Neonatal screening for early detection of hearing impairment[1]

-Final report-

[Commission S05-01]

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EXECUTIVE SUMMARY

Background

In Germany, about 1 child in 1000 is born with congenital hearing impairment. Only a minority of these children are completely deaf. However, in children with hearing impairment, the maturation of neurons in the auditory system of the brain may also be insufficiently stimulated. This may lead to deficits in hearing development, which a child may compensate only with intensive interventions, or not at all. Severe loss of hearing impairs language development and may lead to lifelong damage to a child's cognitive, emotional, and psychosocial development.

Various experts have therefore called for the diagnosis of hearing impairment within the first 6 months of life in the assumption that early treatment of an affected child (e.g. with a hearing aid) can reduce the risk of such damage. In the usual routine paediatric examinations, there is often a delay in the diagnosis of hearing impairment. At the moment, the age of diagnosis for congenital hearing impairment is between 21 to 47 months of age.

In order to achieve early diagnosis and therapy, some countries, for example Great Britain and many US states, have established universal newborn hearing screening (UNHS) programmes. In these programmes, wherever possible, all newborns undergo screening with specific devices to detect signs of hearing impairment. In Germany, such screening programmes have been tested in model projects.

Aims

The aim of this report was to evaluate the benefits and harms of UNHS in the detection of hearing impairment. For such an evaluation, it is insufficient to compare only the time points of diagnosis. The focus of this report was on patient-relevant therapy goals. Through the earliest possible diagnosis and treatment of hearing impairment, developmental deficiencies in a child and their potential lifelong consequences should be avoided or at least attenuated. The effects can be measurable by means of the assessment of quality of life, hearing capacity, language development, psychosocial, emotional, cognitive, and educational development, as well as by assessment of the adverse effects caused by false positive or false negative test results or unnecessary treatment.

Methods

The basis of this report was a systematic literature search for studies on 3 types of research questions. The soundest basis to answer the question as to whether universal newborn hearing screening has a benefit in children would be studies that follow the development of 2 groups of children over several years. For example, such studies would need to compare children

from a region offering hearing screening with children from a region where no screening was available.

In addition, studies were also evaluated for this report in which children with early treatment were compared with children who were treated at a later stage. Such studies may also provide information on how important early treatment is. For this report, studies were also assessed that analysed the accuracy and error rate of the procedures usually applied in the early detection of children with potential hearing impairment.

In order to describe the acceptance and feasibility of UNHS programmes in Germany, as well as their main quality characteristics, reports on German model projects on UNHS were also considered in this report.

Results

Screening studies

The data from the model projects included indicate that UNHS can bring forward the time of diagnosis of congenital hearing impairment in children.

Two comparative studies investigating screening programmes in respect of patient-relevant outcomes were included in this report. With regard to language development at the ages of 3 and 8 years, both screening studies showed a tendency towards an advantage in favour of children whose hearing impairment was diagnosed in a screening programme. This may be due to earlier diagnosis in these children. Data on other patient-relevant outcomes were not available (e.g. quality of life, mental health, satisfaction, and educational and professional development). Potential harms of the screening programme (e.g. due to false positive results) were insufficiently investigated in these studies.

Children treated earlier vs. those treated later

Four studies were included in this evaluation in which children treated earlier were compared with those treated later. Due to the study design, the studies do not allow certain conclusions. They do, however, provide indications that early treatment may be beneficial.

Studies on test accuracy

This report included 9 studies on the test accuracy of procedures applied in early diagnosis of congenital hearing impairment. Neither procedure applied, that is, the testing of spontaneous otoacoustic emissions (S-OAE) or automated auditory brainstem response (A-ABR), has been sufficiently evaluated. One study provided information on the diagnostic quality of a screening programme in which S-OAE and A-ABR were combined. If one transferred the results of this study to 100 000 newborns, about 110 of 120 children with hearing impairment

would be positively identified (sensitivity: 91.7%). The screening programme would lead to false suspicions of hearing impairment in about 1500 children; these suspicions would be dispelled after further tests (specificity: 98.5%). In reality, poor-quality screening programmes may produce substantially worse results.

Conclusions

UNHS can improve the chances that a child with congenital hearing impairment is diagnosed and treated at an earlier stage. It cannot be certainly inferred from the studies available what consequences this has for the development of these children. There are indications (not evidence) that children with hearing impairment identified by UNHS have advantages in language development. The comparison between children treated earlier vs. those treated later also provides indications that children with earlier treatment may have advantages in language development. It is insufficiently investigated how newborn hearing screening affects other outcomes relevant to the children, such as quality of life, development at school, and occupational or social situation. Programmes should therefore be designed in such a way that their quality and the consequences for the children affected can be reliably determined.

EXTENDED EXECUTIVE SUMMARY

Background

The German Federal Joint Committee commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to evaluate the benefits and harms of early detection of hearing impairment in newborns by means of universal newborn hearing screening (UNHS).

Research question

The topic of this report is the evaluation of the benefits and harms of early detection of hearing impairment by means of UNHS. The focus was on patient-relevant therapy goals. Through the preferably early diagnosis and treatment of (congenital) hearing impairment, resulting developmental deficiencies in a child and their potential lifelong consequences should be prevented or at least attenuated.

A screening programme is a complex intervention whose success depends on a series of consecutive elements. The aim of UNHS is the preferably early and complete detection of children with hearing impairment who need treatment. The purpose of a screening programme depends decisively on the effectiveness of available therapies (or may also depend on other positive consequences resulting from early detection of a disorder). If children can be treated at an earlier age and the (long-term and patient-relevant) consequences of a hearing impairment can actually be verifiably reduced by bringing forward the start of treatment, then this is an indication of the benefit of such a procedure. The tests applied to diagnose hearing impairment should have sufficiently high accuracy and deliver as few incorrect results as possible.

The soundest basis for answering the question as to whether UNHS is of benefit to newborns would be studies in which the whole screening chain is examined in adequately large groups of children. The screening programme would be offered to one group, but not to the other. After an adequately long running time, the comparison can then be made to establish whether and in how many children the screening programme has prevented hearing impairment and its consequences. Such studies are complex. A preliminary search indicated that such studies of the complete screening chain had hardly been performed in newborn hearing screening. The present report therefore also examined studies that permit statements about individual screening elements (procedures for the treatment of hearing impairment and diagnostic procedures). An essential argument for the plausibility of newborn hearing screening would be studies that show that if the diagnosis and treatment of children with hearing impairment occur at an earlier stage, this has favourable consequences. We therefore also included studies designed to compare children treated early with those treated later. Moreover, appropriate studies can compare different diagnostic techniques that might be used in hearing screening, and provide conclusions about the reliability and error-proneness of these test procedures.

If there is sufficient evidence for the benefit of early rather than late treatment and if, in addition, hearing impairment can be appropriately diagnosed in the age group of interest, this may also be seen as evidence for the effectiveness of screening.

On the basis of these considerations, objectives in 3 areas may be identified:

1. Evaluation of the effectiveness of screening programmes:

- Comparative evaluation of the benefits and harms of UNHS, versus an approach without screening, and
- Comparative evaluation of the benefits and harms of different screening strategies between each other (for example, different time points of screening, screening for different severities of hearing impairment, universal screening versus screening of at-risk children)

2. Evaluation of the effectiveness of different time points of providing treatment:

- Comparative evaluation of the benefits and harms of providing treatment at different time points (early vs. later)

in each case, with regard to patient-relevant outcomes.

3. Evaluation of the quality of specific diagnostic procedures used in screening:

- Evaluation of the 2 test procedures otoacoustic emission audiometry (OAE) and measurement of auditory evoked potentials (AEP) (e.g. by means of auditory brainstem response [ABR] testing) with regard to their diagnostic quality (e.g. sensitivity/specificity, likelihood ratios) and positive predictive values.
- Comparative evaluation of the suitability of these 2 relevant test procedures in a screening setting (e.g. time needed, influence of investigator/setting, consequences of different test quality criteria).

Methods

For the areas “screening” and “treatment”, the evaluation was performed on the basis of data from randomised controlled trials (RCTs). As a preliminary search showed that RCTs had not previously been performed to study the benefit of newborn hearing screening, for screening and therapy studies, non-randomised intervention studies and cohort studies were also considered. The outcomes selected were parameters that enabled an assessment of patient-relevant therapy goals such as quality of life, hearing capacity, language development, as well as psychosocial, emotional, cognitive and educational development. Adverse effects caused by false positive or false negative test results or by treatment were also assessed.

To investigate the accuracy and suitability of diagnostic tests, diagnostic studies were to be considered in the situation of application in newborns with unknown disease status under everyday conditions. If such studies were not available in sufficient number and/or quality, studies in newborns with known disease status were also to be considered.

In addition to the diagnostic accuracy, the outcomes investigated were also parameters that allowed statements on the suitability of the relevant procedures in a screening setting, for example time invested and the impact of the test conditions on the diagnostic accuracy.

In order to describe the acceptance and feasibility of UNHS programmes in Germany, as well as their main quality characteristics, reports on German model projects on UNHS were also considered in this report.

The systematic literature search was performed in the 11 databases MEDLINE, EMBASE, CINAHL, PsycINFO, PSYNDEX, ERIC, and the databases of the Cochrane Library (Clinical Trials [for primary publications], Systematic Reviews [CDSR], Other Reviews, Economic Evaluations, and Technology Assessments).

The literature screening was performed by 2 reviewers independently of one another.

After an evaluation of the quality of the relevant studies to be included in the report (also performed by 2 reviewers independently of one another), the results of the single studies for each separate area were collated according to therapy goals.

IQWiG's preliminary evaluation, the preliminary report, was published on the Internet (www.iqwig.de). Interested parties could submit written comments. All written comments fulfilling formal criteria were discussed in a scientific debate before production of the final report.

Results

A total of 2 screening studies including 120 and 50 children with hearing impairment were identified by the various steps of the literature search and included in the evaluation. One study prospectively compared alternating screening periods (with and without UNHS) (subpopulation I), and also compared hospitals with UNHS vs. those without UNHS programmes (subpopulation II). The other study retrospectively investigated children with hearing impairment who had either been born in hospitals with or without UNHS. Both studies showed major deficiencies regarding study and publication quality.

A total of 18 therapy studies were identified; after extracting the relevant data, 4 of these studies were included in the evaluation. The number of children who fulfilled the inclusion criteria varied between 86 and 153 in these studies, which directly compared the benefit of early compared with later treatment. All 4 studies were retrospective cohort studies; one study

was population-based. Three studies showed major, and one study showed minor quality deficiencies.

A total of 12 diagnostic studies were identified, of which 9 were included in the actual evaluation. One study assessed 25 609 newborns who were initially screened in a 2-step screening programme, starting with the testing for transient evoked otoacoustic emissions (TEOAE), followed, if this test was failed, by automated auditory brainstem response (A-ABR) testing. Eight studies compared OAE with A-ABR and included 105 to 500 children. All studies showed major quality deficiencies.

The data from the model projects considered indicate that by performing UNHS, congenital hearing impairment in children can be diagnosed earlier. The 2 screening studies identified, which compared screening programmes in respect of patient-relevant outcomes, tend to indicate that children with hearing impairment identified by screening are at an advantage with regard to language development at an (average) age of 3 and 8 years compared with children whose hearing impairment was identified outside a specific screening programme or in a screening programme performed at a later age. The chances of normal language development appear to be higher for screened children, possibly due to earlier diagnostic clarification in these children. Data on other potential long-term patient-relevant outcomes were not available (e.g. quality of life, mental health, satisfaction, educational and professional development). Likewise, no reliable conclusion was possible on potential adverse effects of screening, as the available data were inadequate.

The 4 therapy studies included compared children given early treatment with a hearing aid or a cochlear implant with children given late(r) treatment. These studies also provided indications that early treatment may be of advantage.

The test procedures S-OAE and A-ABR used in UNHS have not been evaluated in adequately large samples of the UNHS-relevant target group – mainly healthy newborns. Only one study on the diagnostic accuracy of 2-stage screening could be identified. The results indicate that the specificity is relatively high (98.5%), with somewhat lower sensitivity (91.7%).

If the group of children (about 17%) is included who remained unscreened (even though a screening programme was offered), the sensitivity of the screening programme drops to 71.0% (95% confidence interval: 52%-86%). This means that approximately 3 of 10 children with profound hearing impairment were not identified by the screening programme. The other diagnostic studies included only allow a statement on the accuracy of measurement of otoacoustic emissions compared with the evaluation of auditory brain stem potentials. The diagnostic accuracy of the OAE varied greatly between the studies; these data do not allow a reliable conclusion.

The 6 additional reports on German UNHS model projects showed that UNHS is widely accepted in Germany too, as is evident from the very low rate of parents who refused to allow their children to participate in the screening programme. The organisational preconditions have in principle already been met. Implementation nevertheless sometimes turned out to be difficult, as seen in the comparatively low coverage rates (relative to all births in a region) and/or the high rates of children lost to follow-up. It is absolutely essential that those children initially identified as having abnormal test results in the (primary) screen must be properly tracked, which requires considerable effort.

Conclusion

There are indications that children with hearing impairment identified in UNHS programmes have advantages with respect to language development. Other patient-relevant outcomes, such as social aspects, quality of life, educational development and finally, professional situation, have not been adequately investigated for evaluation.

If the Federal Joint Committee decides to introduce UNHS in Germany, it is recommended that suitable concomitant measures should be implemented at the same time to provide quality assurance. These measures should comprise the following factors: unambiguous case definitions; specification of clear quality standards (minimal coverage rate, maximal rate of positive tests in the first step, time of confirmatory diagnostic procedures, time of the start of provision of treatment); as complete a tracking as possible of children with abnormal test results and children diagnosed with congenital hearing impairment; and identification of all children with congenital hearing impairment (including those from periods or regions without screening) at a suitable point later in time.

Key words

Congenital hearing impairment, cochlear implant, brainstem response audiometry, hearing aid, early intervention to promote hearing and language development, otoacoustic emissions, universal newborn hearing screening, systematic review

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LIST OF ABBREVIATIONS

Abbreviation	Meaning
A-ABR	automated auditory brainstem response
ABR	auditory brainstem response
AEP	acoustically evoked potentials
AHRQ	Agency for Healthcare Research and Quality
ANAES	Agence Nationale d'Accréditation et d'Evaluation en Santé
ANCOVA	analysis of covariance
BERA	brainstem evoked response audiometry
BPVS	British Picture Vocabulary Scale
CCC	Children's Communication Checklist
CDI	Mc Arthur Communicative Development Inventories
CDSR	Cochrane Database of Systematic Reviews
CHIP	Colorado Home Intervention Program
CHIVOS	Children with Hearing Disability in Victoria Outcome Study
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CNHSP	Colorado Newborn Hearing Screening Project
CONSORT	Consolidated Standards of Reporting Trials
CRD	Centre for Reviews and Dissemination
D-ABR	diagnostic auditory brainstem response
dB	decibel
DEIP	Diagnostic Early Intervention Program
DGPP	Deutsche Gesellschaft für Phoniatrie und Pädaudiologie e.V. (The German Society of Phoniatrics and Paediatric Audiology)
DIMDI	Deutsches Institut für Medizinische Dokumentation und Information (German Institute for Medical Documentation and Information)
DPOAE	distortion products of otoacoustic emissions
DZH	Deutsches Zentralregister für kindliche Hörstörungen (German Central Registry for Hearing Impairment in Children)
EHDI	Early Hearing Detection and Intervention (Program)
EMBASE	Excerpta Medica
ENT	ear nose and throat
ERIC	Education Resources Information Center
f	female
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HAS	Haute Autorité de Santé (French National Authority for Health)

Abbreviation	Meaning
HI	hearing impairment
HTA	health technology assessment
HVDT	Health Visitor Distraction Test
Hz	hertz
I	index test
IGCH	International Working Group on Childhood Hearing
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
JCIH	Joint Committee on Infant Hearing
KBV	Kassenärztliche Bundesvereinigung (Federal Association of Statutory Health Insurance Fund Physicians)
LTFU	lost to follow-up
m	male
MCDI	Minnesota Child Development Inventory
Meck.-WP	Mecklenburg-Western Pomerania
MEDLINE	Medical Literature Analysis and Retrieval System Online
MHTAU	Malaysian Health Technology Assessment Unit
MSAC	Medical Services Advisory Committee
NCCHTA	National Coordinating Centre for Health Technology Assessment
NHS	National Health Service
NICU	neonatal intensive care unit
OAE	otoacoustic emissions
PHU	unit for partially hearing children
PPVT	Peabody Picture Vocabulary Test
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
R	reference test
RBST	Renfrew Bus Story Test
RCT	randomised controlled trial
Ref.	reference
RF	risk factor(s)
ROC	receiver operating characteristic
RPM	Raven’s Progressive Matrices
SBU	Statens Beredning för Medicinsk Utvärdering (Swedish Council on Technology Assessment in Health Care)
SCN	special care nursery
SD	standard deviation
S-OAE	screening-OAE
STAI	Spielberger State-Trait Anxiety Inventory

Abbreviation	Meaning
STARD	Standards of Reporting Studies of Diagnostic Accuracy
S-TEOAE	transient evoked otoacoustic emissions measured with screening instruments
TEOAE	transient evoked otoacoustic emissions
TROG	Test for Reception of Grammar
U3 and U4	third and fourth medical check-up for children
UK	United Kingdom
UNHS	universal newborn hearing screening
US(A)	United States (of America)
WBN	well-baby nursery

1 BACKGROUND

1.1 Definition and description of the disease investigated

According to estimates of the German Central Registry for Hearing Impairment in Children (DZH[2]), the prevalence of congenital hearing impairment in Germany is about 1.2 per 1000 births [1,2]. For children with risk factors (such as premature birth, intrauterine infections, chromosome anomalies [3]), the prevalence is estimated to be 10 to 30 per 1000 [1,2].

Hearing impairment is normally classified according to the degree of hearing loss. This is defined on the basis of a hearing threshold. The hearing threshold is the sound pressure level (usually given in decibels [dB]) from which the hearing still just detects an acoustic stimulus. Hearing impairment can be classified into mild (hearing threshold at 25 to 40 dB), moderate (41 to 60 dB), and severe hearing impairment (61 to 80 dB), and profound hearing impairment or deafness (> 81 dB) [4]. However, this classification is not used consistently. For example, in a recent study, moderate hearing impairment extended to 69 dB and severe hearing impairment to 94 dB [5].

The age of diagnosis for hearing impairment is currently about 21 to 47 months [2]. In the year 2000, the German Central Registry for Hearing Impairment in Children reported the mean age of diagnosis in Germany on the basis of a sample of 3882 children according to the severity of the hearing impairment. The mean age for deafness was 1.9 years, for severe hearing impairment or profound hearing impairment 2.5 years, for moderate hearing impairment 4.4 years, and for mild hearing impairment 6.2 years [6]. According to the HTA report by the German Institute for Medical Documentation and Information (DIMDI[3]), a hearing aid was provided on average only at the age of 3 to 5 years [2].

1.1.1 Clinical relevance of hearing impairment in neonates

The organs of the auditory system are almost completely developed before birth, so that a functional sense of hearing is usually clearly present towards the end of the pregnancy. From about the 29th week of pregnancy onwards, acoustic stimuli can be perceived and processed. This stimulation promotes the additional maturation and development of the sense of hearing (maturation of the auditory pathways) [2].

The hearing development of neonates with congenital hearing impairment may therefore be delayed, even at birth. As a consequence, additional adequate acoustic stimulation does not occur. This can lead to irreversible deficiencies in the auditory system [2,7]. However, studies

[2] Deutsches Zentralregister für kindliche Hörstörungen
[3] Deutsches Institut für Medizinische Dokumentation und Information

on the development of the auditory system in neonates and children are scarce (see, for example, Tibussek 2002 [8]; Klinke 2001 [9]).

More or less severe restrictions in quality of life and (language) development have been reported, depending on the severity of the loss of hearing and the ability to compensate [2,7]. Loss of hearing has direct negative consequences on the acquisition of language [10]. Although loss of hearing of $\geq$ 40 dB is often regarded as the critical threshold in respect of language acquisition, no unambiguous threshold has been defined. In principle, a distinction is made between receptive and expressive language development. Receptive language development is related to both hearing in itself and understanding and comprehension of language, facial expression, and gestures. Expressive language development signifies the ability to articulate and argue with the help of oral or sign language, facial expression and gestures. Receptive and expressive forms of language development are associated with each other. In addition, communicative abilities and spontaneous speech are important. Impairment in cognitive, emotional, and psychosocial development has also been discussed as a secondary consequence of hearing impairment [2,7].

1.2 Methods used in screening studies

1.2.1 Hearing screening in neonates: programmes and strategies

The objective of neonatal hearing screening is to recognise hearing impairment shortly after birth and to initiate treatment. This is to enable a largely normal development of the affected children [2,11].

Screening strategies that have been discussed include testing all newborn children (universal newborn hearing screening; UNHS) and screening of children with risk factors for hearing impairment (screening of at-risk children) [2,7].

The outcome of such a screening test is a screening result: a positive result indicates an abnormality that needs to be tested further; a negative result indicates that no abnormality was identified at the time of screening. After further testing, screening results can turn out to be correct (correct positive or correct negative result) or false (false positive or false negative result). False positive or false negative results are problematical; i.e., children with an abnormal result who are actually not affected, and children with a normal result who are actually affected. Such false results have consequences not only for further treatment, but may, for example, lead to a false sense of security or anxiety that is in fact unfounded.

1.2.2 Additional screening strategies

In addition to screening at the time of birth or shortly afterwards, there are also screening programmes for older babies or toddlers [7]. These can also recognise acquired hearing impairment, making direct comparison with neonatal screening programmes difficult.

1.2.3 Therapeutic interventions

The main treatment for congenital hearing impairment is to provide a hearing aid. If, in spite of the hearing aid and hearing and speech training, the child fails to react to acoustic stimuli (i.e., due to severe hearing impairment, profound hearing impairment or deafness), the possibility is considered of providing the child with a cochlear implant – although the benefits and disadvantages of this in young patients are the subject of controversy [2,12,13].

Supportive treatments include accompanying early intervention to promote hearing and language development, special teaching, speech therapy (oral and/or sign language) and advice and support for the affected families [2,10,14]. This is usually an interdisciplinary intervention with collaboration between specialists for paediatric audiology, ENT specialists and paediatricians, as well as speech therapists and special education teachers. This is not a temporally limited intervention, but a process of continuous support of affected children, particularly also by their parents.

1.2.4 Diagnostic test procedures

Two audiological test procedures have recently become relevant in neonatal hearing screening: the measurement of otoacoustic emissions (OAE or S-OAE, insofar as this is a measurement with screening instruments) and of acoustically evoked potentials (AEP, for example with ABR [auditory brain stem response; brain stem audiometry] or A-ABR, insofar as these are measurements with screening instruments, as well as D-ABR in the case of diagnostic brain stem audiometry) [2,15].

With otoacoustic emissions, a distinction is made between transient evoked acoustic emissions (TEOAE; S-TEOAE) and the distortion products of otoacoustic emissions (DPOAE). Otoacoustic emissions are sound waves that arise in the inner ear after acoustic stimulation and can be measured in the auditory canal with a sensitive microphone. They indicate the intact condition of the outer hair cells and thus the functionality of the peripheral auditory organ [12]. They do not allow an exact statement on the extent of loss of hearing.

Brain stem audiometry allows an exact determination of the hearing threshold. Different acoustic stimuli are released. The electric potentials evoked in the auditory nerve and in the auditory pathway are then recorded with the help of electrodes on the skin of the head. This provides information on both the functionality of the peripheral auditory organ and the transmission of the signal through the auditory pathways to the brain stem [2].

Both procedures – OAE and ABR – are non-invasive and for screening purposes are linked with an algorithm for automatic response recognition and result calculation (S-OAE, A-ABR).

Overviews and explanations of the existing diagnostic and screening methods and their age-appropriate use can be found in the consensus paper of the German Society for Phoniatrics and Paediatric Audiology (DGPP[4]) on the provision of hearing aids in children [16], in the DGPP's guideline "Peripheral hearing impairment in children – long version" [17], in the DIMDI HTA report [2,18], and in the paper by Cone-Wesson 2003 [15].

