local NHSP programme and auditory assessment data
Was the sample size adequate?	Yes	

Were the study subjects and the setting described in detail?	Yes	
Was the data analysis conducted with sufficient coverage of the identified sample?	No	Well-babies were not screened with ABR and it is unclear whether they could have been detected
Were valid methods used for the identification of the condition?	Unclear	Assumed, but detail is not given on the full diagnostic criteria used for ANSD. The study identified those with moderate hearing impairment, unclear whether bilateral or not.
Was the condition measured in a standard, reliable way for all participants?	No	As above detail on detection is not given on diagnosis, but well-babies were not screened with ABR and it is unclear how they would have been detected
Was there appropriate statistical analysis?	Unclear	The numerator and denominator are reported. However, there is uncertainty who the rate is applicable to, as all babies came from NICU and only the total population size is given.
Was the response rate adequate, and if not, was the low response rate managed appropriately?	Unclear	As above, well babies did not receive the same screening test and it is unclear whether there could be babies with ANSD who have not been identified. It is also not reported whether there any screen-detected cases missed further assessments.
Overall the study is included as the aim was to review literature reviewing the prevalence/incidence of ANSD in the UK. However, there is the known caveat that well-babies did not receive ABR screening and it is unclear how they may have been detected and whether cases may have been missed. The study cannot inform NICU and well-baby incidence, specifically. Moderate impairment was included.		

Table 24. Quality assessment of Uus et al (2006)[9]

Assessment	Yes, no, unclear, not applicable	Comment
Was the sample frame appropriate to address the target population?	Yes	Representative of all those screened during the period
Were study participants sampled in an appropriate way?	Yes	NHSP programme and auditory assessment data
Was the sample size adequate?	Yes	
Were the study subjects and the setting described in detail?	No	The main analysis was for PCHI. Only the number with ANSD is given, their characteristics or test results are not reported
Was the data analysis conducted with sufficient coverage of the identified sample?	No	Well-babies were not screened with ABR and it is unclear whether they could have been detected
Were valid methods used for the identification of the condition?	Unclear	Assumed, but detail is not given on the full diagnostic criteria used for ANSD. The study only identified those with bilateral PCHI and of moderate level.
Was the condition measured in a standard, reliable way for all participants?	No	As above detail on detection is not given on diagnosis, but well-babies were not screened with ABR and it is unclear whether they could have been detected
Was there appropriate statistical analysis?	Unclear	The numerator and denominator are reported. However, there is uncertainty who the rate is applicable to, as all babies came from NICU and only the total population size is given.
Was the response rate adequate, and if not, was the low response rate managed appropriately?	Unclear	As above, well babies did not receive the same screening test and it is unclear whether there could be babies with the condition who have not been identified. It is also not

	reported whether there any screen-detected cases missed further assessments.
Overall the study is included as the aim was to review literature reviewing the prevalence/incidence of ANSD in the UK. However, there is the known caveat that well-babies did not receive ABR screening and it is unclear how they may have been available and whether cases may have been missed. The study cannot inform NICU and well-baby incidence, specifically. Focus is on bilateral moderate impairment.	

QUADAS-2 assessment of diagnostic studies

Table 25. Quality assessment of Berg et al (2011)[16]

Domain	Low, high or unclear risk of bias	Comment
Domain I: Patient selection		
Consecutive or random sample of population enrolled?	Low	
Case-control design avoided?	Low	
Inappropriate exclusions avoided?	Low	
Domain II: Index test		
Index test results interpreted without knowledge of reference standard results?	NA	Reference standard essentially is the same as the index test as ANSD is defined by AABR fail/OAE pass. Failure at each stage in the protocol (screen, repeat) guided referral and further testing. Full audiological assessment performed only for those failing the repeat screen.
Threshold pre-specified?	Unclear	Lack of clarity whether the threshold for hearing loss is as the UK.
Domain III: Reference standard		
Reference standard likely to correctly classify condition?	Low	Both tests in combination define the condition. Full audiological assessment may have included CM and additional tests such as behavioural audiometry. This is

		not specified, but fails at repeat testing would have received full audiological assessment.
Reference standard results interpreted without knowledge of index test results?	NA	Fail at ABR/OAE would have been known indication for the complementary test. Retesting would have been due to repeat fail.
Domain IV: Test strategy flow and timing		
Appropriate interval between index test and reference standard?	Unclear	The time between the first screen and outpatient reassessment or audiology follow-up is not reported.
Did all participants receive the same reference standard?	High	Only screen positives received repeat screening +/- full audiological assessment. Not possible to rule out false negatives.
All patients included in analysis?	High	As above, full analysis can be performed for screen positives, but no follow-up of screen negatives to assess Sn, Sp and NPV.
Domain V: Applicability		
Applicable to UK screening population of interest?	Unclear	Representative Western country. However, the study included a majority population of low socioeconomic status which may affect the prevalence of ANSD.
Applicable to UK screening test of interest?	Unclear	Used DPOAE which is not used in UK screening protocols. Similarly the ABBR device is not manufactured in the UK so unclear whether there may be differences.