1.3 Current status of neonatal hearing screening

1.3.1 Review of the literature

Several systematic and non-systematic reviews have been published on various aspects of neonatal hearing screening.

Examples of review articles include Thompson 2001 [11], Kennedy 1991 [19], and the systematic review by the Cochrane Collaboration (Puig 2005 [20]).

Many studies have dealt with specific aspects of neonatal hearing screening. Hayes' paper of 2003 [21] covers the different screening methods, while Hyde 2005 [22] focuses on the planning of screening programmes. Yoshinaga-Itano's 2003 review [23] examines various aspects of the treatment of children with hearing disability.

A wide variety of European and other institutions have published reports (health technology assessments, HTAs) on neonatal hearing screening. For example, the German Institute for Medical Documentation and Information (DIMDI) [2,18], the English National Coordinating Centre for Health Technology Assessment (NCCHTA) [7], the French National Authority for Health (ANAES[5]; now HAS[6]) [24], the Finnish Office for Health Technology Assessment [25], the Swedish Council of Technology Assessment in Health Care (SBU[7]) [26], the American Agency for Healthcare Research and Quality (AHRQ) [27], the Australian Medical Services Advisory Committee (MSAC) [28], and the Malaysian Health Technology Assessment Unit (MHTAU) [29].

Both international [30-32] and national [33-35] recommendations and guidelines for neonatal hearing screening have been published (European Consensus Statement on Screening for Neonatal Hearing Defects [30], Joint Committee on Infant Hearing – Year 2000 Position Statement [31], Consensus Development Conference Statement of the National Institutes of Health [32], Interdisciplinary Consensus Conference on Newborn Hearing Screening[8] [33],

[4] Deutsche Gesellschaft für Phoniatrie und Pädaudiologie
[5] Agence Nationale d'Accréditation et d'Evaluation en Santé
[6] Haute Autorité de Santé
[7] Statens Beredning för Medicinsk Utvärdering
[8] Interdisziplinäre Konsensuskonferenz für das Neugeborenen-Hörscreening

Phoniatrics and Paediatric Audiology Consensus on Universal Newborn Hearing Screening[9] [34], and the Strategy Paper on the Joint Committee "Infant Hearing"[10] [35]).

A brief overview of the various articles and reviews on neonatal hearing screening can be found on the website of the "Geneva Foundation for Medical Education and Research" (http://www.gfmer.ch/Guidelines/Neonatology/Neonatal_hearing_loss.htm).

1.3.2 Current status of neonatal hearing screening in the international context

There are projects on neonatal hearing screening in many countries on all continents. An overview can, for example, be found on the website of the "International Working Group on Childhood Hearing" (IGCH; http://childhearingroup.isib.cnr.it).

Universal newborn hearing screening programmes are already well-established in some countries, for example, in Great Britain and in many states in the USA. An overview of the screening programmes in the USA can be found in Johnson 2005 [36].

1.3.3 Current status of neonatal hearing screening in Germany

Neonatal hearing screening programmes have already been implemented in Germany, too. During a congress in Hanover in autumn 2004 [37], various (model) projects on the early detection of hearing impairment in children in different federal states and regions were presented: Baden-Württemberg, Berlin, Brandenburg, Hamburg, Hanover, Hesse, Mecklenburg-Western Pomerania, Upper Palatinate, Saarland, Saxony-Anhalt, Schleswig-Holstein, and Würzburg. In the conference consensus paper [38], the guidelines of the European Consensus Statement [30] were accepted "without reservation".

Recommendations for Germany have been developed by the German Institute for Medical Documentation and Information (DIMDI) [2,18] and by the Interdisciplinary Consensus Conference on Newborn Hearing Screening 2004, comprising 11 professional societies; these represent gynaecology and obstetrics, otolaryngology, paediatrics, phoniatrics, and paediatric audiology [33] (see also Section 1.3.1).

[9] Phoniatrisch-pädaudiologischer Konsens zu einem universellen Neugeborenenhörscreening
[10] Strategiepapier zum Joint Committee Frühkindliches Hören

2 AIMS OF THE INVESTIGATION

The topic of the present study is to evaluate the benefits and harms of universal newborn hearing screening for early detection of hearing impairment in neonates, focussing on patient-relevant therapy goals. If diagnosis and treatment of a (congenital) hearing impairment take place as early as possible, the resulting developmental deficiencies in a child and the possible lifelong consequences should be avoided, or at least minimised.

A screening programme is a complex intervention and its success depends on a series of consecutive elements. The objective of universal newborn hearing screening is to identify all children with a hearing impairment requiring treatment – as early and as completely as possible. The precondition for this is, therefore, that the investigation and treatment procedures should preferably be completely accepted in the target group. The expedience of screening decisively depends on the effectiveness of the available treatment. If there are no effective treatments, there is no benefit from early detection, unless early diagnosis is linked to other advantages for the patient, for example, that the parents adjust better to the needs of the affected child. However, if children can be treated at an early age and the patient-relevant, long-term consequences of hearing impairment can actually be demonstrably reduced by early treatment, this indicates that the procedure is of benefit. The procedure used to identify hearing impairment must be of adequate accuracy and produce as few false results as possible. The criteria for the evaluation of screening programmes are listed in the corresponding section of the IQWiG methods [39].

The best basis for answering the question as to whether universal newborn hearing screening is of benefit to neonates would be to have studies in which the whole screening chain is examined for an adequately large group of children. The screening programme would be offered to one group, but not to the other. After an adequately long period of operation, the comparison can then be made to establish for how many children (if any) the screening programme has avoided hearing impairment and its consequences. Studies of this sort are demanding. However, our initial research indicates that very few studies of the complete screening chain have been performed in neonatal hearing screening [11,27], but there are examples that indicate that these studies are feasible [5,40,41].

The present report therefore also examines studies that permit statements about individual screening stages (procedures for the treatment of hearing impairment and diagnostic procedures). Evaluation of current screening programmes and model projects can then provide information as to whether a test can be widely used and is accepted. An essential argument for the plausibility of neonatal hearing screening would be studies that show that earlier diagnosis and treatment of children with hearing impairment have favourable consequences. We therefore also included studies designed to compare children treated early with those treated later. Moreover, appropriate studies can compare different diagnostic

techniques that might be used in hearing screening and would allow conclusions as to the reliability and error-proneness of these test procedures.

If there is adequate evidence for the benefit of early rather than late (or later) treatment and if, in addition, hearing impairment can be adequately diagnosed in the age group of interest, this may also be seen as evidence for the effectiveness of screening. On the basis of these considerations, the objectives can be split into 3 areas (screening, treatment, and diagnostic studies), which are discussed below.

The objectives of the present report for the evaluation of the overall screening chain or single links in the chain are presented below.

2.1 Screening studies

Evaluation of the effectiveness of screening programmes with respect to patient-relevant outcomes:

- Comparative evaluation of the benefits and harms of a universal newborn hearing screening programme, compared with a procedure without screening, and
- Comparative evaluation of the benefits and harms of different screening strategies (for example, different time points of screening, screening for different levels of severity of hearing impairment, universal screening versus screening of at-risk children).

2.2 Treatment studies

Evaluation of the effectiveness of different time points for providing treatment with respect to patient-relevant outcomes:

- Comparative evaluation of the benefits and harms at different time points for providing treatment (early versus late or later).

2.3 Diagnostic studies

Evaluation of the quality of specific diagnostic procedures used for screening:

- Evaluation of the diagnostic quality (e.g. sensitivity/specificity, likelihood ratios) and positive predictive values of the 2 different test procedures OAE and AEP (e.g. by means of ABR).
- Comparative evaluation of the suitability of the 2 relevant test procedures in a screening setting (for example, time needed, influence of investigator or setting, consequences of different criteria of test quality).

3 PROJECT PLAN

3.1 Procedures

On 15.03.2005, the Federal Joint Committee commissioned the Institute for Quality and Efficiency in Health Care to evaluate the benefits and harms of the early detection of hearing impairment in neonates (neonatal hearing screening). The commission was based on an application from the Federal Association of Statutory Health Insurance Fund Physicians (KBV[11]) of 10.01.2005 to check the fulfilment of the legal criteria in accordance with §25 Section 3 Social Code Book V for the introduction of a paediatric medical examination in accordance with § 26 Social Code Book V for the early detection of hearing impairment in neonates. The commission was specified on 26.07.2005. The present evaluation aims to support the Federal Joint Committee (G-BA[12]), which, as the body for the self-administration of physicians, health insurance funds, and hospitals, assesses health care services regarding their benefit, medical necessity, and efficiency [42].

External experts were involved in the project. They were involved in the preparation of the report plan, the literature search and literature evaluation, as well the preparation of the preliminary report.

The report plan in the version of 14.10.2005 was published on the Internet on 15.10.2005 [43]. The preliminary evaluation, the preliminary report, [44], was published on the Internet on 04.10.2006. Comments by all interested persons, institutions and societies, including private persons, professional societies and industrial companies, could by made on the preliminary report until 02.11.2006. Substantial comments were discussed regarding their relevance to the final report with the persons submitting comments in a scientific debate on 23.11.2006 (the link to the meeting minutes of this debate [German version only] is included in Appendix F). Moreover, 3 external experts reviewed the preliminary report.

Following the scientific debate, IQWiG produced the present final report, which was published on the Internet 8 weeks after submission to the Federal Joint Committee.

3.2 Summary of changes after publication of the preliminary report

Because of the comments submitted on the preliminary report and the scientific debate, the following changes were made after the publication of the preliminary report:

[11] Kassenärztliche Bundesvereinigung
[12] Gemeinsame Bundesausschuss

- Additional information from the comments and from answers by the relevant project managers was added to the section on the German neonatal hearing screening projects (see Section 5.1.5).

- The criteria defined in the preliminary report regarding the study design of screening and treatment studies were described in more detail. Regarding the comparability of the test and control group, the investigation of participants within a comparable time frame was included (concurrent comparison), according to the report plan.

- The conclusion was amended (see Section 7).

4 METHODS

4.1 Criteria for the inclusion of studies in the investigation

Criteria for inclusion of a study in the present report (inclusion criteria) and criteria for exclusion (exclusion criteria) from further evaluation are described below. The classification corresponds closely to the questions on screening, treatment, and diagnosis as described in the previous section.

4.1.1 Screening studies

Population

Neonates are the target group for hearing screening. This age group is restricted by definition to the first 4 weeks of life. This report will nevertheless include studies that examined children up to an age of 12 months, so that a comparison can be made with screening programmes that were started later.

Intervention and comparator treatment

Only screening studies were to be included in which

- the measurement of OAEs and/or brain stem audiometry (ABR) were used as test interventions, and
- there was either a comparison with a procedure without screening or there was a comparison between different screening strategies including the above-named relevant procedures, for example, hearing screening programmes at different screening time points, screening for different severities of hearing impairment, universal screening versus screening of at-risk children.

Study types

Randomised controlled trials (RCTs) provide the most reliable results for the evaluation of the benefits of a medical intervention, as they are least prone to produce uncertainty of results, insofar as they have been conducted with appropriate methods and in accordance with the relevant research question. As a prior literature search showed that RCTs had not been performed to study the benefit of neonatal hearing screening, non-randomised intervention studies and cohort studies were also included, as long as the intervention and control groups were observed (at least approximately) concurrently.

4.1.2 Treatment studies

Population

Studies were included that considered children with congenital hearing impairment up to the age of 10 years (at the time of the first provision of treatment).

Intervention and comparator treatment

Although the ideal study design to test the benefit of interventions is the RCT (see Section *Study types*), it is difficult to imagine a randomised study to compare early with late (later) intervention, as the arguments that emphasise the benefit of providing treatment for a hearing impairment at an early age seem inherently highly plausible.

Bearing in mind ethical aspects about randomisation at different time points of intervention and the current level of evidence – with many studies of relatively low methodological quality [2,7], a procedure was selected to evaluate the benefit of earlier rather than late (later) intervention on a broad basis. This procedure is described in the following text.

In principle, intervention for a congenital hearing impairment in a child consists of 2 factors – the age at intervention (or the time point) and the type of intervention (e.g. hearing aid or cochlear implant and accompanying or subsequent rehabilitation). The age at intervention is defined as the age of the child when the intervention investigated in the study was performed. The age at intervention may (but need not) correspond to the age of the child at the start of the first accompanying measures to treat the hearing impairment.

There are 2 conceivable approaches to investigate the influence of the age at intervention:

Direct assessment of the effect of early in comparison to late (later) intervention

In an ideal case, the benefit of early treatment would be determined during a single study. In this study, children provided with the intervention at different ages would then be compared with each other. As experience has shown that these studies are not randomised, the results of these studies would be of limited evidential value, as the children given early intervention would differ from those given late (later) intervention in other factors that are also essential for the development of the child. These confounding factors – such as the degree of hearing impairment at the start of treatment or the socioeconomic status of the parents – may bias the study results.

Indirect assessment of the effect of early in comparison to late (later) intervention by comparing the effects of different types of intervention

In this approach, the benefit of the 2 factors described above (type of intervention and age at intervention) are initially determined separately. In a first step, studies are considered in

which the type of intervention was investigated. In this way, the benefit of a treatment for children in a specific age group (in comparison with another treatment or no treatment) can be established. If, for example, a study can be identified in which 2-year-old children were compared who were either given a hearing aid or a cochlear implant and a second study identified with the same comparison, but with 6-year-old children, it would be possible to make an indirect estimate of the magnitude of the early benefit in comparison with a later benefit. The results of an indirect comparison of this sort may nevertheless be subject to bias, even if the treatment studies were randomised for each time point (early or late).

Study types

The following 4 study types, classified according to the level of evidence, were to be included in the present report, as discussed above:

1. Controlled studies (randomised and non-randomised) that compare different types of intervention and investigate children of different ages at intervention (indirect comparison)

   To allow unambiguous allocation of the interventions investigated in these studies to early or late (later) intervention and thus to permit determination of a specific effect of the age at intervention, the studies

   - must deal with the same comparisons; for example, comparison of hearing aid with cochlear implant, where the secondary conditions (e.g. the concomitant treatments) and the outcome parameters investigated should be comparable, both within the study and between studies;

   - must be distinguishable with respect to the age or age range of the children. This is facilitated if there are only minor age differences within a study.

2. Non-randomised intervention studies and cohort studies that compare early with late (later) intervention at a comparable time of evaluation

   An essential criterion for inclusion here is the adequate quality of the studies in the sense of comparability between groups and subsequently the interpretability of the data. “Adequate quality” was defined as (I) adequate consideration of potential confounding factors (adequate control for confounding factors) and (II) adequate description of the intervention.

   (I) Control for confounding factors was regarded as “adequate” if (a) at least 3 potentially confounding factors were considered, always including the severity of hearing impairment at the start of the intervention, and if (b) appropriate statistical methods to control for confounding factors were used.

(II) The intervention was regarded as “adequate” if information was provided for both factors: the type of intervention (hearing aid, cochlear implant or other form of supportive treatment) and age. As regards the age of the children, the following information was required and was to be considered: (a) the age at intervention, and (b) the age of the children when the outcome parameters were assessed (evaluation).

4.1.3 Outcome parameters for screening and treatment studies

For the investigation, outcome parameters were used that enabled the assessment of at least one of the following patient-relevant therapy goals:

- Health-related quality of life
- Hearing ability
- Language development (e.g. language comprehension and production, speech intelligibility and fluency, development of vocabulary)
- Psychosocial impairment (e.g. social communication competence, social integration, development of the concept of self, labelling)
- Emotional development
- Cognitive and educational development (e.g. ability at school, type of school visited, training opportunities)
- Adverse effects of screening/diagnosis due to false positive or false negative test results (e.g. parents’ worries)
- Adverse effects of treatment (e.g. physical: consequences of early/late intervention; psychological: labelling)

The studies included were screened for quantifiable information on all the outcome parameters described above referring to the corresponding therapy goals.

4.1.4 Diagnostic studies

Application studies under everyday conditions in persons with unknown disease status provide the most reliable results on the test quality of diagnostic procedures [45]. If studies of this sort are not available (in adequate number and/or quality), studies in neonates with known disease status should also be considered, but only if at least 20 children with or without congenital hearing impairment are tested, as otherwise a sufficiently precise estimate of sensitivity and specificity values in the individual studies cannot be expected.

Population

In the present report, studies were to be included in which children from an unselected screening population were tested with a relevant diagnostic test procedure (see below) within the first year of life.

Intervention and comparator treatment

The procedures "measurement of OAEs" and/or "brain stem audiometry" (ABR) were regarded as relevant test procedures. In the studies, they were to be compared with any other test procedure to detect a hearing impairment. An additional criterion was the provision of adequate information on criteria of test quality, or of data from which the quality criteria could be inferred (e.g. 2x2 tables).

4.1.5 Inclusion and exclusion criteria

In the evaluation, all studies were included that fulfilled all the following inclusion criteria and none of the following exclusion criteria.

Table 1: Inclusion and exclusion criteria – screening studies

Inclusion criteria – screening studies	
I1	Children up to the first year of life
I2	Universal newborn hearing screening with the procedures OAE and/or ABR
I3	Outcome parameters as defined in Section 4.1.3
I4	Controlled studies including a concurrent control group
Exclusion criteria – screening studies	
E1	Duplicate publications without relevant additional information
E2	No full-text publication available[(a)]
a: In this context, full-text publications also include the non-confidential provision to the Institute of clinical study reports or the non-confidential provision to the Institute of other reports on a study that fulfil the criteria of the CONSORT Statement [46] or relevant standards for non-randomised studies, and enable the evaluation of the study.	

Table 2: Inclusion and exclusion criteria – treatment studies

Inclusion criteria – treatment studies	
I1	Children with congenital hearing impairment aged up to 10 years at the time of first intervention
I2	Interventions for congenital hearing impairment (e.g. hearing aid or cochlear implant and accompanying or subsequent rehabilitation), see also Section 4.1.2
I3	Outcome parameters as defined in 4.1.3
I4a	Indirect comparison: controlled studies as defined in Section 4.1.2
I4b	Direct comparison: controlled studies with a concurrent control group, adequate control for confounding factors, and adequate description of the intervention, as defined in Section 4.1.2
Exclusion criteria – treatment studies	
E1	Duplicate publication without relevant additional information
E2	No full-text publication available [(a)]
a: In this context, full-text publications also include the non-confidential provision to the Institute of clinical study reports or the non-confidential provision to the Institute of other reports on a study that fulfil the criteria of the CONSORT Statement [46] or relevant standards for non-randomised studies, and enable the evaluation of the study.	

Table 3: Inclusion and exclusion criteria – diagnostic studies

Inclusion criteria – diagnostic studies	
I1	Children who were a maximum of one year old when otoacoustic emissions and/or acoustically evoked potentials were recorded
I2a	OAE and/or ABR
I2b	Any sort of reference test
I3	Provision of information on diagnostic quality criteria and/or predictive values or information allowing the deduction of quality criteria (e.g. 2x2 tables)
I4	Study types as defined in Section 4.1.4
Exclusion criteria – diagnostic studies	
E1a	Children who had already been treated when otoacoustic emissions and/or acoustically evoked potentials were recorded
E1b	Children with risk factors for hearing impairment
E2	Duplicate publications without relevant additional information
E3	No full-text publication available[(a)]
a: In this context, full-text publications also include the non-confidential provision to the Institute of clinical study reports or the non-confidential provision to the Institute of other reports on a study that fulfil the criteria of the STARD Statement [47], and enable the evaluation of the study.	

4.2 Literature search

The objective of the literature search was to identify published and unpublished studies providing relevant information on the question of the benefits and harms of universal newborn hearing screening, the benefits and harms of early rather than late (later) treatment of congenital hearing impairment, and on the question of the accuracy of the relevant test procedures.

4.2.1 Literature sources

The literature search for relevant published studies was performed in the following sources:

- 11 bibliographic databases: MEDLINE, EMBASE, CINAHL, PsycINFO, PSYNDEX, ERIC, Cochrane Library databases on primary publications (Clinical Trials), Systematic Reviews (CDSR), Other Reviews, Economic Evaluations, and Technology Assessments
- Reference lists of relevant secondary publications (systematic reviews and HTA reports)
- Reference lists of the 9 comments from interested professional circles forwarded to the Institute by the Federal Joint Committee

Separate searches on 3 separate dates were performed for screening, treatment, and diagnostic studies. The search strategies and search dates for the search in bibliographic databases are shown in Appendix A. The tables on the search strategies contain the individual steps of the search strategies. In addition to the search in databases, relevant websites (e.g. www.otoemissions.org) and professional journals were searched by hand for additional publications of potential relevance.

4.2.2 Search for additional published and unpublished studies

The search for additional published and unpublished studies consisted of several steps, as described below.

4.2.2.1 Written enquiries to manufacturers of screening instruments

In March 2006, written enquiries were sent to a total of 13 manufacturers of screening instruments in Europe and in the USA. Five manufacturers of screening instruments were contacted in Germany (Fischer-Zoth Diagnosesysteme GmbH, GN Otometrics GmbH & Co. KG, Maico Diagnostic GmbH, Pilot Blankenfelde medizinisch-elektronische Geräte GmbH, and Riemser Arzneimittel-AG/Rösch Medizintechnik). In addition, enquiries were sent to the firms of Interacoustics® (Denmark), Labat Biomedical Instruments (Italy), and Otodynamics Limited (Great Britain), as well as the US companies Everest Biomedical Instruments,

Intelligent Hearing Systems, Natus Medical Inc., SonaMed Corp., and Starkey Laboratories Inc.

4.2.2.2 Written enquiries to manufacturers of hearing aids or cochlear implants

In an effort to identify or to find clues to other studies on cochlear implants or hearing aids, a total of 4 manufacturers (5 branches) of cochlear implants were contacted in March 2006 in Germany (Cochlea GmbH), Austria (Med-El Medical Electronics), Great Britain (Cochlear Corporation), and the USA (Clarion®, Etymotic Research Incorporation). In addition, in November 2006, 3 German manufacturers of hearing aids were contacted (Oticon GmbH, Phonak GmbH, Widex Hörgeräte GmbH).

4.2.2.3 Enquiries to hospitals

With the objective of obtaining clues to additional relevant studies or model projects on universal newborn hearing screening in Germany or directly identifying potentially relevant publications online, a search was performed on the websites of German hospitals and clinics with departments for otolaryngology or paediatric audiology. These hospitals were selected on the basis of the HTA report on neonatal hearing screening published in 2004 by the German Institute for Medical Documentation and Information [2] and the final report of the model programme “Improvement in the Early Detection of Hearing Impairment in Children” from Hanover [48]. Interviews were reported there with the institutions running the model projects.

4.2.2.4 Other enquiries and searches

We wrote to the German Central Registry for Hearing Impairment in Children on 15.09.2005, asking them to provide IQWiG with current data on the incidence and prevalence of congenital hearing impairment in children. In addition, a website (http://www.otoemissions.org) with current information on neonatal hearing screening was searched for relevant references in March 2006.

4.2.3 Search for additional information on relevant studies

Where relevant, the documents found in the literature search were complemented with additional relevant studies found in the search described in Section 4.2.2. In addition, authors of studies were contacted if questions came up during the evaluation regarding the relevance of a study for the present report, which could not be answered from the available data (documentation of correspondence in Appendix D).

4.2.4 Identification of relevant studies

The bibliographic details of the identified publications or documents (as described in the sections above) were imported into a database for further processing.

In the first selection step, the identified documents were independently reviewed by 2 assessors on the basis of the title and the abstract (if present), to decide which of these could be assessed by both assessors as certainly non-relevant, following the criteria for inclusion and exclusion as given in Section 4.1.5. In doubtful cases, a consensus was reached. The identified citations were entered into the 3 databases corresponding to the different research questions investigated in the study. References found in the first selection step with potential relevance for one of the other areas were marked and separately assessed for their relevance to the other area.

The assessment of the relevance of the full text was again performed by 2 assessors independently. After this stage, the following studies were designated as relevant: (1) References considered by both assessors to be relevant, and (2) References that were initially considered to be relevant by only one assessor, but that both assessors accepted as relevant after discussion.

The reference lists of relevant secondary publications were searched for additional primary publications that had not been identified in the literature search in the bibliographic databases. The full texts of the publications identified in the review articles were evaluated with respect to their relevance by 2 assessors as described above.

4.2.5 Information from the written hearing on the preliminary report

After the publication of the preliminary report, a written hearing took place, as well as an oral debate of the submitted written comments, which could also refer to the completeness of the literature search or the completion of data on a study. Relevant information from this hearing could be incorporated in the present final report.

4.3 Evaluation of information

The evaluation of the included studies was conducted on the basis of the available information and was therefore highly dependent on the quality of each publication and other sources of information.

The evaluation was conducted in 3 stages:

- Extraction of the study data

- Evaluation of the study and publication quality
- Evaluation of the data consistency within the publication

4.3.1 Data extraction

Extraction of the data of published studies was performed independently by 2 assessors with the help of standardised documentation forms. After this, the 2 assessors compared their assessments for each study. If there were discrepancies between the assessments, these were resolved by discussion between the assessors. In this manner, a consensus documentation form was prepared for each study. The present report is based on both the studies and on their abbreviated representation in the documentation forms.

4.3.2 Evaluation of the study and publication quality

The evaluation of the screening and treatment studies was performed with the help of the quality evaluation instruments of the Centre for Reviews and Dissemination (CRD) [49], as modified by us, with respect to the following factors: sample size planning, blinding of the persons documenting or evaluating outcomes, comparability of the samples, consideration of confounding factors, documentation of study discontinuations, and transparency of the patient flow.

For the evaluation of the quality of the diagnostic studies, the instrument QUADAS (Quality of Diagnostic Accuracy Studies) [50] was used. This consists of 14 items. Information on the following aspects was regarded as particularly important: generalisability (whether the test results can be applied to use in everyday clinical practice), information on the accuracy and independence of the reference test (comparator test) from the test being investigated (index test), blinded interpretation of the test results, presentation of non-interpretable test results, and explanation of study discontinuations.

The questions from all 3 evaluation instruments used could each be answered with “yes”, “no” or “unclear”. Where it appeared to be necessary, selected aspects were described in more detail in the corresponding tables on study and publication quality (Tables 8, 19, and 24).

Finally, on the basis of the aspects mentioned above, a global assessment of the study and publication quality was performed by means of a feature comprising 4 grades (biometric quality). The possible grades were “no evident deficiencies”, “minor deficiencies”, “major deficiencies”, and “unclear”.

The grades were defined in advance as follows: “minor deficiencies” are present when it is assumed that their correction will have essentially no effect on the results and thus the overall conclusion of the study. With “major deficiencies”, the overall conclusion of the study would have to be called into question, since, if the deficiencies were rectified, this could possibly

result in different conclusions. A study is described as having “no evident deficiencies” when at most it exhibits trivial deficiencies. “Unclear” means that no unambiguous statement on the biometric quality of the study can be made on the basis of the available documents.

As described above, the evaluation of the study quality is directly influenced by the quality and consistency of the available information, so that the designation of “major deficiencies” is not necessarily a description of the quality of the study itself, but may be caused by the quality of the underlying publication(s).

This quality classification was to be used potentially in a sensitivity analysis within the framework of a meta-analysis.

The evaluation of the biometric quality of the screening, treatment, and diagnostic studies was performed separately.

4.3.3 Consistency of information

Where relevant, the data extraction was followed by a comparison with information found in the extended search for published studies described in Section 4.2.2. If either this comparison or the comparison of differing information on any aspect within the publication itself revealed discrepancies that could have had a major influence on the interpretation of results, this was noted in the results section.

4.4 Information synthesis and analysis

4.4.1 Characterisation of the studies

The aspects of the study design and study quality described above were represented separately for all 3 areas and, where appropriate, were presented in tables to increase clarity. For diagnostic studies, the results were classified depending on the test procedures investigated. For treatment studies, the results were presented separately for comparisons by different methods, as explained in Section 4.1.2.

4.4.2 Comparison of the results of individual studies

The results of the individual studies are collated according to therapy goals and outcome parameters (Sections 5.1.4, 5.2.4, and 5.3.4). The results from the model projects on acceptance and feasibility of a universal newborn hearing screening programme are discussed separately (Section 5.1.5).

For the screening studies, the results of statistical analyses (effect estimates, corresponding confidence interval, p-value) are presented. For the most part, this did not appear to be meaningful for the treatment studies, due to the different methods of evaluation. These results

are mostly reported here as a narrative. The results on the quality of the relevant diagnostic test procedures were taken from the study publications, insofar as they were present. We calculated values that were not presented ourselves, for example, for sensitivity and specificity.

4.4.3 Meta-analysis

A quantitative summary of the individual results was planned in the form of a meta-analysis in accordance with the methods of the Institute [39,51]. However, on the basis of the screening, treatment, and diagnostic studies included, a meta-analysis was not meaningful either for methodological reasons or reasons of content.

4.4.4 Sensitivity analyses

Sensitivity analyses were planned in particular for:

- The evaluation of biometric quality, for example, on the basis of the classification given in the standardised documentation forms
- The per-protocol analyses as described in some publications (versus intention-to-treat or intention-to-screen analyses), where possible, and
- A (statistical) model with fixed effects (versus a model with random effects), if a meta-analysis was performed.

On the basis of the available data, the planned sensitivity analyses could not be performed in a meaningful manner.

4.4.5 Subgroup analyses

Subgroup analyses were planned for the following characteristics:

- Gender
- Age at screening
- Age at start of treatment and when outcome parameter was measured
- Type/frequency of the intervention
- FAIL-PASS criterion (severity/complexity of the hearing impairment)
- Type of screening (mono-/bilateral, single or multiple stages)
- Study setting (inpatient, outpatient)

- Expertise/experience of the investigator

On the basis of the available data, subgroup analyses could not be performed.

4.5 Deviations from the report plan

In the course of the report preparation, there were changes from the methods described in advance in the report plan. On the one hand, these were related to the necessity of specifying or clarifying issues, without essential relevance to the content. On the other hand, there were changes in the methodological procedure itself. These changes are described below.

4.5.1 Changes during the preparation of the preliminary report

Methodological changes from the previously planned procedure

- In accordance with the inclusion criteria in the report plan, screening studies were only to be included if they compared universal newborn hearing screening with another procedure and provided information on patient-relevant outcome parameters. In order to provide a better assessment of the acceptability and practical feasibility of screening of this sort in Germany, model project reports on hearing screening programmes in Germany were included, even if they had no control group and did not investigate patient-relevant outcome parameters.

- In accordance with the inclusion criteria of the report plan, treatment studies were only to be included if they investigated a randomised comparison of early and late (later) treatment or if they made an indirect comparison. The methodological procedure was specified for treatment studies (evaluation of the benefits and harms of early in comparison to late [later] intervention). In addition to the consideration of non-randomised intervention studies and cohort studies for an indirect comparison, studies were also considered when they made a direct comparison between early and late (later) intervention. These are studies in which an early intervention in children with hearing impairment was compared with late (later) intervention in comparable children. The comparability of the children was regarded as adequate when the studies (a) performed adequate control for confounding factors, and (b) the intervention was described adequately. The relevant Section 4.1.2 was amended accordingly.

Changes of content in comparison to the previously planned procedure

- In accordance with the inclusion and exclusion criteria in the report plan, diagnostic studies were only to be excluded if the children investigated for hearing impairment were older than one year of age or had already been treated. To ensure the transferability of the results on the diagnostic quality of the test procedure to the situation of use (universal newborn hearing screening), exclusion criterion E1b “Children with risk factors for

hearing impairment" was added. For this reason, the previously planned subgroup analysis for risk factors in diagnostic studies was no longer necessary and was removed from Section 4.4.5.

Changes without relevant consequences for the content

- To improve legibility and to aid comprehension, a consistent structure was used, classified into the areas of "screening studies", "treatment studies", and "diagnostic studies". The corresponding text passages in the report plan, which were orientated in structure towards the objectives of the study, were taken over and integrated into this structure. As the same patient-relevant outcome parameters apply to the screening and treatment studies, this aspect was treated in a single section (Section 4.1.3). The inclusion and exclusion criteria were, however, tabulated separately to improve clarity, with one table for each area (Tables 1, 2 and 3).

- We did not contact the National Confederations of Regional Associations of the Health Insurance Funds, as due to the very broad literature search and after examining other reviews of this subject, we concluded that no additional studies could be expected.

- For the same reason, we dispensed with a search in Social Sci Search.

- We also contacted institutions involved in neonatal hearing screening projects and considered the information provided in the report.

4.5.2 Changes after publication of the preliminary report

Changes without relevant consequences for the content

- For a more exact description, the wording of the outcome parameters was changed, so that no description of the direction of the effects was anticipated. The outcome parameters themselves were not changed.

- Compared with the terms used in the preliminary report for study types to be included for treatment studies (non-randomised intervention studies and correlation studies), the term "correlation study" was replaced by "cohort study". The difficult distinction between correlation studies and cohort studies had already been noted in the preliminary report.

- The inclusion criteria in Tables 1 and 2 were specified more precisely following the information presented in the relevant sections. In particular this refers to the inclusion criterion I4 for screening studies (Table 1) and to the inclusion criteria I1, I2, and I4 for treatment studies (Table 2). The following exclusion criteria in Tables 1 to 3 were deleted, as they were redundant: 1) Screening studies: exclusion criterion E1 "Animal studies" (Table 1); 2) Treatment studies: exclusion criteria E1 "Children without hearing

impairment" and E2 "Animal studies" (Table 2); 3) Diagnostic studies: exclusion criterion E2 "Animal studies" (Table 3).

Individual arguments, statements, and quoted publications from the comments submitted on the preliminary report and from their discussion in the oral debate on 23.11.2006 were reviewed carefully. Comments regarded by the authors of this report as relevant were considered and led to further amendments without essential changes in content. These particularly referred to:

- The completion of data on the German projects on universal newborn hearing screening.
- The correction of the inclusion criterion for treatment studies, I1 "Children with congenital hearing impairment up to the age of 10 years at the time of evaluation" to "Children with congenital hearing impairment aged up to 10 years at the time of first intervention". No further changes or specifications of the methodology resulted from the submission of comments.
- The outcome parameters: The reduction in the admission rate to special schools after the implementation of universal newborn hearing screening was named as a hard endpoint to assess the benefit of a screening programme. This parameter was allocated to the outcome parameter already defined "cognitive and educational development".
- The categorisation of studies identified in the literature search and reviewed in full text: 2 Japanese publications and a Spanish publication, which had been allocated to the exclusion criterion E4 "No full-text publication available" [52–54], were acquired and translated. None of these publications was included, as they did not fulfil the inclusion criterion I3 "Provision of information on diagnostic quality criteria and/or predictive values or information allowing the deduction of quality criteria (for example, 2x2 tables)".
- The consideration of the update [18] of the German HTA report on newborn hearing screening by the German Institute for Medical Documentation and Information (DIMDI) [2], which was already cited and discussed in the preliminary report and which was published during the preparation of the preliminary report. This update was screened for relevant studies, but did not lead to the inclusion of further studies.
- The discussion of other HTA reports and systematic reviews: A short description of all papers named in Appendix C was added. The review by Cone-Wesson 2003 was removed, as this is not a systematic review in the strict sense, i.e., no systematic search for primary studies was performed, and these studies were not selected and critically evaluated according to explicitly defined criteria.
- Additional enquiries to 3 manufacturers of hearing aids (Oticon GmbH, Phonak GmbH and Widex Hörgeräte GmbH) within the framework of the literature search in November

2006. There was no response to these enquiries by the time of the completion of the report.

5 RESULTS

First, the results of the search for published and unpublished studies will be presented. This is followed by the summary of the relevant studies and their evaluation. The results for the outcome parameters will then be reported (according to therapy goals and quality criteria/performance of the relevant test procedures). The results for screening, treatment, and diagnostic studies will be shown separately.

5.1 Screening studies

5.1.1 Literature search (screening studies)

This section presents the results of the systematic search for screening studies in bibliographic databases, of hand searches, and of enquiries to manufacturers, authors, and hospitals.

5.1.1.1 Results of the literature search (screening studies)

The systematic literature search for screening studies was performed in November and December 2005 in a total of 11 databases. A search update was performed in 2 stages: First, a search was performed in 4 databases at the start of June 2006 and then another search was performed in the remaining 7 databases in August 2006.

Figure 1 shows the results of the search for published screening studies in bibliographic databases and references lists of relevant secondary publications. It also shows the results of the search in comments to the Federal Joint Committee and of the hand search.

The systematic literature search identified a total of 5473 citations (MEDLINE N = 2113, EMBASE N = 2161, Clinical Trials N = 9, ERIC N = 114, CINAHL N = 667, PsycINFO N = 150, PSYNDEX N = 1, CDSR N = 75, Other Reviews N = 149, Economic Evaluations N = 24, Technology Assessments N = 10). A total of 22 additional references were found in the systematic search for diagnostic studies. The search for treatment studies found an additional reference of potential relevance to the area of screening. A total of 54 references were cited in the 9 comments to the Federal Joint Committee. The enquiries to hospitals gave 17 additional references. We also considered the 7 references sent spontaneously to the Institute. After subtraction of 1168 duplicates (references with the identical bibliographic information), we were left with 4406 references, which were assessed on the basis of the titles and abstracts. A total of 4334 of these were excluded as being definitely irrelevant to the question of screening. These included 3 systematic reviews; their references lists – together with those from 8 systematic reviews or HTA reports identified by a hand search – were inspected for additional relevant studies (see Appendix C). No additional relevant articles were found. The full texts of the 72 potentially relevant references were then inspected and 9 of these publications (2 studies) were included in the evaluation.

After removal of duplicates, the search update gave a total of 339 hits. This included an additional relevant primary publication. Thus a total of 10 publications on 2 studies were included as relevant to the screening question.

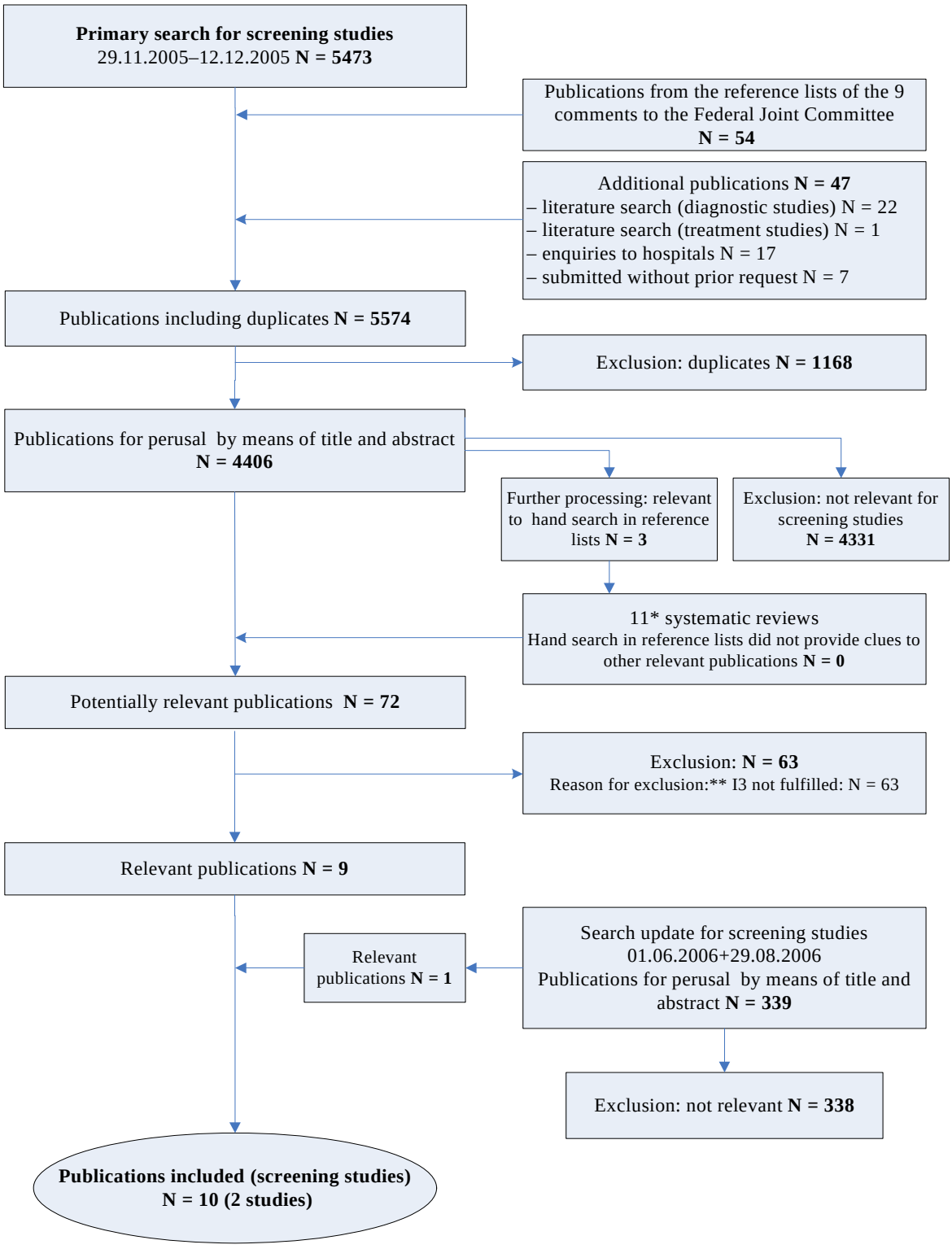

Figure 1: Results of the literature search and literature screening (screening studies)

* Eight systematic reviews were identified by a hand search.
** According to Table 1: Inclusion and exclusion criteria – Screening studies.

5.1.1.2 Results of the search for additional published and unpublished studies (screening studies)

Results of written enquiries to manufacturers of screening instruments

A total of 13 enquiries were sent to manufacturers of screening instruments. None of these resulted in clues to additional studies not found in the literature search or to unpublished studies.

Results of enquiries to hospitals

On 16.01.2006, a total of 43 websites of departments for otolaryngology or paediatric audiology were searched with the aim of finding additional model projects on universal newborn hearing screening or of directly identifying potentially relevant publications. Sections such as “Research”, “Articles” or “Publications” were screened. As a result of the Internet search, a total of 13 institutions were identified that run model projects on neonatal hearing screening. The final report from the Hanover model project [48] was published while the present report was being written, so that we wrote to 12 of the 13 institutions. This enquiry gave rise to a total of 17 references, including publications on German newborn hearing screening programmes (12 references) and general publications on newborn hearing screening (5 references). None of the model projects fulfilled the inclusion criteria of the present report with respect to an unselected population of newborns, the inclusion of an adequate control group and/or investigation of patient-relevant therapy goals, so that none was incorporated into the actual evaluation. As an example, of the 12 references on newborn hearing screening, model projects from 6 regions were chosen, which are presented in detail in Section 5.1.5 (Hamburg [55,56], Hanover [48], Hesse [57–60], Mecklenburg-Western Pomerania [61], Upper Palatinate [62–64] and Saarland [65,66]). The selection criterion was that the project publications had to include relevant information on the feasibility and acceptance of universal newborn hearing screening programmes. We also note here that further regions in Germany are conducting such programmes (Berlin [67], other parts of Hamburg [68], Marburg [69–71], Schleswig-Holstein [72–74] and Würzburg [75,76]).

Of the 6 reports on model projects, 4 were specifically prepared for the present report.[13] References containing additional information could be allocated to the following projects: Hamburg and Hesse (one [56] and 3 references [58–60] obtained from the submission of comments on the preliminary report), Upper Palatinate (2 references [63,64] obtained by the hand search), and Saarland (one reference [65] obtained by the systematic literature search). Section 5.1.5 includes a description of the 6 model projects from Hamburg, Hanover, Hesse, Mecklenburg-Western Pomerania, Upper Palatinate, and Saarland, with the objective of

[13] We would like to thank all those responsible for the model projects for their collaboration.

reaching conclusions about the acceptance and feasibility of universal newborn hearing screening in Germany.

Results of enquiries to authors

There were no enquiries to authors related to the questions on screening.

Results of other enquiries and searches

On 23.09.2005, the German Central Registry for Hearing Impairment in Children responded to an enquiry by IQWiG regarding the provision of current data on the incidence and prevalence of hearing impairment in children and stated that this would be possible in principle, but would require a commission. Two further enquires by IQWiG on 18.10.2005 and 20.12.2005 did not lead to any results.

The search on the website http://www.otoemissions.org, which includes current information on newborn hearing screening, did not lead to the retrieval of further relevant studies.

5.1.1.3 Further results (screening studies)

Eight publications were sent to IQWiG spontaneously: 7 during the preparation of the preliminary report and one after publication of the preliminary report (outside the submission of comments). None of these references fulfilled the inclusion criteria for screening studies of the present report. One reference referred to the report on the newborn hearing screening programme in Upper Palatinate [62], which was considered in the description of the German model projects on newborn hearing screening.

5.1.1.4 Information from the written hearing (screening studies)

No studies were named in the comments on the preliminary report that fulfilled the inclusion and exclusion criteria for screening studies of the underlying report plan of this report and had not already been considered in the preliminary report. A list of the references named in the comments is provided in Appendix G.

5.1.2 Resulting study pool (screening studies)

The various steps in the search resulted in the identification of a total of 2 screening studies, reported in 10 publications (see Table 4).

Table 4: Screening studies included in the evaluation

Study	Full publications	Reference
Kennedy 2006	Kennedy CR et al. N Engl J Med 2006; 354(20): 2131-2141.	[5]
	Kennedy C et al. Research Letter. Lancet 2005; 366(9486): 660-662.	[77]
	Mutton P et al. Comment. Lancet 2005; 366: 612-613.	[78]
	Kennedy C et al. Lancet 2000; 356(9245): 1903-1904.	[79]
	Kennedy CR (Wessex Universal Neonatal Hearing Screening Trial Group). Acta Paediatr Suppl 1999; 88(432): 73-75.	[80]
	Watkin PM et al. Arch Dis Child 1999; 81(5): 380-389.	[81]
	Watkin PM et al. Br J Audiol 1998; 32(1): 27-37.	[82]
	Wessex Universal Neonatal Hearing Screening Trial Group. Lancet 1998; 352(9145): 1957-1964.	[83]
Yoshinaga-Itano 2001	Yoshinaga-Itano C et al. Semin Neonatol 2001; 6(6): 521–529.	[41]
	Yoshinaga-Itano C et al. J Perinatol 2000; 20: S132–S137.	[40]

An alphabetical list of the references included can also be found in Section 8. There is an overview in Appendix B of the references that were viewed in full text and then excluded, with a reason for exclusion.

5.1.3 Characteristics of the screening studies included in the evaluation

The screening studies included are described below. Tables 5-7 at the end of this section portray the main aspects of the study design, study population, and the groups compared.

5.1.3.1 Study design and study population (screening studies)

Yoshinaga-Itano 2001 is a study related to a model project on neonatal hearing screening in the US state of Colorado (Colorado Newborn Hearing Screening Program). This was initially planned to run from 1992 to 1996, but has evidently since been continued. Since 1997, 26 of the 36 obstetric clinics in this state have been participating in this programme. Children with hearing impairment born in hospitals with screening were compared with those born in hospitals without screening.

The study population in Kennedy 2006 consisted of two parts: The first part consisted of the children in the Wessex study born between 1993 and 1996, in which screening periods

(universal newborn hearing screening) in the 4 participating hospitals alternated with periods without this screening. The second part consisted of children born in the Greater London region between 1992 and 1997, from 2 districts with and 2 districts without a universal newborn hearing screening programme (Watkin 1999). During this period, hearing screening was performed in Great Britain in children aged 7-8 months using visually conditioned distraction audiometry ("Health Visitor Distraction Test"). This approach was continued in both study regions.

Because of the heterogeneous composition of the groups to be compared, Yoshinaga-Itano 2001 used a matched-pair design. In this approach, a screened child diagnosed as suffering from a hearing impairment was paired with an unscreened child also diagnosed as suffering from a hearing impairment, where the 2 children were comparable with respect to measurable confounding factors. The pairs were assigned on the basis of (a) age (at the time of measurement of outcome parameters), (b) cognitive development (development quotient) and (c) severity of the hearing impairment (in this order of priorities). In Kennedy 2006, the confounding factors considered in the evaluation were non-verbal development quotient, level of education of the mother, and severity of the hearing impairment (see Table 8).