Appendix 4 – UK NSC reporting checklist for evidence summaries

All items on the UK NSC Reporting Checklist for Evidence Summaries have been addressed in this report. A summary of the checklist, along with the page or pages where each item can be found in this report, is presented in Table .

Table 26. UK NSC reporting checklist for evidence summaries

	Section	Item	Page no.
1.	TITLE AND SUMMARIES		
1.1	Title sheet	Identify the review as a UK NSC evidence summary.	Title page
1.2	Plain English summary	Plain English description of the executive summary.	5
1.3	Executive summary	Structured overview of the whole report. To include: the purpose/aim of the review; background; previous recommendations; findings and gaps in the evidence; recommendations on the screening that can or cannot be made on the basis of the review.	6
2.	INTRODUCTION AND APPROACH		
2.1	Background and objectives	Background – Current policy context and rationale for the current review – for example, reference to details of previous reviews, basis for current recommendation, recommendations made, gaps identified, drivers for new reviews	13

		Objectives – What are the questions the current evidence summary intends to answer? – statement of the key questions for the current evidence summary, criteria they address, and number of studies included per question, description of the overall results of the literature search.	17
		Method – briefly outline the rapid review methods used.	19
2.2	Eligibility for inclusion in the review	State all criteria for inclusion and exclusion of studies to the review clearly (PICO, dates, language, study type, publication type, publication status etc.) To be decided *a priori*.	21
2.3	Appraisal for quality/risk of bias tool	Details of tool/checklist used to assess quality, e.g. QUADAS 2, CASP, SIGN, AMSTAR.	24
3.	SEARCH STRATEGY AND STUDY SELECTION (FOR EACH KEY QUESTION)		
3.1	Databases/ sources searched	Give details of all databases searched (including platform/interface and coverage dates) and date of final search.	19
3.2	Search strategy and results	Present the full search strategy for at least one database (usually a version of Medline), including limits and search filters if used. Provide details of the total number of (results from each database searched), number of duplicates removed, and the final number of unique records to consider for inclusion.	47
3.3	Study selection	State the process for selecting studies – inclusion and exclusion criteria, number of studies screened by title/abstract and full text, number of reviewers, any cross checking carried out.	20, 24
4.	STUDY LEVEL REPORTING OF RESULTS (FOR EACH KEY QUESTION)		
4.1	Study level reporting,	For each study, produce a table that includes the full citation and a summary of the data relevant to the question	Study level reporting: 60

	results and risk of bias assessment	(for example, study size, PICO, follow-up period, outcomes reported, statistical analyses etc.). Provide a simple summary of key measures, effect estimates and confidence intervals for each study where available. For each study, present the results of any assessment of quality/risk of bias.	Quality assessment: 71
5.	QUESTION LEVEL SYNTHESIS		
5.1	Description of the evidence	For each question, give numbers of studies screened, assessed for eligibility, and included in the review, with summary reasons for exclusion.	26, 34, 39
5.2	Combining and presenting the findings	Provide a balanced discussion of the body of evidence which avoids over reliance on one study or set of studies. Consideration of four components should inform the reviewer's judgement on whether the criterion is 'met', 'not met' or 'uncertain': quantity; quality; applicability and consistency.	27, 35, 40
5.3	Summary of findings	Provide a description of the evidence reviewed and included for each question, with reference to their eligibility for inclusion. Summarise the main findings including the quality/risk of bias issues for each question. Have the criteria addressed been 'met', 'not met' or 'uncertain'?	32, 38, 43
6.	REVIEW SUMMARY		
6.1	Conclusions and implications for policy	Do findings indicate whether screening should be recommended? Is further work warranted? Are there gaps in the evidence highlighted by the review?	44
6.2	Limitations	Discuss limitations of the available evidence and of the review methodology if relevant.	46

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1. BSA. Recommended Procedure Assessment And Management of Auditory Neuropathy Spectrum Disorder (ANSD) in Young Infants [Online]. British Society of Audiology, 2019. Available from: https://www.thebsa.org.uk/resources/assessment-and-management-of-auditory-neuropathy-spectrum-disorder-ansd-in-young-infants/.
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