Language development in children diagnosed as suffering from a hearing impairment was assessed in both studies. Kennedy 2006 also performed an additional study on 2 random samples of the first subpopulation (Wessex study), consisting of 100 screen-positive and 100 screen-negative children without hearing impairment, in which the mothers were asked in writing about their anxiety and negative consequences for their attitude to the child. In addition, 288 mothers from the second subpopulation (Greater London) were questioned shortly after the first screening stage; 57 of these mothers (whose children had a definitively false positive screening result) were questioned at a later stage. Finally, Kennedy 2006 provided a cursory report of the development of the children's hearing ability. Outcome parameters such as quality of life or psychosocial development were not considered in the studies.

In Yoshinaga-Itano 2001, a total of 50 children with an average age of 2.5 years were initially included. Kennedy 2006 included 120 children with an average age of 8 years. Only Kennedy 2006 included specific information on the type of treatment. In this study, on average 2 months after admission into a comprehensive treatment programme, children were provided with a hearing aid or a cochlear implant,

As far as possible, Kennedy 2006 explicitly excluded children with acquired hearing impairment. However, this point was unclear in Yoshinaga-Itano 2001. The average age of the children when the outcome parameters were measured was 3 years (Yoshinaga-Itano 2001) and 8 years (Kennedy 2006).

5.1.3.2 Study and publication quality (screening studies)

Table 8 provides an overview of selected criteria and the evaluation of the study and publication quality. Both of the studies included in the evaluation exhibited deficiencies, which are discussed in more detail below.

In Kennedy 2006, 168 children with bilateral hearing impairment were originally identified; 120 of these children were included in the study. Frequent reasons for exclusion were lack of parental consent for participation (15) and the generally low response rate to the enquiry (25). Participating and non-participating children were comparable with respect to age, gender distribution, and degree of hearing impairment. It is nevertheless unclear why results were only reported for 87-101 of the 120 children involved – depending on the test procedure. It is also not clear whether each child was in fact tested with each procedure and whether data were retrospectively excluded from the analysis. Considerations about sample size planning and power are a positive aspect of this study, even though the assumed sample size (154) could not eventually be achieved. However, a priori sample size planning was not performed.

In Yoshinaga-Itano 2001, it was not reported how the 50 children were selected for this study. For example, there is no information on the total number of screened or unscreened children, or on how many of these children were diagnosed as suffering from a hearing impairment. There was only a report on an additional group of children (with hearing impairment) who had “probably” been screened (29) or who had not been screened (52). Here too, it is unclear why not all children could be analysed in some test procedures.

In Kennedy 2006, language development was evaluated with the help of standardised test procedures by a researcher who was blinded with respect to group allocation (neonatal hearing screening or no neonatal hearing screening). At the same time, the parents (mostly the mother) were asked about the communicative abilities of the children by a researcher who was also blinded, also using standardised test procedures. In Yoshinaga-Itano 2001 on the other hand, language development was only based on questions to the parents with the help of standardised measuring instruments. It is unclear whether or to what extent this questioning was blinded. In addition, both studies included objective investigations based on video film and tape recordings. These results have not (yet) been reported for Kennedy 2006. In Yoshinaga-Itano 2001, the corresponding analyses (on the number of different vowel and consonant forms) were performed automatically.

The biometric quality of both studies must ultimately be assessed as showing major deficiencies. In Kennedy 2006, this applies particularly to the large proportion (> 10%) of children who were not analysed and in Yoshinaga-Itano 2001 to the unclear selection of the children included.

Table 5: Study characteristics (screening studies)

Study	Study design	Comparison	Number of births	Number of children with abnormal results	Country/ Setting	Main outcome criteria
Kennedy 2006	Subpopulation I: non-randomised intervention study Subpopulation II: cohort study multicentre (8 districts)[a]	Two study arms: alternating periods with/without UNHS Two groups: hospitals with/without UNHS	UNHS: 68 714 without UNHS: 88 019	168 children[b] UNHS: 77 children without UNHS: 91 children	UK/unclear	- Language development and communicative abilities - Mother's anxieties and attitude to child [c] - Development of hearing ability [d]
Yoshinaga-Itano 2001	Cohort study multicentre (36 obstetric clinics)[e]	2 groups: hospitals with/without UNHS	No information	No information	USA CNHSP/non-specialised general hospitals	- Language development, communicative abilities and spontaneous speech

CNHSP: Colorado Newborn Hearing Screening Project. UK: United Kingdom. UNHS: universal newborn hearing screening. USA: United States of America.

a: No information on number of centres (hospitals).
b: 120 of these children were included in the study. Reasons for non-participation included lack of parental consent and a generally low response rate.
c: With 2 random samples from subpopulation I of 100 screen-positive and 100 screen-negative children without hearing impairment, with written questioning of the mother [80], also 288 mothers from subpopulation II shortly after the first screening stage and later 57 mothers whose children had definitively false positive results [81].
d: Only for subpopulation I.
e: 26 of these participated in CNHSP. It is unclear to what extent all remaining clinics served as the control group.

Table 6: Basic data (screening studies)

Study	Number of children primarily included in the study	Threshold value (hearing loss in dB)[a]	Case definition (hearing loss in dB)[b]	Age of children at diagnosis[c]	Age of children at start of treatment (in months)	Age of children when outcome parameters recorded [d]	Proportion of children with RF (%)
Kennedy 2006	UNHS: 61 children without UNHS: 59 children	≥ 40 dB	Bilateral hearing impairment, of at least moderate severity (≥ 40)	UNHS ≤ 9 months: 41 (67%) > 9 months: 20 (33%) without UNHS ≤ 9 months: 16 (27%) > 9 months: 43 (73%)	Admission to an intervention programme: 13 (8-23)[e] Provision of a hearing aid or cochlear implant: 15 (10-40)[e]	7.9 years (5.4-11.7)	UNHS: 65%[f] without UNHS: 43%[f]
Yoshinaga-Itano 2001	UNHS: 25 children without UNHS: 25 children	≥ 26 dB[g]	Bilateral hearing impairment, degree of hearing loss (dB) unclear	UNHS < 3 months: 75% < 6 months: 84% > 6 months: 16% without UNHS < 6 months: 8% > 6 months: 92%	No information	UNHS: 29.9 months (13.2) without UNHS: 30.5 months (13.4)	16% with additional disability

dB: decibel. RF: risk factor(s). UNHS: universal newborn hearing screening.

a: Degree of hearing impairment in decibels from which the screening finding is rated as abnormal.
b: Criterion for the diagnosis of hearing impairment after clarification.
c: Corresponds to the age at clarification of a positive screening finding.
d: Mean (range).
e: Median (range); no information for separate groups.
f: Data for subpopulation I (Wessex study) [83]. Proportion of children with RF in all screened neonates (Wessex study): 8%.
g: mild: 26 – 40 dB, moderate: 41 – 55 dB, moderate to severe: 56 – 70, severe: 71 – 90 dB, deaf: > 90 dB.

Table 7: Description of the intervention (screening studies)

Study	Procedure		Type of treatment	Main inclusion criteria
Kennedy 2006	UNHS Subpopulation I: Primary screening: S-TEOAE Rescreening: A-ABR[(a)] Diagnostic clarification after 6 – 12 weeks Both subpopulations: HVDT at age of 7 – 8 months	UNHS Subpopulation II: Primary screening: S-TEOAE Rescreening: S-TEOAE[(a)] Diagnostic clarification: D-ABR and other medical investigations	Weekly advice provided at home by a trained expert in paediatric audiology; provision of a hearing aid or cochlear implant	Birth cohorts, different for the 2 study arms Born 1993-1996 (subpopulation I) or 1992-1997 (subpopulation II)
	Without UNHS HVDT at age of 7 – 8 months			None
Yoshinaga-Itano 2001	No information		No information	Unclear; For the UNHS group, in principle neonates born during the CNHSP

A-ABR: automated auditory brain stem response. CNHSP: Colorado Newborn Hearing Screening Program. HVDT: Health Visitor Distraction Test (distraction audiometry). S-TEOAE: transient evoked otoacoustic emissions measured with screening instruments. UNHS: universal newborn hearing screening programme.

a: If findings were abnormal.

Table 8: Study and publication quality (screening studies)

Study	Sample size planning	Blinded recording of outcome parameters	Comparability of groups	Consideration of confounding factors	Transparency of patient flow	Biometric quality
Kennedy 2006	Yes[(a)]	Yes	Provision of a cochlear implant: UNHS:[(a)] 5 children without UNHS: 11 children (yes)[(b)] The groups were comparable with respect to the degree of hearing impairment.	Nonverbal intelligence, degree of hearing impairment, mother's level of education	120 children were enrolled in the study; results were reported for 87-101 children, depending on test procedure and group; no reason provided for the lack of consideration of children in the analysis.	Major deficiencies
Yoshinaga-Itano 2001	No	Unclear[(c)]	Yes	Age at recording of outcome parameters, cognitive development, degree of hearing impairment	The selection process up to inclusion of the 25 matched pairs is not documented.[(d)]	Major deficiencies

UNHS: universal newborn hearing screening

a: No planning a priori. However, a power of 80% was calculated on the basis of a realistic sample size and effect strength (0.5 standard deviations).

b: No more precise information. It was only reported that the basic characteristics of the children (including the degree of hearing impairment) were comparable.

c: No information on the blinding of the questioning of parents and the evaluators of the objective tape recordings and video films. However, there was automatic evaluation of the number of different vowel and consonant forms by computer.

d: There was only a report of an additional group of children (with hearing impairment) who had "probably" been screened (29) or who had not been screened (52).

5.1.4 Results on therapy goals (screening studies)

Only 2 cohort studies could be identified that performed a comparative investigation of the benefit of universal newborn hearing screening with respect to the patient-relevant outcomes predefined for this report (including one study with a subpopulation in the sense of a non-randomised intervention study). None of the 6 model project reports on neonatal hearing screening in Germany (see Section 5.1.5) contained (comparative) information on these outcomes.

The included studies contained results on language development, general communicative ability, and spontaneous speech. Kennedy 2006 also contained very limited data on the development of hearing ability, the mother's anxiety, and the effects on the mother-child relationship. No data were reported on other relevant outcome parameters, such as general and social development, quality of life, or emotional or educational impairment (such as school failure).

5.1.4.1 Health-related quality of life

As already mentioned, the studies reported no data on the outcome parameter "health-related quality of life".

5.1.4.2 Hearing ability

Kennedy 2006 mentions in a cursory manner that in the subpopulation of the Wessex study, it must be assumed that there was a further deterioration in hearing during childhood in about 23% (15 of 66) of those children with hearing impairment identified when they were infants. This also included children with false negative screening tests. This proportion in the group with neonatal screening was much lower than that with later screening (13% versus 31%, $p = 0.141$, exact Fisher test, our calculation). However, no more exact information is available. This proportion is said to have been lower in subpopulation II (Greater London).

5.1.4.3 Language development

The results on language development were reported in different manners in the 2 studies: (a) Mean test values were compared for the children with hearing impairment in the screened and unscreened groups, (b) the difference was determined between cognitive or non-verbal development and language development as an indication of a deficiency in language development and (c) the percentage of children in the normal range was given. In both studies, the raw test values were converted into standardised values, allowing a direct assessment of the extent to which the language development of the children lay within the normal range as well as an assessment of the magnitude of the advantages or delays in development.

For the sake of clarity, these results (insofar as reported) are classified by these modes of evaluation. Tables 9, 10, and 11 at the end of this section contain comparisons of these aspects where this seemed reasonable.

1. Receptive language development

Both studies report statistically significant differences in receptive language development in favour of universal newborn hearing screening. However, in the study by Kennedy, the statistical significance only applied to the analysis adjusted for the degree of hearing impairment, the mother's level of education, and the cognitive development. The group difference in Kennedy 2006 corresponded to about a third of a standard deviation ($p = 0.04$), and in Yoshinaga-Itano 2001 to about 0.75 standard deviations ($p < 0.001$). On average, the UNHS children in Kennedy 2006 were still about 2 standard deviations under the normal values. In contrast, in Yoshinaga-Itano 2001 the children in the screened group achieved receptive language development quotients which were in the normal range, whereas the mean values for the unscreened group were under average.

Moreover, the receptive language development in children in the UNHS group in Kennedy 2006 was more consistent with their cognitive development, indicating fewer deficits in language development than in the group with late screening. The difference corresponded to about half a standard deviation, but was only statistically significant for the adjusted evaluation ($p = 0.03$).

2. Expressive language development

Yoshinaga-Itano 2001 reported that unscreened children exhibited a significantly lower expressive vocabulary than the screened group. The difference in the test value corresponded to one standard deviation ($p < 0.001$). In Kennedy 2006, there were no statistically significant differences between the groups with respect to expressive language development (vocabulary and sentence construction), although the values indicated a favourable trend for the children in the UNHS group (of the dimension of about a quarter of a standard deviation; $p = 0.25$ for the adjusted evaluation). This also applies to the difference between language development and cognitive development – which tended to be lower for the UNHS group, indicating that the children were exploiting their individual possibilities for language development better ($p = 0.18$ for the adjusted evaluation).

3. General language development

As data on general language development were only available for one study, this is not presented in a table, but only in narrative form.

Yoshinaga-Itano 2001 reported how many children exhibited delayed language development if expressive and receptive language development were assessed together. Then 17 of the 25

children in the unscreened group (68%) exhibited delayed language development, in comparison with 6 of 25 children (24%) in the screened group. Conversely, a higher proportion of screened children exhibited normal development (56% versus 24%, $p = 0.008$). Moreover, the general language development of the screened children was more in accordance with their cognitive development than was the case with the unscreened children. For this purpose, the results of the scales on situation-comprehension and self-help (cognition) were compared with results of the scales for receptive and expressive language development in the same test procedure, the Minnesota Child Development Inventory. The difference in the discrepancy between language and cognition corresponded to 1.3 standard deviations ($p < 0.001$).

4. Communicative abilities and spontaneous speech

In addition to the standardised evaluation of expressive vocabulary, Kennedy 2006 included an evaluation of communicative abilities. No significant differences between the groups were found ($p = 0.68$ for the adjusted evaluation).

In Yoshinaga-Itano 2001, an assessment of tape and video recordings was undertaken. The number of different vowel and consonant forms used in spontaneous speech was recorded, together with the number of comprehensible words. Overall speech intelligibility was also assessed. To allow for differences in the mode of communication, both oral and sign language were always evaluated. The screened children gave statistically better values for the size of vocabulary (number of consonants; $p < 0.01$) and speech intelligibility (number of intelligible words; $p = 0.004$).

Taken together, the study results indicate a benefit for universal newborn hearing screening for the language development of children with hearing impairment at average ages of 3 or 8 years. The chances of normal language development appear to be higher for screened children. This effect is associated with an earlier time point for diagnosis. In Yoshinaga-Itano 2001, 84% of the children identified by universal newborn hearing screening were diagnosed by an age of 6 months, whereas this only applied to 16% of the children in the unscreened group. Kennedy 2006 also reported that a larger proportion of children in the universal newborn hearing screening group were diagnosed by 9 months (67% versus 27%).

The methodologically superior study of Kennedy 2006 – albeit with major deficiencies – arrived at much less optimistic results. However, it must be borne in mind that, in contrast to Yoshinaga-Itano 2001, the control group also received screening, but at a much later age (7-8 months).

5.1.4.4 Psychosocial development

As already mentioned, the studies reported no data on the outcome parameter “psychosocial development”.

5.1.4.5 Emotional development

As already mentioned, the studies reported no data on the outcome parameter “emotional development”.

5.1.4.6 Cognitive and educational development

As already mentioned, the studies reported no data on the outcome parameter “cognitive and educational development”.

5.1.4.7 Adverse effects of screening

Kennedy 2006 includes the results of 2 investigations in both subpopulations. These results will also be presented in the narrative form.

The Wessex study found no differences between the mothers of screen-positive and screen-negative children (with a low risk of hearing impairment) with respect to attitude to the child or anxiety about the child on the corresponding scales (Attitude towards the Baby Scale and Spielberger State-Trait Anxiety Inventory). Moreover, the results were very similar to those in a population-based sample of women of child-bearing age. However, it must be borne in mind that it is unclear which group these children came from (UNHS or late screening; a comparison between these 2 groups would be particularly interesting) and that the questionnaires were sent to the women only 2 to 12 months after the screening. The response rate was 75%.

For the second subpopulation (Greater London), the results are available for a questioning of 288 mothers directly after the first screening stage. A total of 17% of the children of the mothers questioned had positive screening findings. The mothers were asked about their worries before and directly after the test. Before the test, 23% were mildly or moderately worried and 5% were very worried. The corresponding figures directly after the test were 69% and 1%, respectively. No comparison was made here between mothers of screen-positive and screen-negative children. In addition, the mothers of 95 children with positive or doubtful screening results were invited to take part in a retest after 4-6 weeks, and were asked to answer further questions (during this retest). However, only 57 mothers (60%) participated. This questioning included the Spielberger State-Trait Anxiety Inventory (STAI). Only 39% of the mothers were still mildly or moderately worried and 4% very worried. There were no significant differences in the STAI compared with a control group of 61 mothers (of 102 mothers approached) 6 weeks after giving birth in the department of obstetrics in a

neighbouring hospital. It remains unclear how the mothers were selected for all of these questionings.

An interpretation of the results presented on the outcome parameter “adverse effects of screening” is hardly possible, as the mothers who were given the questionnaire were selected according to unclear criteria. Moreover, the response rate was low to very low, so that they represented highly selected groups. It is possible that the readiness to respond was correlated with the mothers’ attitude to screening or with their anxieties and/or worries. In addition, in the Wessex subpopulation, a comparison between the group with universal newborn hearing screening and the group with late screening would have been relevant. Moreover, the time of questioning (up to 12 months after screening) does not appear to be adequate.

Table 9: Results on receptive language development (screening studies)

	Study	Number of children	Test procedure (scales)	UNHS[a]	Without UNHS[a]	Results
Comparison of the group means	Kennedy 2006	101 children	TROG, BPVS	-1.89 [b] (1.65)	-2.32[b] (1.61)	The adjusted[c] difference of the group means was 0.56 (95% CI: 0.03 – 1.08; p = 0.04).
	Yoshinaga-Itano 2001	50 children	MCDI (conceptual language comprehension)	81.5[d] (18.5)[e]	66.8[d] (20)[e]	The difference of the group means was 14.7 (p < 0.001).
Difference cognition – language	Kennedy 2006	101 children	Cognition: RPM language: TROG, BPVS	-0.94[b] (1.45)	-1.67[b] (1.29)	The adjusted[f] difference of the mean discrepancy between cognitive and language development was 0.60 (95% CI: 0.07 – 1.13; p = 0.03).
	Yoshinaga-Itano 2001	No information				

BPVS: British Picture Vocabulary Scale. CI: confidence interval. MCDI: Minnesota Child Development Inventory. RPM: Raven's Progressive Matrices. TROG: Test for Reception of Grammar. UNHS: universal newborn hearing screening.

a: Means with standard deviations (in brackets), if not otherwise reported.
b: For both test procedures, aggregated mean age-adjusted z-standardised value; negative values indicate deficits in comparison with children with normal hearing.
c: Adjusted for the degree of hearing impairment, mother's level of education, non-verbal intelligence.
d: Development quotient (test score/chronological age x 100) for receptive language development.
e: Our own calculation from the standard error.
f: Adjusted for degree of hearing impairment, mother's level of education.

Table 10: Results on expressive language development (screening studies)

	Study	Number of children	Test procedure (scales)	UNHS[a]	Without UNHS[a]	Results
Comparison of the group means	Kennedy 2006	87 children	RBST (sentence information, 5 longest sentences)	-0.74[b] (1.23)	-0.99[b] (1.33)	The adjusted[c] difference of the group means was 0.30. (95% CI: -0.22 – 0.81; p = 0.25).
	Yoshinaga-Itano 2001	50 children	MCDI (expressive language development)	82.9[d] (18.5)[e]	62.1[d] (21.5)[e]	The difference between the group means was 20.8 (p < 0.001).
		38 children	CDI (words/gestures, words/sentences)	No information	No information	There was a significant difference in the development of expressive vocabulary, in favour of the screened group (p < 0.001).
Difference cognition – language	Kennedy 2006	87 children	Cognition: RPM Language: RBST (sentence information, 5 longest sentences)	-0.02[b] (1.34)	-0.44[b] (1.35)	The adjusted[f] difference of the mean discrepancy between cognitive and language development was 0.39 (95% CI: -0.19 – 0.98; p = 0.18).
	Yoshinaga-Itano 2001	No information				

CDI: (McArthur) Communicative Development Inventories. CI: confidence interval. MCDI: Minnesota Child Development Inventory. RBST: Renfrew Bus Story Test.
RPM: Raven's Progressive Matrices. UNHS: universal newborn hearing screening.

a: Means with standard deviations (in brackets), if not otherwise reported.
b: Mean age-adjusted z-standardised value; negative values indicate deficits in comparison with children with normal hearing.
c: Adjusted for the degree of hearing impairment, mother's level of education, non-verbal intelligence.
d: Development quotient (test score/chronological age x 100) for expressive language.
e: Our own calculation from the standard error.
f: Adjusted for degree of hearing impairment, mother's level of education.

Table 11: Results on communicative abilities, spontaneous speech (screening studies)

	Study	Number of children	Test procedures (scales)	UNHS[a]	Without UNHS[a]	Results
Comparison of group mean values	Kennedy 2006	97 children	CCC (speech scale)	-1.20[b] (1.50)	-1.30[b] (1.47)	The adjusted[c] difference of the group mean values was 0.12 (95% CI: -0.46 – 0.71; p = 0.68).
	Yoshinaga-Itano 2001	48 children	Number of different vowel forms	10.8 (6.24)[d]	9.7 (4.16)[d]	The difference in the mean number of different vowel forms was 1.1 (p = 0.22).
		48 children	Number of different consonant forms	13.3 (10.39)[d]	9.4 (8.31)[d]	The difference in the mean number of different consonant forms was 3.9 (p < 0.01).
		44 children	Number of intelligible words	No information	No information	There was a significant difference in speech intelligibility in favour of the screened group (p = 0.004).

CCC: Children's Communication Checklist. UNHS: universal newborn hearing screening.

a: Means with standard deviations (in brackets), if not otherwise reported.
b: Mean age-adjusted z-standardised value; negative values indicate deficits in comparison with children with normal hearing.
c: Adjusted for the degree of hearing impairment, mother's level of education, non-verbal intelligence.
d: Our own calculation from the standard error.

5.1.5 Model projects in Germany on universal newborn hearing screening

This section describes results from selected model projects in Germany on neonatal hearing screening (see also Section 5.1.1.2 for the selection criteria). These projects were conducted in 6 federal states or regions: Hamburg [55,56], Hanover [48], Hesse [57-60], Mecklenburg-Western Pomerania [61], Upper Palatinate [62-64], and Saarland [65,66].

None of these projects fulfilled the inclusion criteria for screening studies in the present report, as there was either no control group without screening (Hamburg, Mecklenburg-Western Pomerania, Upper Palatinate, Saarland), or no patient-relevant outcome parameters were investigated corresponding to those defined in the report plan for the current report (Hanover), or there was no direct comparison between the groups with and without screening for the patient-relevant outcome parameters (Hesse). The results of the studies were therefore not incorporated into the actual evaluation, but only serve to describe the implementation of UNHS programmes in Germany and essential quality characteristics.

The reports provided on the model projects were very heterogeneous with respect to the manner and level of detail of the reporting. Essential parameters were not reported in a consistent manner, so that only a very restrictive summary of the results can be presented.

Data on the following points will be reported below, insofar as these could be gathered from the model project reports:

- The implementation of the programmes,
- The proportion of neonates participating in the screening (coverage rate),
- The proportion of parents who rejected screening (rejection rate),
- The proportion of the neonates classified as abnormal in screening (referral rate),
- The proportion of neonates classified as abnormal in screening, but not followed up (lost to follow-up),
- The proportion of neonates with hearing impairment identified by screening of this sort,
- The proportion of neonates then treated,
- The age at final confirmation of the diagnosis and the initiation of treatment.

Table 12 contains detailed descriptions of the individual model projects.

Implementation

In the primary screening (stage 1), if the findings were abnormal, the first screening test was followed by a retest. If the findings were still abnormal, children were re-screened (stage 2). In children who still had abnormal results after this stage, a final diagnostic clarification was performed (stage 3). In one model project (Hesse), the second stage was not routinely planned; further details in this regard were not presented. There were only minor differences between the projects with respect to the time point of the primary screening of the neonates in the departments of obstetrics; this was 2 to 3 days after birth. The retest was to take place as soon as possible after the first test.

TEOAE screening instruments were used for the first screening test in all projects; in 3 projects (Hamburg, Hesse, Upper Palatinate), ABR instruments were used for the retest or rescreening. At-risk children (or children screened in paediatric departments or neonatal institutions) were – insofar as reported – to be investigated immediately with A-ABR in these 3 projects. In the Hanover model project, it was intended to give at-risk children an A-ABR measurement. For outpatient screening tests, the A-ABR measurement was carried out for some children, depending on its availability.

In projects in which a rescreening was routinely planned, this was to take place in the Department of Obstetrics in one project (Hamburg). In the other projects, this was to be performed by office-based ENT physicians (Hanover, Mecklenburg-Western Pomerania) or either ENT physicians or paediatricians (Upper Palatinate, Saarland). The (planned) time point for the rescreening varied greatly in the various projects, ranging from Day 14 (Hamburg) to the time of the regular paediatric medical examinations U3 or U4 (Saarland). In one case (Hamburg), the investigation method applied was A-ABR, in all other cases it was TEOAE or A-ABR (depending, among other things, on the availability of the instruments or the children's risk status).

In 2 of the 6 projects, the definition of an abnormal finding in the first stage was unclear. In the other 4 projects, an abnormal finding was evidently defined as a monolateral hearing impairment. An abnormality in the second stage was defined in 3 projects as monolateral hearing impairment, in one project as bilateral hearing impairment (or also monolateral for at-risk children), and in 2 cases this remained unclear. The need for therapy was defined in 5 projects as the existence of bilateral hearing impairment, and in one project (Hesse) as the existence of monolateral hearing impairment. Of the first-mentioned 5 projects, 2 specified a hearing threshold ≥ 40 dB, one specified a hearing threshold $\underline{\geq}$41 dB, and 2 specified "severe" hearing impairment. In most cases, the information provided on diagnostic confirmation (gold standard) was rather vague. In 5 cases, thorough paediatric-audiological diagnosis was required, although this did not always have to be performed by a specialist in paediatric audiology.

Coverage rate

A distinction must be made between whether the coverage rate applies to all births in a region within the period of observation or only those reported in the hospitals participating in the programme. This also affects one aspect of the implementation, namely whether children not born in hospital (home births or birth houses) should be included in the screening. In 2 projects, it was not clear that this was the case (Hesse, Mecklenburg-Western Pomerania). In the remaining cases, this was either explicitly stated or could be inferred from the reports.

The coverage rates for the hospitals participating in the project were as follows: 93.2% (Hamburg), 95.0% (Hesse) and 98.6% (Mecklenburg-Western Pomerania). The coverage rates for all the children born in the region were, in contrast: 86.6% (Hamburg), 90.3% (Hanover), 94.8% (Mecklenburg-Western Pomerania), 94.6% (Saarland), and 95.3% (Upper Palatinate).

Rejection rate

Information on this point was available for 4 model projects (Hanover, Hamburg, Hesse, Upper Palatinate). The proportion of children whose parents rejected screening lay between 0.1% (Hamburg, Upper Palatinate) and 1.3% (Hanover).

Referral rate

With the referral rate, it was not always unambiguously clear which time point it referred to (primary screening or rescreening). The referral rate in primary screening allows an estimate of the proportion of parents who were initially anxious because of the abnormal finding, as well as the effort needed for rescreening. The referral rate for rescreening, if performed, is of relevance for estimation of the effort required for final diagnostic clarification. For interpretation of the referral rate, it is also necessary to know if monolateral or only bilateral abnormal findings led to further diagnosis (rescreening or diagnostic clarification). As mentioned, this was often unclear. It is also important to know whether the screening was monolateral or bilateral. The initial screening in Saarland in 10 of the 15 participating hospitals was only monolateral; in Mecklenburg-Western Pomerania, it can be inferred indirectly from the description of the screening that some of the children were only screened monolaterally. These are reservations that must be borne in mind when the data below are considered.

In the Hanover model project (TEOAE), 8.1% of the children exhibited a monolateral abnormal finding in primary screening; 3.2% of children exhibited bilateral abnormalities. The ENT specialists involved in primary screening detected particularly high abnormality rates of 20.0% (monolateral) and 10.4% (bilateral). Upper Palatinate (TEOAE-/A-ABR sequence) reported the lowest abnormal rates of 1.6% (monolateral) and 0.4% (bilateral). In

Saarland (TEOAE), the referral rate of primary screening for monolateral abnormal findings was 6.9%. The other projects did not distinguish between mono- and bilateral abnormal rates. Primary screening referral rates for an at least monolateral abnormal test result were 4.0% in Hamburg (S-TEOAE or A-ABR for non-hospital births) and 3.0% in Hesse (TEOAE-/A-ABR sequence). In Mecklenburg-Western Pomerania, the definition of an abnormal primary screening result remained unclear. For bilaterally screened children (TEOAE), the referral rate was reported to be 4.2%.

For the Hanover model project, it was reported that of the children who were rescreened (by ENT physicians), 31.6% still exhibited a monolateral abnormal finding, and 18.6% exhibited a bilateral abnormal finding. In contrast, in Saarland the referral rate of the rescreening was only 5.4%, although it is unclear whether this refers to monolateral or bilateral abnormalities. No data in this regard can be inferred from the other projects.

Lost to follow-up

"Tracking" is a decisive factor in maximising the follow-up of children identified as abnormal in the screening programme; this includes the identification of children with abnormal findings, but without subsequent clarification, as well as contact with parents in an attempt to persuade them to allow clarification of their children's abnormal findings. In principle, it would also be desirable to split the lost-to-follow-up rate into primary screening and rescreening, to help recognising at which stage problems occur. However, this was mostly not possible with the model project reports provided; for projects where clear information was available (Hamburg), this is presented. For the other projects, the overall lost to follow-up rates of children with abnormal findings are presented below.

For projects where the tracking system was evidently very rudimentary (consisting of a single reminder letter), such as in Hamburg or Mecklenburg-Western Pomerania, high lost-to-follow-up rates were reported. In Hamburg, the lost-to-follow-up rate for children with an abnormal test result in the primary screening was 38.0%. The rate for children with an abnormal test result in the rescreening was 36.0%, which, under consideration of the children not already followed up in the primary screening, leads to a rate of 60.3%. In Mecklenburg-Western Pomerania, the lost-to-follow-up rate was 56.1%. The lost-to-follow-up rate was also very high in the Hanover model project (31.7%); the tracking system for the actual screening was unclear.[14] The lost-to-follow-up rates were markedly lower in the model projects in which the parents were contacted by telephone, with 10.5% (Saarland) and 7.8% (Hesse). Finally, the model project in the Upper Palatinate produced the unusually low lost-to-follow-

[14] However, in the screening period of this model project, a particular effort was made to identify as many children as possible with hearing impairment needing treatment, including contact with the regional centres for paediatric audiology and the Register for Hearing Impairment in Children in Berlin.

up rate of only 3.0%; the tracking system here also included visits from the Health and Youth Office.

Prevalence

The term “prevalence” is not used consistently in neonatal hearing screening. Some authors of the model project reports used the term “incidence” instead. As the objective of neonatal hearing screening can only be to identify congenital hearing impairment, the use of the term “prevalence” seems more appropriate, especially as no report described the incidence in a specific period of time (for example, rate per 1000 per year).

When considering prevalence figures, the case definition must be borne in mind, in particular whether monolateral hearing impairment is included and the handling of (postnatal) acquired hearing impairment (not detectable with neonatal hearing screening) and developmental abnormalities (in which hearing improves postnatally, even without intervention). It should also be noted that the prevalence figures mostly refer to the neonates investigated and not to all neonates in the region.

The Hanover model project has the special feature that the objective was to identify all neonates with a (congenital) hearing impairment in the screening period, as subsequent comparison was planned with a control region (Munich) in which no neonatal hearing screening took place. This objective was not evident in any other model project; in one project, it was explicitly assumed that the sensitivity was 100% (Hesse). In another project (Upper Palatinate), a child with a hearing impairment was identified outside the screening programme, more or less by chance, due to the initiative of the parents.

With the inclusion of monolateral hearing impairment, the following prevalence rates were reported: 0.5‰ (Saarland[15]), 0.8‰ (Hanover), 0.9‰ (Upper Palatinate), 1.4‰ (Mecklenburg-Western Pomerania), 1.6‰ (Hamburg), and 2.7‰ (Hesse). If only bilateral and congenital hearing impairment were considered,[16] the prevalence rates were reduced to 0.9‰, (Mecklenburg-Western Pomerania), 1.2‰ (Hamburg), and 2.1‰ (Hesse). The variability of these estimates is further increased if it is considered that 3 of 18 children were identified outside the screening programme in Hanover, and 1 of 15 in Upper Palatinate. Two of the 3 children not identified by screening in Hanover were non-participants in the model project. The third child initially showed normal screening findings and exhibited a 35delG-mutation in the *gjb2* gene, which codes for connexin 26; this was also the case for the child in Upper Palatinate; therefore these were both children with false negative screening results. Children

[15] One child with a hearing impairment who moved into the region after primary screening (and so did not belong to the birth cohort) was not considered here.
[16] In the Mecklenburg-Western Pomerania model project, 5 children were treated by inserting eardrum drainage.

with developmental abnormalities were excluded from these estimations, insofar as this could be clearly inferred from the reports.

The proportion of at-risk children with hearing impairment in the total of children with hearing impairment could be calculated for 4 model projects. The figures lay between 43.2% (Hamburg) and 65.0% (Hesse). The proportion of at-risk children in each birth cohort could not be inferred with sufficient accuracy from the model project reports.

Proportion of children treated

The proportion of all children with hearing impairment who were actually treated varied greatly between the model projects. The difficulties in definition must be considered here. In Upper Palatinate and in Saarland, all identified children were treated. However, it should be borne in mind that in Saarland only 2 children were identified during primary screening (a third child exhibited delayed development and was therefore excluded from the prevalence calculations). If the Saarland calculations include a fourth child, who moved into the region after the primary screening (and was therefore not in the birth cohort), the proportion of treated children drops to two thirds, as the parents of this child rejected treatment. In Hamburg, 55 of the overall 88 children with the diagnosis “hearing impairment” were treated. Fourteen of the 33 non-treated children were classified as either not in need of treatment (9 children with monolateral mild hearing impairment) or as not treatable (5 children with monolateral severe hearing impairment). According to the authors, children who did not receive a hearing aid were followed up. In this project, the treatment rate was 62.5% (or 74.3%, if one only considers children who needed treatment or were treatable). The following treatment rates were reported for the other model projects: 94.4% (Hanover), 85.1% (Hesse), and 33.3% (Mecklenburg-Western Pomerania). If monolateral hearing impairment was excluded for Hamburg, Hesse, and Mecklenburg-Western Pomerania, and the children with presumed postnatal acquired hearing impairment and 12 children with unknown clinical course are excluded for Mecklenburg-Western Pomerania, as well as 2 children in Hamburg who did not turn up for further examinations, the treatment rates increase to 87.1% (Hamburg), 97.4% (Hesse), and 54.5% (Mecklenburg-Western Pomerania).

Age at confirmation of the diagnosis and at initiation of treatment

Data on the time of confirmation of the diagnosis and for initiation of treatment were available for 5 and 4 model projects respectively. For the Saarland project, this was unclear; for Mecklenburg-Western Pomerania, no data were reported on the median age at initiation of therapy. The median time for definitive clarification was between 2.7 and 4.7 months. The median age for initiating therapy was 3.4 to 5.5 months. The Hanover model project included a comparison of this region with a control region without screening (Munich), which had been planned in advance. There was a statistically significant reduction in the median age of diagnosis, from 5.4 months in Munich to 2.7 months in Hanover ($p = 0.015$). There was,

however, no statistically significant difference in the time point for the start of treatment ($p = 0.076$), with median values of 9.1 months (Munich) and 5.5 months (Hanover).

Test duration

Four of the 6 model projects provided information on the duration of the test to measure otoacoustic emissions or on the duration of brain stem audiometry.

The mean test duration to measure otoacoustic emissions was reported to be between 6.0 minutes (Saarland) and 13.0 minutes (bilateral, Hesse). However, in Hesse, the test duration for one ear was not much shorter (mean 11.0 minutes). The mean test duration for brain stem audiometry lay between about 14.0 minutes (monolateral) and 18.0 minutes (bilateral, Hesse). The Hesse model project report also reported the time needed for sequential measurement with OAE and ABR. This had the average value of 22.0 minutes for bilateral measurements and 17.0 minutes for monolateral measurements.

The Hanover model project report contained not only information on test duration, but also on additional time needed in connection with primary screening. The mean time needed for an informative discussion before the test and for presenting the result was 5.3 and 3.7 minutes respectively.

5.1.5.1 Summary of the model projects on universal newborn hearing screening in Germany

This overview of model projects on neonatal hearing screening in Germany cannot claim to be complete because when preparing this report, we did not receive responses from all parties who perform or participate in such projects (see Section 5.1.1.2). The reporting of these projects was very heterogeneous and unambiguous identification of essential information was not always possible. For example, a flow diagram would have been helpful, portraying all stages of the screening up to the final diagnostic clarification and initiation of therapeutic measures, including the operationalisation (e.g. the definition of FAIL/PASS criteria in each stage and the criteria for need of treatment) and the number of children included in each stage. This would have improved and clarified the identification and interpretation of important parameters, such as coverage rates (for different time points, too), referral rates, and lost-to-follow-up rates. Some basic conclusions may nevertheless be drawn.

The results from the model projects indicate that by applying universal newborn hearing screening, the time of diagnosis of congenital hearing impairment can be made at an earlier stage. The data also indicate that the structural preconditions for universal newborn hearing screening in Germany are either already present or can be created. Insofar as reported, the proportion of children whose parents rejected participation in screening was low (0.1-1.3%), which indicates that the acceptance of screening is good. The coverage rates were close to

95%, which is the criterion demanded for UNHS [34,84,85], but this only referred to hospital births. At the level of the overall population, the coverage rates were either much lower in some cases, or cannot be inferred from the reports. There are indications that the sequential procedure in primary screening – with initial measurement of OAE, followed, in the event of abnormal findings, by the recording of acoustically evoked potentials (in each case using suitable screening instruments) – leads to lower referral rates than with TEOAE instruments alone. In the projects with this sequential procedure, the referral rate was in the range of the required criterion of 4% [34,84,85] or much lower.

Some of the lost to follow-up rates reported were unacceptably high. This emphasises how extremely important it is to have a well-functioning tracking system. The lost to follow-up rates could be kept very low in projects in which a special effort was made to identify children who had not turned up for further clarification. The information on prevalence of congenital hearing impairment must be seen in the context of some differences and ambiguities in definition and the problem already mentioned of the lost-to-follow-up rates. Nevertheless, the prevalence values lie within the range reported in the literature of 1-2 cases per 1000 births [1,6]. It is also consistent with the literature that the proportion of at-risk children in the children identified with hearing impairment was about 50%.

A wide range of values were given on the rate of children with identified hearing impairment who were then treated. This emphasises once again the problem of unambiguous (case) definition. The median ages at (final) diagnosis and at the start of treatment were 3 and 6 months respectively, as demanded [34,84,85]. This means that some of the children were diagnosed and treated (much) later.

Table 12: Overview of model projects on universal newborn hearing screening

Study	Period of births	Birth setting	Place of recording	Primary screening (Stage I)			
				First screening test		Retest (if findings were abnormal)	
				Method	Time point	Method	Time point
Hamburg	08/02 – 07/05	Inpatient	Obstetrics department	S-TEOAE[a]	Day 2 (median)	A-ABR[b]	Shortly after first measurement
			Neonatology department		Day 7 (median)		
			Paediatrics department		Day 10 (median)		
		Other	Paediatric Audiology departments and other institutions	A-ABR	Planned till day 14, took place on day 47 (median)		Unclear
Hanover	07/00 – 12/02	Inpatient	Obstetrics department	TEOAE	Planned days 2-3, performed on day 3 (mean)	S-TEOAE	Next day
			Paediatrics/neonatal dept.	TEOAE[c]	Day 19 (mean)	S-TEOAE[d]	Unclear
		Other	ENT specialist	TEOAE, partially also A-ABR	Day 39 (mean)	S-TEOAE, sometimes also A-ABR	Unclear
Hesse	01/05 – 12/05	Inpatient	Obstetrics department	S-TEOAE	Day 3 (median)	A-ABR[d]	Shortly after first measurement
			Neonatal dept. (NICU)	A-ABR			Unclear
Meck.-WP	01/03 – 12/05	Inpatient	Obstetrics department	S-TEOAE	Planned from day 2	S-TEOAE	Shortly before discharge
Upper Palatinate	06/03 – 03/05	Inpatient	Obstetrics department	S-TEOAE[e]	In the hospital	A-ABR[f]	In hospital, if possible
			Paediatrics department	A-ABR	In the hospital		Unclear
		Other	Paediatrician/ ENT specialist	S-TEOAE or A-ABR	Planned up to day 42 / U3		Unclear
Saarland	02/02 – 07/02	Inpatient	Obstetrics department	S-TEOAE	Day 3-5	S-TEOAE	In hospital, if possible
		Other	Unclear	S-TEOAE	Unclear	S-TEOAE	Unclear

continued

Table 12 (continued I): Overview of model projects on universal newborn hearing screening

Study	Rescreening (Stage 2) (if findings abnormal)			Diagnostic clarification (Stage 3)	Case definition for			Coverage rate	Referral rate
	Performance	Method	Time point		Rescreening	Clarification	Therapy		Primary screening
Hamburg	Obstetrics department, paediatric audiology unit	A-ABR[g]	Planned to day 14, took place in mean on day 35 [g]	Click/frequency-specific ABR, paediatric audiological diagnosis, subjective hearing test	Monolateral abnormality	Monolateral abnormality needing treatment	Bilateral abnormality ≥ 41 dB	93.2%[h]	4.0%
Hanover	ENT specialists	TEOAE, sometimes + A-ABR	Planned to day 28, took place in mean on day 57	ENT specialists, ENT dept., paed. audiology/ABR, detailed diagnosis in paed. audiology	Monolateral abnormality	Unclear	Bilateral, permanent, ≥ 40 dB	90.3%	8.1%, of these 3.2% bilateral[i]
Hesse	Not regularly, otherwise unclear	TEOAE (or DPOAE; if appropriate, ABR)[j]	Max. 14 days after registration	Click/frequency-specific ABR, paediatric audiological diagnosis	Monolateral abnormality	Monolateral abnormality	Monolateral, permanent	95.0%	3.0%
Meck.-WP	ENT specialists	S-TEOAE	Unclear	ABR in sedation in unit for paediatric audiology	Unclear	Monolateral abnormality	Bilateral, severe	98.6%	4.2%
Upper Palatinate	Paediatricians or ENT specialists	S-TEOAE or A-ABR	Planned to day 42/U3	Unit for paediatric audiology	Monolateral abnormality	Bilateral abnormality[k]	Bilateral, severe	95.3%	1.6%[g]
Saarland	Obstetrics department, paediatrician or ENT specialists	TEOAE[g,l]	U3/U4[g]	Detailed paediatric audiological diagnosis from paediatric audiologist or ENT specialist	Monolateral abnormality[i]	Unclear	Bilateral, ≥ 40 dB	94.6%	6.9%[g,m]

continued

Table 12 (continued II): Overview of model projects on universal newborn hearing screening

Study	Number of cases after clarification	Prevalence (‰)	Proportion of at-risk children (%)	Tracking[m]	LTFU	Rejection rate	Proportion treated	Median age at diagnosis confirm-ation (months)	Median age at start of therapy (months)
Hamburg	88, of these 24 with monolateral HI[o]	1.6	43.2	Reminder letters	Primary screening 38%[n] Rescreening 36%[o]	0.1%	55/88 (62.5%) or 55/74 (74,3%)[p]	3.9 (mean)	For children with bilateral hearing loss > 41 dB: 4.6 (mean: 6.6)
Hanover	18[q]	0.8	44.4	Unclear[r]	31.7%	1.3%	17/18 (94.4%)	2.7	5.5
Hesse	47, of these 10 with monolateral HI[s]	2.7	65.0	Letters, telephone calls as reminder	7.8%	0.6%	40/47[q,r] (85.1%)	3.1	3.5
Meck.-WP	51, of these 12 with monolateral HI[u]	1.4	Unclear	1x in writing (6 weeks)	56.1%	Unclear	17/51 (33.3%)[v]	3.4	Unclear
Upper Palatinate	15[w]	0.9	Unclear	Letters, telephone calls as reminder, house visits by health and youth offices	3.0%[x]	0.1%	15/15 (100%)	4.7	4.7
Saarland	2[y]	0.5	50.0	Letters of reminder, Telephone calls	10.5%[x]	Unclear	2/2 (100%)	Unclear	Unclear

(A)-ABR: (automated) auditory brainstem response. dB: decibel. DZH: Deutsches Zentralregister für kindliche Hörstörungen (German Central Registry for Hearing Impairment in Children). ENT: ear nose throat. HI: hearing impairment. LTFU: lost to follow-up. Meck.-WP.: Mecklenburg-Western Pomerania. NICU: neonatal intensive care unit. (S)-TEOAE: transient evoked otoacoustic emissions (measured with screening instruments). U3/U4: paediatric medical examinations (at ages 4–6 weeks and 3–4 months).

a: At-risk children directly with A-ABR.
b: Only in non-at-risk children.
c: A-ABR planned.
d: Did not take place in 22.5% of cases.
e: At-risk children and children not born in hospital: directly A-ABR.

continued

Table 12 (continued III): Overview of model projects on universal newborn hearing screening

f: Non-at-risk children and children born in hospital.
g: Data refer to children born in hospital; unclear for children not born in hospital.
h: Data refer to children born in hospital; 38.0% for children not born in hospital.
i: Average value, weighted according to size of subgroups; obstetrics clinics: 6.8% (2.3% bilateral), paediatric/neonatal clinics: 8.2 % (3.9 % bilateral), and ENT physicians: 20.0% (10.4% bilateral). For rescreening in all institutions: 31.6 %, thereof 18.6 % bilateral.
j: Family history, ENT examination, tympanogram.
k: For prematurely born children or children treated in intensive care: also in the case of monolateral abnormality.
l: In at-risk children: ABR
m:5.4% for rescreening.
n: There were normally entries into the "Yellow Book".
o: Information related to births in hospital, otherwise unclear.
p: Without children who did not need treatment / were not treatable.
q: Not detected by screening: 3/18; 2 children were not tested, one child with negative screening findings.
r: Tracking for the actual screening unclear; however, special efforts were made to identify, if possible, all children within the period of screening with a hearing impairment needing treatment, including contacting the centres for paediatric audiology based in the region and the DZH (German Central Registry for Hearing Impairment in Children).
s: Two children with delayed development not listed.
t: 37/38 (97.4%) for bilateral HI.
u: Another 12 children with unclear HI; 5 with HI which was presumably non-congenital.
v: 12/34 (35.3%) for bilateral congenital HI (not including presumably non-congenital HI).
w:One child included who was not identified by screening.
x: Information applies to births in hospital, unclear for births outside hospital.
y: Two other diagnosed children not listed (one child with delayed development; one child not a member of the birth cohort).

5.2 Treatment studies

5.2.1 Literature search (treatment studies)

In this section, the results will be presented of the systematic search for treatment studies in bibliographic databases and of enquiries to manufacturers and authors.

5.2.1.1 Results of the literature search (treatment studies)

The systematic literature search for treatment studies was performed in November and December 2005 in a total of 11 databases. A search update was performed in 2 steps: a search was performed in 4 databases at the start of June 2006 and in the remaining 7 databases at the end of August 2006.

For treatment studies, the results of the search for published studies in bibliographic databases, in the reference lists of relevant secondary publications and the comments to the Federal Joint Committee, as well as the results of the search by hand, are illustrated in Figure 2.

The systematic literature search and the search by hand gave a total of 2397 references (MEDLINE N = 911, EMBASE N = 556, Clinical Trials N = 9, ERIC N = 181, CINAHL N = 432, PsycINFO N = 12, PSYNDEX N = 33, CDSR N = 76, Other Reviews N = 148, Economic Evaluations N = 24, Technology Assessments N = 9, hand search N = 6). An additional 7 references were identified in the systematic search for screening studies and an additional 4 references in the search for diagnostic studies – all with potential relevance for the area of treatment. A total of 54 references were given in the 9 comments to the Federal Joint Committee. Enquiries to hospitals produced a further 17 references. In addition, 7 references were considered that had been sent spontaneously to the Institute. After removing the duplicates (490), there remained 1996 citations and these were assessed on the basis of titles and abstracts. Of these, 1929 were excluded as being definitely irrelevant to the question of treatment. The reference lists of 11 systematic reviews or HTA reports were searched for additional relevant studies (see Appendix C). However, this produced no additional relevant studies. The total of 67 potentially relevant references was then viewed in full text.

The search update gave 314 hits, including 4 additional relevant publications. A survey of the reference list in a study publication identified in the search update and included in the area of screening led to the identification of a further publication. The relevant data were extracted in the documentation forms intended for this purpose for a total of 19 references. After this detailed screening, a total of 4 studies (4 publications) were finally included as relevant for the evaluation.

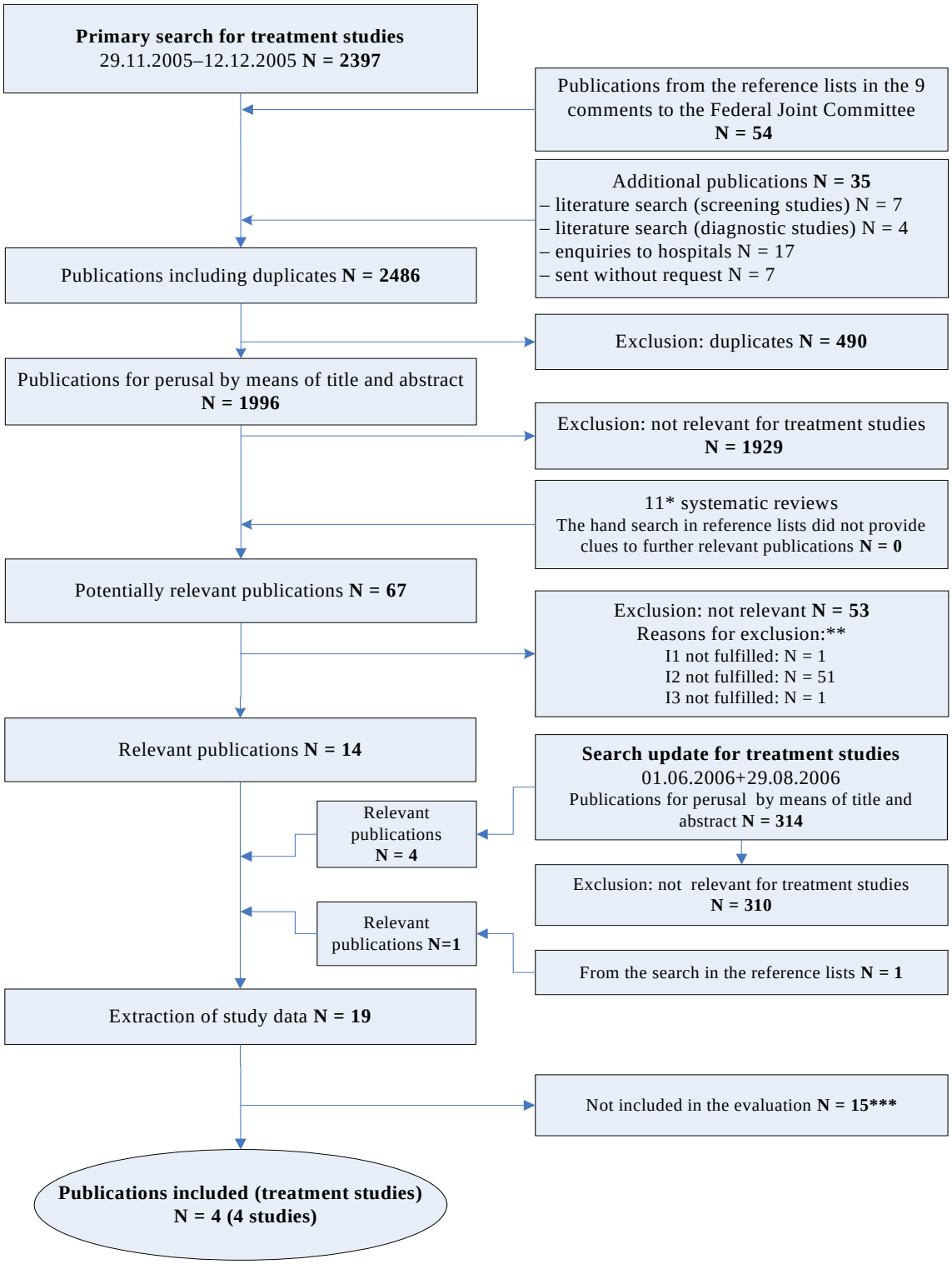

Figure 2: Results of the literature search and literature screening (treatment studies)

* Eight systematic review articles were identified by the search by hand.
** According to Table 2: Inclusion /exclusion criteria – Treatment studies.
*** Explanation in Section 5.2.3.1 (not suited for an indirect comparison).

5.2.1.2 Results of the search for further published and unpublished studies (treatment studies)

Results of the written enquiries to manufacturers of cochlear implants/hearing aids

The enquiry to a total of 4 manufacturers of cochlear implants and 3 manufacturers of hearing aids brought no additional information.

Results of the enquiries to authors

The authors of 2 study publications (Hassanzadeh 2002 [86], Kennedy 2006 [5]) were contacted with questions about the content of the publications. Details on the content of the enquiries and the responses received can be found in Appendix D.

5.2.1.3 Information from the comments submitted on the preliminary report (treatment studies)

No studies were named in the comments that fulfilled the inclusion and exclusion criteria for treatment studies outlined in the underlying report plan of this report and that had not already been considered in the preliminary report. A list of the literature cited in the comments can be found in Appendix G.

5.2.2 Resulting study pool (treatment studies)

As a result of the various steps in the search, a total of 19 publications (18 studies) were identified, from which the relevant data were extracted. However, only 4 publications on 4 studies were included in the evaluation. The exact procedure is explained in Section 5.2.3.1.

Table 13: Studies on the indirect comparison – cochlea implant versus hearing aid

Study	Full publication	Reference
Geers 1995	Geers AE et al. Ann Otol Rhinol Laryngol Suppl 1995; 166: 328–329	[87]
Horga 2006	Horga D et al. Clin Linguist Phon 2006; 20(2-3): 211–217.	[88]
James 2005	James D et al. J Speech Lang Hear Res 2005; 48(6): 1511-1528.	[89]
Meyer 2000	Meyer TA et al. Ann Otol Rhinol Laryngol Suppl 2000; 185(12): 49–51.	[90]
Meyer 1998	Meyer TA et al. J Speech Lang Hear Res 1998; 41(4): 846–858.	[91]
Mildner 2006	Mildner V et al. Clin Linguist Phon 2006; 20(2–3): 219–292.	[92]
Miyamoto 1997	Miyamoto RT et al. Acta Otolaryngol 1997; 117(2): 154–157.	[93]
Rittenhouse 1990	Rittenhouse RK et al. Br J Disord Commun 1990; 25(2): 195–208.	[94]
Svirsky 1999	Svirsky MA et al. Ann Otol Rhinol Laryngol Suppl 1999; 177(4): 104–109.	[95]
Tharpe 2002	Tharpe AM et al. J Speech Lang Hear Res 2002; 45(2): 403–413.	[96]
Tobey 1995	Tobey EA et al. Adv Otorhinolaryngol 1995; 50: 146–153.	[97]
Truy 1998	Truy E et al. Rev Laryngol Otol Rhinol (Bord) 1998; 119(4): 271–275. Truy E et al. Int J Pediatr Otorhinolaryngol 1998; 45(1): 83–89.	[98] [99]
van Lierde 2005	Van Lierde KM et al. Int J Audiol 2005; 44(8): 452–465.	[100]
Vermeulen 1995	Vermeulen AM et al. Ann Otol Rhinol Laryngol Suppl 1995; 166(9): 215–217.	[101]

Table 14: Studies included in the evaluation – early versus late (later) treatment

Study	Full publication	Reference
Markides 1986	Markides A. Br J Audiol 1986; 20(2): 165–167.	[102]
Moeller 2000	Moeller MP. Pediatrics 2000; 106(3): e43.	[103]
Wake 2005	Wake M et al. Arch Dis Child 2005; 90(3): 238–244.	[104]
Yoshinaga-Itano 1998	Yoshinaga-Itano C et al. Pediatrics 1998; 102(5): 1161–1171.	[105]

An alphabetical list of the references included can also be found in Section 8. An overview of the references viewed in full text but excluded (together with the reason for exclusion) can be found in Appendix B. If there were several reasons for excluding a publication (as was often the case), only the most important reason is given.

5.2.3 Characteristics of the treatment studies considered in the evaluation

The procedure with respect to general aspects of the evaluated treatment studies (for example, study design, study population, study and publication quality) is described below. The presentation is subdivided into the 2 different types of study included: studies undertaking an indirect comparison (Section 5.2.3.1) and studies undertaking a direct comparison (Section 5.2.3.2).

5.2.3.1 Studies that compared different types of interventions with each other

A total of 14 non-randomised studies (15 publications) could in principle have been used for an indirect comparison. However, after extraction of the relevant data, not a single study could be used for the evaluation. To help make the continuous evaluation process intelligible, aspects of the individual studies are presented, together with the reasons for their exclusion from the evaluation, on the basis of the criteria listed in Sections 4.1.2 and 4.1.5.

Explanation of the evaluation process

No study could be used for an indirect comparison. This became clear after intensive scrutiny of the full text publications and the extraction of relevant data from these. Information on age is needed for an indirect comparison and this was missing in 5 studies. In 3 of these studies, either no information at all was provided on the age of the children at intervention/the start of treatment or this information was inadequate. In 6 studies, there was marked variability within the studies regarding the age at intervention or the age at which the outcome parameters were recorded, so that reliable allocation to a time point at intervention (as a precondition for an indirect comparison) was not possible. In 3 studies, the presentation of the results was

inadequate (no point estimates or confidence intervals provided). In another study, 2 groups of children with cochlear implants were compared with 2 groups of children with hearing aids with respect to language comprehension. However, the results were only presented for the children who had been given cochlear implants. In the remaining 3 studies, either the interventions were not comparable or different outcome parameters were recorded. In one study, behaviour, attention, and concentration were examined and in the other, receptive language development. Neither of these studies was comparable with another study, in which different types of early intervention programmes were compared with each other. An overview of the reasons for exclusion of the 14 studies is given in Table 15.

Table 15: Indirect comparisons – Reasons for exclusion of treatment studies

Study	Inadequate information on age	Major differences in age	Inadequate presentation of results	No comparable intervention	No comparable outcome parameters
Geers 1995	x		x		
Horga 2006		x			
James 2005					x
Meyer 2000		x			
Meyer 1998		x	x		
Mildner 2006		x			
Miyamoto 1997	x	x			
Rittenhouse 1990	x			x	
Svirsky 1999			x		
Tharpe 2002					x
Tobey 1995	x				
Truy 1998			x		
van Lierde 2005		x			
Vermeulen 1995	x				

5.2.3.2 Studies that compared early with late (later) intervention

Studies are described below in which early treatment of a (congenital) paediatric hearing impairment was compared with late (later) treatment (direct comparison). The study design and study population are presented first (see Tables 16 to 18), followed by the study and publication quality (see Table 19).

Study design and study population (treatment studies)

As all identified studies are cohort studies, in which only correlations were or could be investigated, it is particularly important to allow for the extent of possible bias. For this

reason, as an essential inclusion criterion for the selection of studies, it was specified that they required adequate quality regarding the comparability of groups and the subsequent interpretability of the data.

Four studies fulfilled this criterion (USA: 2; UK: 1; Australia: 1). The Australian study Wake 2005 (CHIVOS: Children with Hearing Disability in Victoria Outcome Study) is a population-based cohort study in which pupils were investigated from schools for children with hearing impairment in the state of Victoria. For the investigation, the attempt was made to recruit all children diagnosed as suffering from a hearing impairment in the region. At the time the study was performed, screening of children with risk factors for hearing impairment and universal screening with distraction audiometry for children aged 8-10 months had been implemented. In the other studies, a retrospective analysis was performed on the basis of available data. The Yoshinaga-Itano 1998 study was performed as part of the Colorado Home Intervention Program (CHIP). The Moeller 2000 study was performed as part of an early intervention programme, which was not described in more detail. In both programmes, children with hearing impairment were given early inpatient and outpatient treatment with a multidisciplinary approach.

All studies investigated the language development of children aged 1-12 years. The Wake 2005 study also incidentally reported on the development of hearing ability. The treatment groups (the age of the children at the start of treatment) were defined differently in each study. The patients were normally categorised at 6-month intervals. The studies used different assessment instruments and analysis methods to record the treatment effects. Between 86 and 153 children were initially enrolled in the studies.

Study and publication quality (treatment studies)

Essential aspects of the study and publication quality of the studies considered are compared in Table 19. Three studies exhibited major methodological deficiencies within the designs used. Only the Wake 2005 study exhibited minor deficiencies.

Three studies used standardised test procedures. In contrast, the Markides 1986 study based the evaluation exclusively on the external evaluation of speech intelligibility by the class teacher. Three studies provided no clear information on the blinding of the assessor/evaluator of the outcome parameters with respect to the age of the children at intervention. However, it must be assumed that there was often an assessment (for example, of language ability) by the parents (who could not be blinded). This was mostly supported by the argument that the parents could provide more accurate information about the child's language development. Blinding is therefore impossible in the first place. The issue of blinding was only dealt with in the Wake 2005 study. In this study, the parents' evaluation was combined with objective and blinded evaluation of tape recordings and video films.

Only the Yoshinaga-Itano 1998 study contained an adequate description of the sample and relevant prognostic factors. Two studies contained a detailed listing of the sample characteristics, but these were not stratified according to age at intervention. One study contained only sparse information, so that it is not easily possible to estimate comparability at the start of these 3 studies.

An a priori sample size planning was not performed in any study; nor were considerations about the power of the studies made on the basis of the given sample size.

As the number of data sets (number of children) originally available was unclear, as well as the number of children who in principle fulfilled the inclusion criteria, it is not possible to infer how many children/parents refused further participation before the study was completed or how many data sets were excluded from further evaluation. In principle, only children were included for whom test values were available. For this reason, selective enrolment cannot be excluded. It is possible that the children with available test values and who continued to be treated in the intervention programmes achieved better values than the children who had already dropped out. This could lead to an overestimate of the effects of early treatment. Only the Wake 2005 study portrayed the patient flow in a flow diagram in accordance with CONSORT. There were, however, discrepancies between the number of children primarily enrolled in the study (86) and the number of children included in the evaluation (77 or 81, depending on the outcome parameter).

Another critical aspect is the classification of the age groups in Markides 1986 and Yoshinaga-Itano 1998. It is not reported whether these were planned a priori. The 2 other studies modelled the effect of age at intervention as a continuous variable, without classification into age groups.

Specific aspects of the treatment studies

Markides 1986 [102]

This relatively old study investigated the influence of the age of provision of a hearing aid on speech intelligibility in 153 school children (aged 8-12 years). Four groups were formed. All children attended schools for people with hearing impairment (or comparable institutions) and exhibited severe hearing impairment. Although the study included a control for confounding factors with “matching”, the non-verbal development of the children was not considered as an important confounding factor. Moreover, it is unclear how the 153 children were selected from the total of 5172 children available for this study. In addition, the publication does not explain the mechanism used for matching.

Moeller 2000 [103]

This study investigated the correlation between the age at admission to a comprehensive treatment programme (Diagnostic Early Intervention Program, DEIP) and the scores for receptive and expressive language development determined at the age of about 5 years. It was only implied in the publication that not all of the 112 children who were evidently enrolled in the study could be considered in the evaluation. No exact information was provided on the number of missing data sets for each test procedure. A subgroup of 80 children was investigated for expressive language development (verbal reasoning).

The extent of the hearing impairment varied from 25 to 120 dB, though the proportion of mild hearing impairment was low (about 8%). In all cases, the hearing impairment was a prelinguistic bilateral retrocochlear hearing disability (sensorineural hearing disability). Universal newborn hearing screening was not implemented at the time the children were identified. The children were identified from a risk register, by selective screening or on the basis of parents' suspicions. There were no signs of other disabilities in any of the children. It is nevertheless unclear to what extent the results of this selected population can be transferred to an unselected population, as in universal newborn hearing screening. Besides provision of hearing aids, the children were treated in a comprehensive early intervention programme. In addition to the confounding factors examined in other studies, this study investigated the effects of the extent of family ties and support on language development. A positive aspect of this study is the detailed description of the statistical modelling for each factor investigated.

Wake 2005 [104]

This was a population-based cohort study (CHIVOS: Children with Hearing Disability in Victoria Outcome Study). The correlation was investigated between age at diagnosis, the severity of the hearing impairment at the time of diagnosis, and language abilities in 86 children aged from about 7 to 8 years. On average, the children were treated about 2 months after diagnosis; 11 children (about 13%) were treated till they were 6 months old. Treatment usually consisted of provision of a hearing aid; only 14% of the children were given a cochlear implant. A total of 46% of the children attended a school for the deaf. The children had generally suffered from bilateral hearing impairment since birth. About 21% of the children suffered only mild hearing disability. 241 children were initially identified, but only 86 of these were actually enrolled. It was reported in the study publication that the children who did not participate, in spite of being suitable in principle, did not differ from the participating children with respect to essential characteristics. Eight children did not participate in all tests. The reasons for this are not given. Two positive aspects of this study are the consideration of many different confounding factors (2 different confounding factors were always considered in parallel in the analysis) and the good description of the regression model used.

Yoshinaga-Itano 1998 [105]

This study compared the receptive and expressive language abilities of 72 children who had been diagnosed as suffering from hearing impairment up to an age of 6 months, with 78 children who had been diagnosed after this period. At the time point of the evaluation, the children were 1 to 3 years old. Most of the children were treated by provision of a hearing aid and/or cochlear implant about 2 months after diagnosis. No additional information was provided on the type of treatment. The children suffered from congenital bilateral hearing impairment. The loss of hearing was mild in about 10% of the children ($\leq$ 40 dB). It is a negative aspect of this study that the selection criteria for the 150 children were not clearly described. Moreover, the procedure for modelling (ANCOVA) is unclear. There is therefore a great risk that the study results are biased.

Table 16: Characteristics of the treatment studies – Comparison of early with late (later) treatment

Study	Study design	Number of groups	Number of children primarily included [a]	Country/Setting	Main outcome parameters
Markides 1986	Multicentre[b] cohort study with matched groups retrospective	4	153 children 1. ≤ 6 months: 32 children 2. 7 – 12 months: 32 children 3. 13 – 24 months: 38 children 4. 25 – 36 months: 51 children	UK/ Schools for the deaf	- Language development
Moeller 2000	Cohort study retrospective	-[c]	112 children 1. 0 – 11 months: 24 children 2. 11.1 – 23 months: 42 children 3. 23.1 – 35 months: 24 children 4. > 35 months: 22 children	USA/ Community (DEIP)	- Language development
Wake 2005	Population-based cohort study retrospective	-[c]	86 children[d,e] 1. ≤ 12 months: 29 children[f] 2. 12 – 23 months: 20-21 children 3. 24 – 35 months: 14-16 children 4. ≥ 36 months: 15-16 children	Australia/ Schools for the deaf[g]	- Language development - Development of hearing ability
Yoshinaga-Itano 1998	Cohort study retrospective	2	150 children[e] 1. ≤ 6 months: 72 children 2. > 6 months: 78 children	USA/CHIP	- Language development

CHIP: Colorado Home Intervention Program. DEIP: Diagnostic Early Intervention Program. PHU: unit for partially hearing children. UK: United Kingdom. USA: United States of America.

a: Unless otherwise stated, the classifications refer to the time of the start of the intervention.
b: 272 PHU, 44 Schools for the deaf.
c: The influence of age on language development was determined as a continuous variable.
d: Although 88 children were originally enrolled, the diagnosis turned out to be wrong for 2 children at the time of the evaluation.
e: Group classification by age at diagnosis. Treatment provided at a mean of about 2 months after diagnosis.
f: 11 children were treated up to an age of 6 months. The number per category refers to the children evaluated in each group.
g: Also schools without special care for children with hearing disability. In this case, 93% of the children were cared for by a teacher.

Table 17: Basic data in treatment studies – Comparison of early with late (later) treatment

Study	Degree of hearing impairment at the start of treatment (in dB)[a]	Gender f/m (%)	Age of children at evaluation
Markides 1986	75.4 – 78.9 (8.6 – 9.3)[b] Severe to profound hearing impairment/deaf	About equally distributed in each group	8 – 12 years
Moeller 2000	77.8 (25 – 120)[c] Proportion of children with mild hearing impairment: approx. 8%	48/52[d]	5 years
Wake 2005	65 (30 – 120)[e] 26 – 40 dB: 17 children, 41 – 60 dB: 28 children, 61 – 80dB: 17 children, > 80 dB: 20 children Proportion of children with mild hearing impairment: approx. 21%	38/62[d]	7 – 8 years
Yoshinaga-Itano 1998	1. ≤ 6 months: 58 (27 – 110+)[c, f] 2. > 6 months: 67 (30 – 107+)[c, f] Proportion of children with mild hearing impairment: approx. 10%	1. ≤ 6 months: 53/47 2. > 6 months: 47/53	1 – 3 years

dB: decibel. f: female. m: male.

a: If not otherwise stated, measured by Pure Tone Average for the better ear.
b: Range of the means in the groups (range of the standard deviations in the groups), each for the better ear, with a frequency range of 250-4000 Hz.
c: Median (range).
d: No separate information for groups (the influence of age on language development was determined as a continuous variable).
e: Mean (range).
f: The + presumably means that a hearing impairment of at least 110 or at least 107 dB is present.

Table 18: Description of the intervention in the treatment studies – Comparison of early with late (later) treatment

Study	Age of children at start of treatment	Type of treatment	Main inclusion criteria	Main exclusion criteria
Markides 1986	4 age groups (n): 1. ≤ 6 months (32) 2. 7 – 12 months (32) 3. 13 – 24 months (38) 4. 25 – 36 months (51)	Provision of hearing aid; no information on concomitant treatment	Children from schools for the deaf	Children with additional disabilities
Moeller 2000	22 months[a] (0.4 – 54)	Provision of hearing aid and/or cochlear implant[b]; treatment in the context of a multidisciplinary early intervention programme	Prelinguistic bilateral sensorineural hearing impairment[c]; participation in DEIP in the period 1981 – 1994 up to the age of 5 years; at least one parent with normal hearing; no signs of additional disability	Intelligence quotient (non-verbal) < 70; non-English speaking family
Wake 2005	23.2 (1.2 – 53.4)[d]	Provision of hearing aid and/or cochlear implant (13.6%); 88% of the children attended an early intervention programme	Permanent congenital bilateral hearing impairment; birth cohort (Victoria, Australia) 01/1991 – 07/1993; resident in Victoria; participation in CHIVOS; provision of hearing aid up to the age of 4.5 years.	Intellectual disabilities; > 9 years; non-English speaking family
Yoshinaga-Itano 1998	2 age groups[e] 1. ≤ 6 months: 72 2. > 6 months: 78	Provision of hearing aid and/or cochlear implant [b], other treatments: about one hour a week of hearing and speech therapy	Children with congenital bilateral hearing impairment; resident in Colorado; participation in CHIP	No information

CHIP: Colorado Home Intervention Program. CHIVOS: Children With Hearing Disability in Victoria Outcome Study. DEIP: Diagnostic Early Intervention Program.

a: Median (range).
b: "Amplification".
c: Congenital or onset before 12 months of age.
d: Mean (range).
e: Group classification according to age at diagnosis; treatment at a mean of about 2 months after diagnosis.

Table 19: Study and publication quality (treatment studies)

Study	Blinded recording of outcome parameters	Consideration of confounding factors	Transparency of patient flow	Biometric quality
Markides 1986	No precise information	Comparability of the groups with respect to the matching variables: age, age at start of hearing impairment, degree of hearing impairment, school attended, gender	No information on the criteria for the selection of the 153 children from the total of 5172 children with hearing impairment	Major deficiencies
Moeller 2000	No precise information, rather improbable	Adjusted for degree of hearing impairment at the start of treatment, family involvement, non-verbal intelligence The enrolled children were identified using a risk register and selective screening. Risk factors not given	The number of children basically suited for the study is unclear. Selection of 112 children who fulfilled the study inclusion criteria. For one outcome parameter, only 80 of the 112 data sets were considered. Proportion of children excluded from evaluation: 29%	Major deficiencies
Wake 2005	Yes, partially	Consideration of degree of hearing impairment at start of treatment, non-verbal intelligence, mother's level of education, professional status, family support	Yes. Differences between study participants and non-participants checked. Data recording for 8 of 88 children incomplete.	Minor deficiencies
Yoshinaga-Itano 1998	No	Adjustment for degree of hearing impairment, age at time of test, mode of communication, socio-economic status Low proportion of children with underaverage scores for non-verbal intelligence in the group with early intervention (29% versus 56%), also lower proportion of severe hearing impairment in this group (34% versus 46%)	No information on procedure for the selection of the 150 children enrolled in the study	Major deficiencies

5.2.4 Results on therapy goals (treatment studies)

Four studies could be considered that investigated the benefit of early in comparison to late (later) intervention with respect to the patient-relevant outcome parameters defined in advance.

These studies only provided information on the language development of children with hearing impairment. In addition, the Wake 2005 study provided limited information on the development of hearing. Other patient-relevant outcome parameters – such as general and social development, quality of life and emotional or educational disability (for example, school failure) – were not investigated. A regression analytical evaluation procedure was used in 2 studies (Moeller 2000 and Wake 2005) and, for this reason, presentation of all the results would demand a great deal of space. The results will therefore be reported below by study rather than outcome parameter. The estimates, confidence limits and p-values in these studies will not be given.

Markides 1986. The Markides 1986 study reported a statistically significant difference between children provided with treatment at an age of up to 6 months and children with later treatment, with respect to speech intelligibility at the age of 8 to 12 years ($p = 0.01 – p = 0.02$, depending on the comparator group). The disadvantage was greater, the later the intervention took place. About half the children given early treatment could make themselves understood in a normal manner or were very easy to understand. This only applied to 10-15% of the children given late (later) treatment. In this context, it is interesting that there were no significant differences between the groups given treatment after the age of six months (7-12 months, 13-24 months, and 25-36 months).

Yoshinaga-Itano 1998. Just as in the Yoshinaga-Itano 2001 study included in the screening section, the authors of the Yoshinaga-Itano 1998 study converted the raw test values into so-called development quotients,[17] thus allowing an estimation of language development in comparison to children with normal hearing. The children with normal cognitive development who had been diagnosed and treated up to the age of 6 months exhibited statistically significantly better values for receptive language development at the age of about 13-36 months than children who had been diagnosed and treated later. The test difference corresponded to about 1.4 standard deviations ($p < 0.001$). The average values for the children given early diagnosis and treatment lay within the normal range, whereas this was not the case for the children given later diagnosis and treatment. There were also statistically favourable differences in expressive language development in favour of the children given early (earlier) care. The difference in the test values was about 1.5 standard deviations ($p<0.001$).

[17] Test raw values (=development age in months) / chronological age in months x 100.

Moeller 2000. In this study, the age at intervention turned out to be a good predictor of receptive vocabulary when the children were followed up at the age of 5 years. The older the children were at the intervention, the poorer their results in comparison to the children with the early intervention (up to 11 months of age). The children with the early intervention were within the normal range; the children treated later were about 1-1.5 standard deviations lower. Children appeared to benefit in principle from early intervention. The study found underaverage scores for expressive language development (verbal reasoning ability) at the age of 5 years for children with both the early and the late (later) intervention. There was, however, a trend for the children with the late (later) intervention to lag behind those with the early (earlier) intervention. This study also measured an additional important factor – the extent of family involvement. This included, for example, family adjustment to the child's disability, regularity of participation in treatment sessions, and the appropriateness of the communication with the impaired child. All of these factors had an effect at least as great as that of the age at intervention. Another of the results in Moeller 2000 is therefore also of relevance, namely that family involvement is markedly less for the children with a late diagnosis, so that confounding when evaluating the age at diagnosis cannot be excluded. This aspect could also call into doubt the other studies included in this investigation. None of these studies considered the degree of family involvement, so that the extent to which these results are biased by this factor cannot be estimated. The possibility must also be borne in mind for this study that the children possibly did not correspond to those children with hearing impairment identified and treated in the context of a universal newborn hearing screening programme, as they were selected either by selective screening or from a risk register.

Wake 2005. In contrast to Moeller 2000 and Yoshinaga-Itano 1998, the Wake 2005 study found no statistically significant difference with respect to receptive language abilities and reading ability at the age of about 8 years between children with early intervention and those with late (later) intervention. Only the receptive vocabulary (determined with the Peabody Picture Vocabulary Test; PPVT) was weakly correlated with age at intervention. The severity of the hearing impairment had a much greater influence. The more severe the hearing impairment was, the greater the language disability. The discrepancies between the individual studies with respect to the relevance of the age at intervention may be partially explained by the fact that in Wake 2005 only 11 of the 86 children (about 13%; compare Yoshinaga-Itano 1998: 48%) were identified before the sixth month, so that the study had only a limited possibility of identifying the effects of very early intervention. The interesting additional information was provided that severity of the hearing impairment for all children on average remained stable (mean difference: 0.06 dB, standard deviation: 14 dB, range: -27 to +50 dB). 14 children exhibited deterioration of their hearing by 10 dB or more; the hearing of another 14 children improved by 10 dB or more. No group-specific information was provided for children given an early rather than a late (later) intervention or for children with different severities of hearing impairment.

Taken together, most of the study results indicate statistically significant differences with respect to language development in favour of early rather than late (later) intervention for children with bilateral hearing impairment. Because of the severe deficiencies in study design in 3 of the 4 studies, this can only be regarded as an indication that the receptive and expressive language abilities, the communicative abilities and spontaneous speech are better in the children after an early intervention rather than a later intervention. The differences amount to about 1-1.5 standard deviations. The children with the early intervention are also more often within the normal range for language development than the children after a late (later) intervention. In particular, the studies with better methodology indicate that other variables are also important for language development, including family involvement, support from the parents, and the severity of the hearing impairment. Wake 2005 included only a few children for whom the intervention started before the sixth month of life. The fact that he could find no effect of early intervention and that in Markides the effects were essentially limited to the children with very early intervention might indicate the importance of starting treatment at a very early point in time.

5.3 Diagnostic studies

5.3.1 Literature search (diagnostic studies)

In this section, the results are presented of the systematic search for diagnostic studies in bibliographic databases and of enquiries to manufacturers, authors and hospitals.

5.3.1.1 Results of the literature search (diagnostic studies)

The systematic literature search for diagnostic studies was performed in November and December 2005 in a total of 11 databases. A search update was performed in 2 steps: a search was performed in 4 databases at the start of June 2006 and in the remaining 7 databases at the end of August 2006.

The results of the search for published studies in bibliographic databases, in the reference lists of relevant secondary publications and the comments to the Federal Joint Committee, as well as the results of the search by hand are illustrated in Figure 3.

The systematic literature search gave a total of 3064 references (MEDLINE N = 1789, EMBASE N = 978, ERIC N = 73, CINAHL N = 158, PsycINFO N = 56, PSYNDEX N = 3, Technology Assessments N = 1, hand search N = 6, no hits for Clinical Trials, CDSR, Other Reviews, Economic Evaluations). An additional 79 references were identified from the systematic search for screening studies and classified as potentially relevant for the diagnostic studies. No further references from the search for treatment studies were regarded as potentially relevant. In an analogous manner to the procedure described for the screening and treatment studies, the references cited in the comments to the Federal Joint Committee

(N = 54), references identified from enquiries to hospitals (N=17) and unsolicited references sent to us (N = 7) were also considered. After removing the duplicates (149), 3072 references remained and these were evaluated on the basis of titles and abstracts. Of these, 2917 were excluded as being definitely irrelevant to the question of diagnosis. The identified references included 3 systematic reviews. The reference lists of these, together with those of 8 systematic reviews or HTA reports identified by the hand search, were searched for additional potential studies (see Appendix C). The total of 155 potentially relevant references was then viewed in full text.

After removal of duplicates, the search update gave a total of 99 hits, although no additional relevant study was identified. For a total of 15 references to 12 studies, the relevant data were extracted in the documentation forms intended for this purpose. Three of these studies (3 publications) were not included in the evaluation (see Section 5.3.3).

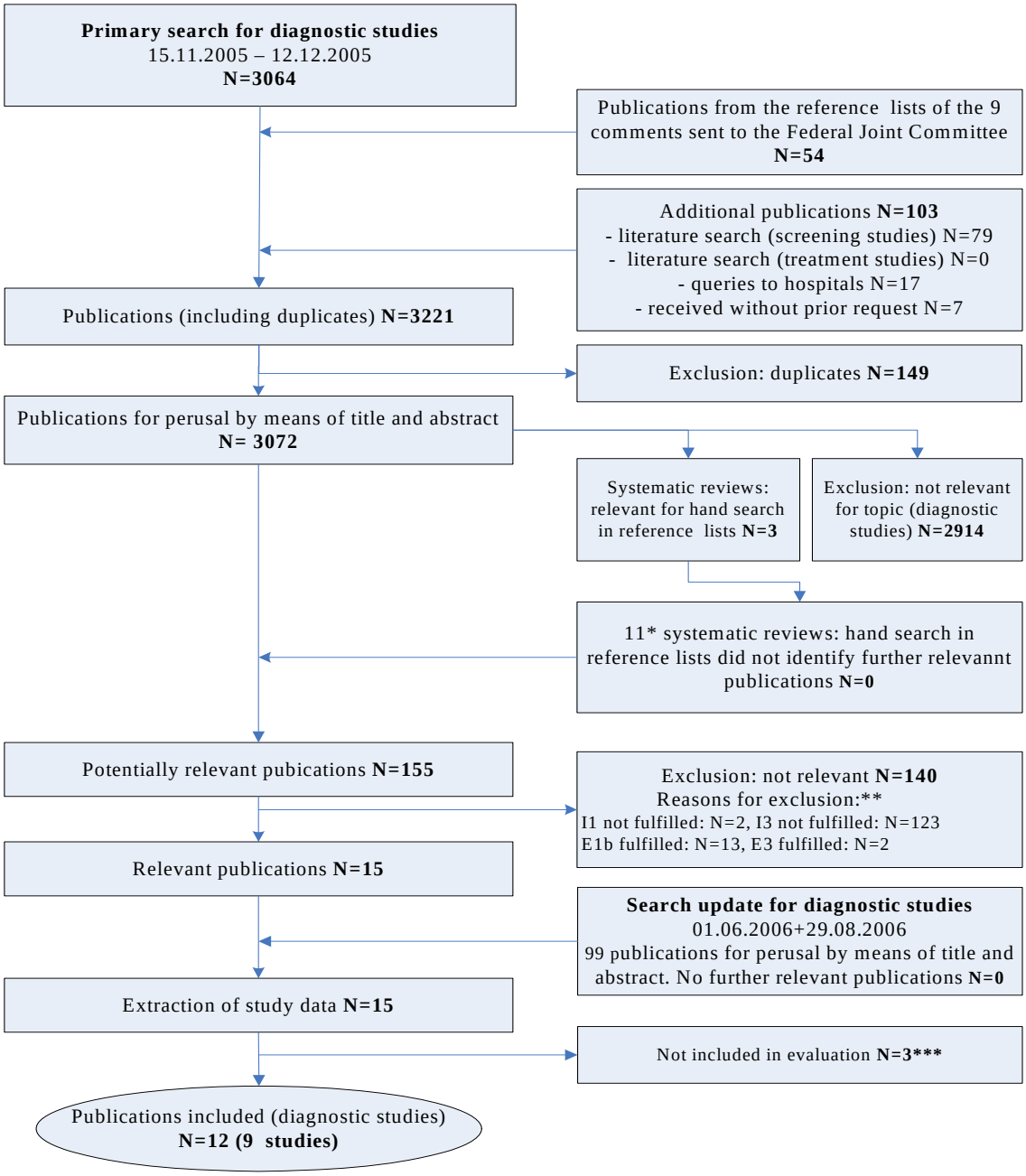

Figure 3: Results of the literature search and literature screening (diagnostic studies)

* Eight systematic review articles were identified by hand search.
** In accordance with Table 3: Inclusion and exclusion criteria – Diagnostic studies.
*** Comparison of different instruments to measure otoacoustic emissions, see also Section 5.3.3.

5.3.1.2 Results of the search for additional published and unpublished diagnostic studies

Results of the written enquiries to manufacturers of screening instruments

The 13 enquiries to manufacturers of screening instruments did not provide any clues to additional unpublished studies or published studies that had not been identified in the literature search.

Results of enquiries to authors

As part of the literature search, a letter was written to the author of a study discussed in the section on treatment studies (Rittenhouse 1990 [94]; see Section 5.2.3.1), with the aim of identifying other publications related to this study – in particular, on the quality of the diagnostic test procedures. We also wrote to the Wessex study manager regarding the publication by Kennedy 2005 [77] to request an explanation of the results in the publication. A detailed overview of enquiries and responses is provided in Appendix D.

5.3.1.3 Information from the comments submitted on the preliminary report (diagnostic studies)

No studies were named in the comments that fulfilled the inclusion and exclusion criteria of the underlying report plan of the present report and had not already been considered in the preliminary report. A list of the references named in the comments is attached in Appendix G.

5.3.2 Resulting study pool (diagnostic studies)

A total of 12 diagnostic studies were identified. One study investigated 2-stage screening, starting with the measurement of otoacoustic emissions (S-TEOAE), followed, if these were abnormal, by automated brain stem audiometry (A-ABR). The references were distraction audiometry (HVDT: Health Visitor Distraction Test) at the age of 8 months and an extensive follow-up. This included all institutions in the screening region participating in the treatment of children with hearing impairment (Wessex study). Eight studies compared the measurement of otoacoustic emissions with automated brain stem audiometry (A-ABR). Three studies compared different instruments to measure otoacoustic emissions (OAE).

Table 20: Studies on diagnostic quality

Study	Full text publications	Reference test	Ref.	In evaluation
Studies evaluating 2-stage screening (OAE and ABR)				
Kennedy 2005 (Wessex study)	Kennedy C et al. Lancet 2005; 366(9486): 660-662.	Audiological investigation; HVDT; follow-up and recording of new identified cases	[77]	Yes
	Kennedy C et al. Lancet 2000; 356(9245): 1903-1904.		[79]	Yes
	Kennedy CR (Wessex Universal Neonatal Hearing Screening Trial Group). Acta Paediatr Suppl 1999; 88(432): 73-75.		[80]	Yes
	Wessex Universal Neonatal Hearing Screening Trial Group. Lancet 1998; 352(9145): 1957-1964.		[83]	Yes
Studies comparing OAE with ABR				
Abbott Gabbard 1999	Abbott Gabbard S et al. Semin Hear 1999; 20(4): 291-305.	A-ABR	[106]	Yes
Dort 2000	Dort JC et al. J Otolaryngol 2000; 29(4): 206-210.	A-ABR	[107]	Yes
Doyle 1998	Doyle KJ et al. Int J Pediatr Otorhinolaryngol 1998; 43: 207-211.	A-ABR	[108]	Yes
Doyle 1997	Doyle KJ et al. Int J Pediatr Otorhinolaryngol 1997; 41(2): 111-119.	A-ABR	[109]	Yes
Jacobson 1994	Jacobson JT et al. Int J Pediatr Otorhinolaryngol 1994; 29(3): 235-248.	D-ABR and A-ABR	[110]	Yes
Liao 1999	Liao H et al. Zhonghua Er Bi Yan Hou Ke Za Zhi 1999; 34(1): 21-24.	A-ABR	[111]	Yes
Luppari 1999	Luppari R et al. Acta Otorhinolaryngol Ital 1999; 19(2): 57-63.	A-ABR	[112]	Yes
Reuter 1998	Reuter G et al. HNO 1998; 46(11): 932-941.	A-ABR	[113]	Yes
Studies comparing different OAE instruments				
Brass 1994	Brass D et al. Ear Hear 1994; 15: 467-475.	OAE	[114]	No[(a)]
Grandori 2002	Grandori F et al. Int J Audiol 2002; 41: 267-270.	OAE	[115]	No[(a)]
Maxon 1996	Maxon AB et al. Early Hum Dev 1996; 45: 171-178.	OAE	[116]	No[(a)]

(A)-ABR: (automated) auditory brain stem response. D-ABR: diagnostic auditory brain stem response. HVDT: Health Visitor Distraction Test. OAE: otoacoustic emissions. Ref.: reference.

a: Explanation in Section 5.3.3

Section 8 gives an alphabetical list of the references included by research question. Appendix B gives an overview of the publications reviewed in full text and then excluded, together with the reason for exclusion.

5.3.3 Characteristics of the evaluated diagnostic studies

The general characteristics of the diagnostic studies included are described below (see Tables 21 to 23) and their biometric quality evaluated (see Table 24). Three studies (Brass 1994, Grandori 2002 and Maxon 1996) compared older with newer procedures for the measurement of otoacoustic emissions. As a comparison of this sort does not allow any statement about the diagnostic quality of the index test, these studies were not included in the evaluation and will not be presented in more detail in the following text. It should nevertheless be noted that the test results of these studies exhibit a high degree of consistency and reflect the changes over time which these tests are subject to. These studies are, however, irrelevant to the question of the accuracy of the test procedures within the screening population, as they did not employ a reference standard.

5.3.3.1 Study design and study population (diagnostic studies)

Of the 9 studies included in the evaluation, 8 investigated the diagnostic quality of the OAE (the index test) with respect to the identification of a hearing impairment in neonates. One study (Wessex study) investigated a 2-stage screening procedure, a combination of OAE and ABR measurements, in the context of a universal newborn hearing screening programme. The studies were performed in North America, China and Europe – including one study in Germany. With one exception, between 105 and 500 neonates were tested as inpatients in a hospital, usually a university hospital. The Wessex study investigated 25 609 neonates recruited in 4 hospitals in the region of Wessex, Great Britain. As defined for the inclusion and exclusion criteria for diagnostic studies to be considered in the present report (see Sections 4.1.4 and 4.1.5), these studies mostly investigated healthy neonates without risk factors. Only the Jacobson 1994 study investigated a population in which more than half the children were at risk. In the Dort 2000 study, 12% of the children were from a special neonatal ward, although it is unclear whether this was a ward for intensive neonatal care. It is stated that 8% of the children in the Wessex study were at risk. In the Luppari 1999 study, all neonates were included in principle, independently of whether they were healthy or exhibited risk factors. The proportion of at-risk children was not given.

Eight of the 9 studies were cross-sectional studies, i.e. the index and reference tests were performed at the same time or shortly after each other. The sequence of the performance of the tests was randomised in 2 studies (Doyle 1997, Dort 2000) and pseudo-randomised in another 2 studies (according to the availability of the instruments) (Jacobson 1994, Abbott Gabbard 1999). In another 3 studies, the OAE measurement was performed first; in Liao 1999 brain stem audiometry was performed first. The average age of the neonates investigated in these studies ranged between a minimum of 15 hours and a maximum of 5 days. In Luppari 1999 and Reuter 1998, some children were older. Brain stem audiometry (ABR) was used as a reference test in all 8 studies to clarify or to check the results. This was – insofar as reported – almost always automated (A-ABR) (see Table 23). In one study, the ABR instrument was

not named explicitly (Luppari 1999). In another study (Jacobson 1994), both automated and diagnostic brain stem audiometry were used as reference tests, and it is unclear which of these 2 reference methods was used for which or how many children. With one exception, the tests were performed in a quiet environment. In contrast, explicit care was taken in Jacobson 1994 that the background noise was “normal”.

In the Wessex study, automatic brain stem audiometry (A-ABR) was performed on neonates with abnormal results on the same day as the first investigation (S-TEOAE). Comprehensive audiological clarification was planned for weeks 6-12 of life for the children who still gave abnormal results. The actual comparison for the question of screening was performed with distraction audiometry (HVDT: Health Visitor Distraction Test) at the age of 8 months. In addition, extensive follow-up testing was performed after about 8 years, including all institutions in the region treating children with hearing impairment.

The cross-sectional studies also differed with respect to the observational or evaluation unit. In 4 studies, this was the neonate (Abbott Gabbard 1999, Dort 2000, Luppari 1999, Reuter 1998) and in the other 4 studies the ears. In 2 of these studies including adequate evaluation of individual neonates, not all neonates were investigated bilaterally (Luppari 1999, Reuter 1998). In 8 of the 9 studies, an abnormal monolateral result was rated as a “FAIL criterion” (pathological test result) for the index test. In Luppari 1999, different “FAIL criteria” were given for the children with monolateral and bilateral tests. Children were only rated as “FAIL” after a bilateral test if both ears were abnormal.

In the reference test, a child was rated as abnormal in the studies if the extent of hearing loss was at least 35 or 40 dB. This was only defined with respect to both ears in the Wessex study (case definition).

5.3.3.2 Study and publication quality (diagnostic studies)

In all studies, the initial hearing status was unknown, so that these were studies conducted under “real-life” conditions. The overall study and publication quality of the included studies must nevertheless be rated as inadequate. In many of the studies, information was missing on essential aspects of the performance, analysis and interpretation of the test procedures. In only half the cross-sectional studies were sensitivity and specificity calculated on the basis of the number of neonates investigated. In the other studies, the results are reported relative to the number of ears investigated. This is not adequate, as statistical analysis assumes that the units investigated are independent. Moreover, this procedure makes it impossible to calculate interpretable estimates of prevalence. Finally, no explicit effort was made in any study to achieve mutual blinding of the results of the index and reference test or to ensure that the tests were performed in a mutually independent manner. As a consequence, the possibility that there is bias in the results from (possible) knowledge of the results of the other test procedure cannot be excluded with sufficient certainty. Even though test results from most of the

screening instruments used are automated, so that they are not open to subjective influence, the test procedure can vary and therefore influence the probability of achieving a PASS (normal findings) or FAIL. For example, in one study with randomised allocation of the sequence (Doyle 1997), it was reported that there were statistically significant differences in the OAE measurement (higher PASS rate) when this was performed after the ABR measurement.

An a priori sample size planning was not performed in any study.

Bearing in mind the expected prevalence of hearing impairment, the number of neonates investigated was too low. The Wessex study was exceptional in this respect, as extensive measures were taken to follow up 25609 neonates (21279 of whom were screened and 392 with positive screening findings). This study is accordingly of particular importance, particularly with respect to the transferability of the test results to the situation of use. The study nevertheless exhibits deficiencies. It is not totally clear in the study publications to what extent all initially screened neonates were followed up. In fact, on the basis of the information provided, this seems rather improbable. However, an extensive follow-up was performed regarding the children with hearing impairment identified on screening, also covering all institutions in the region that dealt with children with hearing impairment. It can be assumed that this led to information about children who were initially negative on screening and the subsequent HVDT and about children who did not take part in either of the 2 screening tests, but who nevertheless turned out later to be suffering from a hearing impairment (false negatives in the screening). Estimates of the sensitivity can be made, although these must be regarded as too optimistic. In addition, there are minor inconsistencies between the data reported in different publications.

The main problem in all studies is the reference standard. The diagnostic quality of both (automated) brain stem audiometry and distraction audiometry is inadequate. The “gold standard” for the diagnosis of hearing impairment in small children is visual enhancement audiometry, although this can only be used in children from about the age of 8 or 9 months [11,117].

Table 21: Characteristics of the diagnostic studies

Study	Study design	Test sequence	Number of neonates	Country/Setting	Main outcome parameters
Studies evaluating 2-stage screening (OAE and ABR)					
Kennedy 2005 (Wessex study)	Longitudinal study	I → R[(a)]	25 609 neonates	UK, 4 hospitals	Test quality
Studies comparing OAE with ABR					
Abbott Gabbard 1999	Cross-sectional study	Pseudorandomised[(b)]	110 neonates	USA, university hospital, WBN	Test quality, test duration
Dort 2000	Cross-sectional study	Randomised	105 neonates	USA, specialised hospital, WBN/SCN	Test quality, test duration
Doyle 1997	Cross-sectional study	Randomised	200 neonates	USA, university hospital	Test quality, test duration
Doyle 1998	Cross-sectional study	I → R	116 neonates	USA, university hospital	Test quality, test duration
Jacobson 1994	Cross-sectional study	Pseudorandomised	119 neonates	USA[(c)]	Test quality
Liao 1999	Cross-sectional study	R → I[(d)]	108 neonates	China, specialised hospital	Test quality
Luppari 1999	Cross-sectional study	I → R	500 neonates	Italy, non-specialised hospital	Test quality, test duration
Reuter 1998	Cross-sectional study	I → R	111 neonates	Germany, university hospital	Test quality

ABR: auditory brain stem response. I: index test. OAE: otoacoustic emissions. R: reference test. SCN: special care nursery (neonatal follow-up ward). UK: United Kingdom. USA: United States of America. WBN: well-baby nursery (normal obstetrics ward).

a: First the index test (I), then the reference test (R).
b: Sequence depending on the availability of the instruments.
c: No information on the type of hospital.
d: First the reference test (R), then the index test (I).

Table 22: Basic data of the diagnostic studies

Study	Number of non-evaluated neonates [a]	Age [b]	Gender f / m (%)[c]	Population (according to study information)	Exclusion criteria
Studies evaluating 2-stage screening (OAE and ABR)					
Kennedy 2005 (Wessex study)	0	Exact age at screening unclear	No information	Neonates, 8% with RF	Postnatally acquired HI (for example, from meningitis)
Studies comparing OAE with ABR					
Abbott Gabbard 1999	0	15 hours	46 / 54	Healthy neonates	None
Dort 2000	41 (of 105) neonates	31 hours	47 / 53	Neonates, WBN/SCN[d]	None
Doyle 1997	0	24 hours	50 / 50	Healthy neonates	Neonates (NICU)
Doyle 1998	0	24 hours	55 / 45	Healthy neonates	No information
Jacobson 1994	7 (of 119) neonates	Unclear	41 / 59	Stable neonates[e]	No information
Liao 1999	0	120 hours	46 / 54	Neonates without RF	None
Luppari 1999	56 (of 500) neonates[f]	89 hours	No information	All neonates (including those with RF)	None
Reuter 1998	0[g]	1 – 17 days, mostly 48 – 120 hours	No information	Neonates	No information

ABR: auditory brain stem response. HI: hearing impairment. f: female. m: male. NICU: neonatal intensive care unit. OAE: otoacoustic emissions. RF: risk factor(s).
SCN: special care nursery (neonatal follow-up ward). WBN: well-baby nursery (normal obstetrics ward).

a: If number > 0, then number in brackets is the number of children primarily enrolled in the study.
b: Means, if not otherwise stated.
c: Percentages relative to the number of neonates primarily enrolled in the study.
d: Proportion of children from the SCN: about 12%.
e: Proportion of children with risk factors: about 56%.
f: Number of “ears” not investigated or children given monolateral investigation: 96/444 (21.6%).
g: Number of “ears” not investigated or children given monolateral investigation 5/111 (4.5%).

Table 23. Description of the diagnostic tests

Study	Index test	Reference test	Threshold (dB)	Performed by (qualification)	Environment and acoustic conditions
Studies evaluating 2-stage screening (OAE and ABR)					
Kennedy 2005 (Wessex study)	S-TEOAE (ILO88) + A-ABR	For children with positive screening findings: audiological investigations at age of 6 – 12 weeks; for all children: HVDT + intensive follow-up	40	No information	None
Studies comparing OAE with ABR					
Abbott Gabbard 1999	S-TEOAE (ILO88, Quickscreen)	A-ABR (ALGO-2)	No information	I: Experienced audiologist R: Trained personnel	Quiet room
Dort 2000	S-TEOAE (ILO88, Quickscreen) DPOAE (Otoscape 942)	A-ABR (Smartscreener)	40	No information	Quiet room
Doyle 1997	TEOAE (ILO88)	A-ABR (ALGO-1)	35	No information	Quiet room
Doyle 1998	TEOAE (ILO88)	A-ABR (ALGO-2)	35	No information	Quiet room
Jacobson 1994	TEOAE (ILO88)	A-ABR (ALGO-1) D-ABR (Navigator)[(a)]	35	No information	Normal noise background
Liao 1999	TEOAE (Celesta 503 Cochlear)	A-ABR (Amplaid MK-15)	40	No information	I: Quiet room; R: room with sound insulation
Luppari 1999	DPOAE (Virtual model 330)[(b)]	ABR (no information on instrument)	40	No information	Quiet room
Reuter 1998	TEOAE (ILO88), S-TEOAE (Echosensor)	A-ABR (ALGO-2)	35	No information	Quiet room

(A-)ABR: (automated) auditory brain stem response. dB: decibel. HVDT: Health Visitor Distraction Test. I: index test. OAE: otoacoustic emissions. R: reference test.
(S-)TEOAE: transient evoked otoacoustic emissions (measured with screening instruments).
a: Either diagnostic or automated brain stem audiometry was used as reference test; no further information.
b: Two different methods were used (“sweep”, “input/output”).

Table 24: Study and publication quality (diagnostic studies)

Study	Verification of (index) test result[a]	Continuity of reference test[b]	Evaluation unit[c]	Blinding or mutually independent test performance [d]	Documentation of uninterpretable tests or tests not performed	Biometric quality
Kennedy 2005 (Wessex study)	(Yes)[e]	No	Adequate	No	(Yes)[f]	Major deficiencies
Abbott Gabbard 1999	Yes	Yes	Adequate	No	None[g]	Major deficiencies
Dort 2000	Yes	Yes	Adequate	No	No	Major deficiencies
Doyle 1997	Yes	Yes	Inadequate	No	None	Major deficiencies
Doyle 1998	Yes	Yes	Inadequate	No	None	Major deficiencies
Jacobson 1994	Yes	Yes	Inadequate	No	No	Major deficiencies
Liao 1999	Yes	Yes	Inadequate	No	None	Major deficiencies
Luppari 1999	Yes	Yes	Adequate	No	No	Major deficiencies
Reuter 1998	Yes	Yes	Adequate	No	None	Major deficiencies

This table contains a selection of the total of 14 evaluation aspects for diagnostic studies (see QUADAS [39]) and the datum "evaluation unit"; HVDT: Health Visitor Distraction Test.

a: Clarification of the result of the index test with another test (reference test) for the total sample or for a randomly selected part of the sample.
b: Use of the same reference test independently of the result of the index test.
c: Inadequate, if "ears" were used.
d: Applies to both tests; depending on the sequence, one of the tests is always performed independently of the other test.
e: According to plan, all the screen-negative children should be given the HVDT at the age of 8 months. However, it is unclear how many were actually given the HVDT.
f: Intention-to-screen approach.
g: "None" means that it is unclear whether children were excluded from the evaluation.

5.3.4 Results on test quality and test duration (diagnostic studies)

The quality of the measurement of otoacoustic emissions (OAE) was investigated in 8 of the 9 studies. In one study, a sequential procedure was investigated (OAE/ABR). In all studies, the test quality criteria were either given or could be calculated. Five studies provided information on test duration.

When given, the definition of positive test results – i.e., the severity of the hearing impairment to be detected with the test – was relatively consistent between studies, with a hearing loss of > 35 – 40 dB. However, some of the variance may have been due to other parameters that partially determine the threshold, such as the signal noise separation, the percentage reproducibility or the frequency ranges tested (usually 500, 1000 and 2000 Hz). In addition, the sensitivity in 4 of the 8 studies comparing OAE and ABR was reported on the basis of ears investigated. In the other studies, it was reported on the basis of children investigated.

The absolute duration of the test performance, including preliminary and subsequent steps, ranged between 5 and 13 minutes.

Studies on the diagnostic quality of 2-stage screening

The only study supplying data on the diagnostic quality of 2-stage screening (OAE and ABR) is the Wessex study. Even though there was no actual follow-up of the screen-negative children in the strict sense, it can be assumed that identification of at least a portion of the false negatives in the test was ensured. An estimate of the sensitivity is then possible, although this will still be too optimistic. Two children with negative screening findings were later reported to be suffering from hearing impairment. Seven children who had not taken part in the screening were later diagnosed as suffering from hearing impairment.

The over-optimistic estimate of the sensitivity of the 2-stage screening is then 22/24 (0.917; 95% confidence interval [CI]: 0.742 to 0.977). This means that about 92 of 100 children with a hearing impairment did in fact give a positive screening finding. The specificity is 0.985 (95% CI: 0.983 to 0.987).

If the children not participating in the screening are included (intention-to-screen), the programme sensitivity can then be calculated as 22/31 (0.710; 95% CI: 0.520 to 0.858). This means that approximately 30% of the children with hearing impairment are not identified by the programme. There is, however, hardly any change in the programme specificity, as the unscreened children have the same effect on numerator and denominator. The risk of a hearing impairment is slightly increased for children who did not participate in the screening or whose parents rejected participation (1.6 per 1000 versus 1.1 per 1.000; p = 0.344).

Studies on the diagnostic quality of otoacoustic emissions

In the comparison of OAE with (automated) brain stem audiometry, the values for sensitivity vary between 0.50 and 1.0 and the values for specificity between 0.49 and 0.97. A quantitative summary of the results in a meta-analysis was not possible, due both to the great heterogeneity and the use of different evaluation units (neonates or ears). However, these differences in evaluation units cannot explain the observed heterogeneity. Because of the low number of children with abnormal ABR findings (prevalence), even an approximately robust estimate of sensitivity is impossible. This is also evident in the broad confidence intervals. It is nevertheless clear that the agreement between the 2 screening methods is suboptimal. However, as the reference test used in the studies (ABR) itself also exhibits a marked error rate [118], it is impossible to infer from the data whether the generally low specificity of the OAE measurement does in fact lead to false positives, or whether conversely, the generally low sensitivity actually leads to children with hearing impairment being overlooked.

To help orientation, the results are illustrated in Figures 4 and 5. Because of the methodological problems, we have dispensed with additional tabular listings and with the derivation of predictive values.

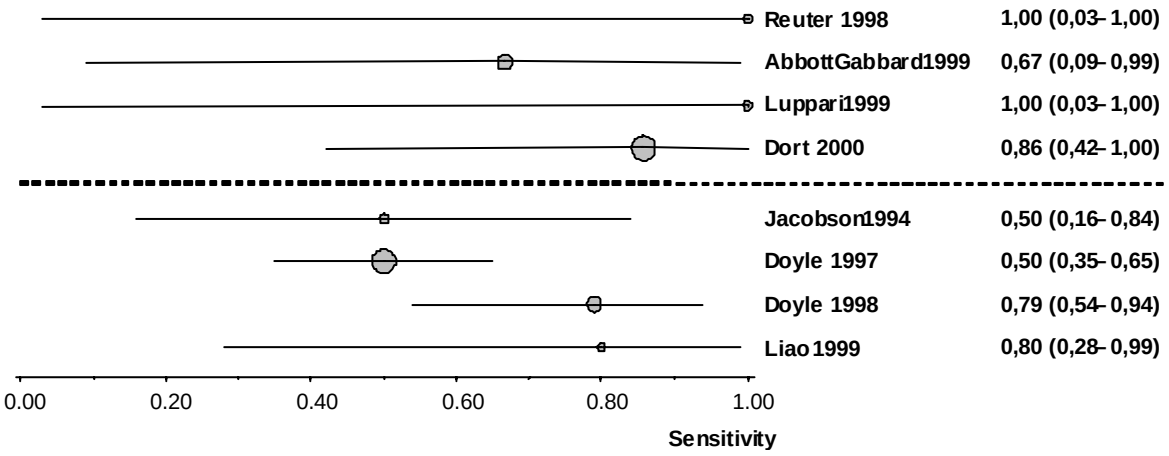

Figure 4: Sensitivity (OAE versus ABR)

ABR: auditory brain stem response. OAE: otoacoustic emissions. TEOAE: transient evoked otoacoustic emissions.

The first 4 studies (above the dotted line) deal with children. The other 4 studies use the ear as the evaluation unit. The area of the circles corresponds to the weight of each study, separated for the 2 different evaluation units and measured by the case number. The 95% CIs are given in brackets.

Values in Reuter 1998 for Echoscreen; values in Abbott Gabbard 1999 for a signal noise separation of 6 dB ("strict criterion"); values in Dort 2000 for TEOAE.

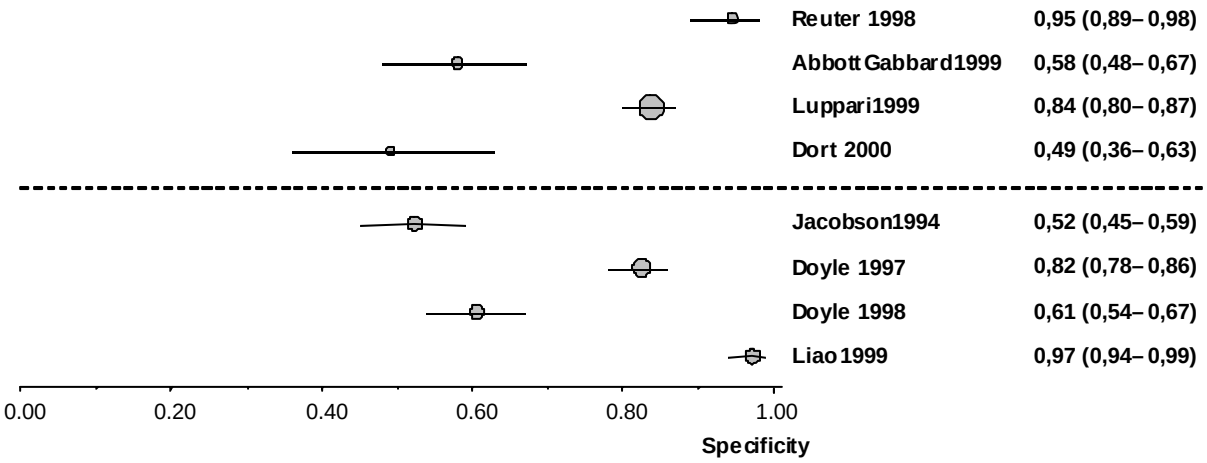

Figure 5: Specificity (OAE versus ABR)

ABR: auditory brain stem response. OAE: otoacoustic emissions. TEOAE: transient evoked otoacoustic emissions.

The first 4 studies (above the dotted line) deal with children. The other 4 studies use the ear as the evaluation unit. The area of the circles corresponds to the weight of each study, separated for the 2 different evaluation units and measured by the case number. The 95% CIs are given in brackets.

Values in Reuter 1998 for Echoscreen; values in Abbott Gabbard 1999 for a signal noise separation of 6 dB ("strict criterion"); values in Dort 2000 for TEOAE.

Test duration

Comparative information on test duration for OAE and ABR can only be found in 2 studies. In one of these studies (Dort 2000), the test duration for the OAE measurement was much shorter than for the ABR measurement (mean 11.0 [for TEOAE] versus 18.5 minutes). However, there is no information on the measure of variability, which allows only very restricted interpretation. There was practically no difference in the other study (12.5 versus 11.5 minutes). The other 3 studies contained only data on the test duration for the OAE measurement; the mean values varied between 5.2 and 13.0 minutes (see Table 25). The interpretation of these results must also consider the manner of calculation (e.g. number of repeated measurements, time for documentation and reporting of the results) and the time point of the performance of the study [119].

Table 25: Results on test duration – OAE versus ABR (diagnostic studies)

Study		Mean test duration[a]	
		OAE	**ABR**
Abbott Gabbard 1999		12.8 minutes (10.2 minutes)	11.5 minutes (8.3 minutes)
Dort 2000	TEOAE	11.0 minutes	18.5 minutes
	DPOAE	10.5 minutes	
Doyle 1997		13.0 minutes (range: 4.0-40.0 minutes)	No information
Doyle 1998		5.2 minutes	No information
Jacobson 1994		No information	No information
Liao 1999		No information	No information
Luppari 1999		6.1 minutes[b]	No information
Reuter 1998		No information	No information

ABR: auditory brain stem response. DPOAE: distortion products of otoacoustic emissions. OAE: otoacoustic emissions. TEOAE: transient evoked otoacoustic emissions.

a: Means and standard deviations (in brackets), insofar as reported.
b: Per ear, for a sample of 100 “ears” .

5.4 Summary of the results on screening, treatment, and diagnostic studies

This report deals with the results of studies that allow a relatively reliable conclusion on the benefit of universal newborn hearing screening (UNHS). These are (a) Screening studies, which compare a procedure with UNHS with a procedure without UNHS, both for children with hearing impairment, (b) Treatment studies, in which the benefit of early treatment is compared with late (later) treatment and (c) Diagnostic studies, which investigate the test quality of 2 tests relevant to neonatal hearing screening. In order to be able to evaluate the feasibility and acceptance of universal newborn hearing screening in Germany, model project reports on German programmes for neonatal hearing screening were also included.

After a comprehensive systematic search in bibliographic databases and in other sources, a total of only 15 studies were identified which, with reservations, allow reliable statements on the benefit of universal newborn hearing screening. These were 2 screening studies, 4 treatment studies and 9 diagnostic studies. None of the screening or treatment studies was randomised. The studies were mostly retrospective cohort studies and of mediocre quality, so that the results must be interpreted with caution. A specific problem with the diagnostic studies was that – with one exception – (automated) auditory brainstem response (A-ABR)

was used as reference standard, although this is not suitable as the definite “gold standard”. As a consequence, only a rough estimate of the quality of the relevant diagnostic procedures was possible.

The 2 screening studies identified [5,40,41] tend to indicate that children with hearing impairment identified by screening are at an advantage with respect to language development at an (average) age of 3 or 8 years in comparison to children whose hearing impairment was identified outside a specific screening programme. The chances of normal language development appear to be higher for screened children, possibly due to an earlier time point of diagnosis in these children. There were no available data on other patient-relevant outcome parameters which may be longer term (e.g. quality of life, psychological health, satisfaction, educational and professional development). No reliable conclusions could be drawn on possible adverse effects of screening either, as the available data were inadequate.

The 4 treatment studies included compared children given early treatment with a hearing aid or a cochlear implant with children given later treatment. These also provided indications that early treatment may be of advantage. However, the quality of these studies is, in some respects, rather mediocre.

The test procedures S-OAE and A-ABR used for universal hearing screening have not been investigated in adequately large samples of the target group that is relevant for universal newborn hearing screening – mainly healthy neonates. Only one study could be identified on the diagnostic quality of 2-stage screening. The results indicate that the specificity is relatively high (98.5%), with somewhat lower sensitivity (91.7%). If the group of children who were not screened even though screening was offered (about 17%) is included, the sensitivity drops to 71.0% (95% CI: 52% to 86%), implying that approximately 3 of 10 children with profound hearing impairment were not identified by the screening programme. The other diagnostic studies included only allow a statement on the quality of measurement of otoacoustic emissions in comparison to the measurement of auditory brain stem potentials. The quality of the OAE varied greatly between the studies. The data do not allow a reliable conclusion.

Six additional reports were included on German model projects on universal newborn hearing screening. These reports make it clear that universal newborn hearing screening is widely accepted in Germany, too, as is evident from the very low rate at which parents rejected participation of their children in the screening. The organisational preconditions have in principle already been met. Nevertheless, implementation sometimes turned out to be difficult, as seen in the comparatively low coverage rates (relative to all births in a region) and/or the high rates of children lost-to-follow-up found in some model projects. What is of absolutely essential importance is that the “tracking” of the children identified as abnormal in the primary screen must function well and therefore requires considerable effort.

6 DISCUSSION

The main points of the discussion from the comments on the preliminary report are presented below. Relevant results on individual aspects of universal newborn hearing screening are evaluated and discussed. The procedures of the present report, the type of studies discussed, and the conclusions are somewhat different from other HTA reports and systematic review articles on this theme. Relevant discrepancies in the studies reviewed and in the recommendations made are discussed.

Written hearing on the preliminary report

In the written hearing, a total of 14 comments were submitted on the preliminary report that fulfilled the formal requirements (see Appendix H). All the corresponding 20 representatives were invited to an oral scientific debate on unclear aspects of these comments. Of these 20, 16 accepted the invitation, representing 12 of the 14 submitted comments (see Appendix F).

A total of 64 scientific publications were named in the comments (see Appendix G). However, none of these papers fulfilled the inclusion criteria for the evaluation defined in the report plan:

- 21 cohort studies: no investigation of patient-relevant outcome parameters or no specification of diagnostic parameters for test accuracy;
- 7 cohort studies: no adequate control for confounding factors;
- 4 cohort studies: no concurrent control group;
- 13 studies: no relevant target population (no congenital hearing impairment);
- 4 consensus papers;
- 2 cohort studies comparing early with late/later treatment, which had already been considered in the preliminary report;
- 13 articles with background information.

In the comments, 3 main points of discussion became clear: (a) Inclusion criteria for the outcome parameters and study design investigated; (b) the organisational procedure of a universal newborn hearing screening programme; (c) the weighing of potential benefits and harms of universal newborn hearing screening.

Outcome parameters

In the written comments on the preliminary report and in the oral scientific debate, it was noted that outcome parameters such as language development or quality of life were useful to evaluate the benefit of universal newborn hearing screening, but that due to a lack of or limited data in these areas, the age of diagnosis should be considered as a valid surrogate and that normative data on hearing development should be drawn upon. In addition, further studies were named that the persons submitting comments considered relevant (see Appendix G).

“Hearing ability” was named as an outcome parameter of this report from the beginning. However, in most cases, no data could be extracted from the studies included (as presented in the Sections 5.1.4.2 and 5.2.4).

An earlier age of diagnosis alone is no sufficient argument for the benefit of universal newborn hearing screening, insofar as it is not proven that this earlier diagnosis is associated with advantages in later life. Even if screening leads to earlier diagnosis, it can only be seen as meaningful if earlier treatment is beneficial to the patient. The clarification of the question as to whether diagnosis and treatment can take place at an earlier stage by means of universal hearing screening is nevertheless of relevance. If this were not the case, the necessary argument for implementation of universal hearing screening would no longer exist. For this reason, for this report, German hearing screening projects were also investigated as to whether they have led to an earlier age of diagnosis and whether treatment followed shortly after diagnosis.

The impact of the age of a child with hearing impairment on the benefit of treatment can in principle also be assessed outside the framework of screening studies. In this evaluation, therefore, studies were also considered that compared early (earlier) with late (later) intervention in children with congenital hearing impairment. However, as far as their study design was concerned, the 23 studies that were named in the comments and investigated patient-relevant outcome parameters did not fulfil the inclusion criteria defined in Section 4.1.5. In 11 studies, no population with congenital hearing impairment was investigated; in 8 studies, potential confounding factors were not considered adequately; in 4 studies, no concurrent control group was investigated (see Appendix G: List of the references cited in the comments). Because of these characteristics, the studies could not provide information as to whether differences observed were actually due to the time point of intervention or, for example, were alternatively due to the unintended selection of the participating children.

Study design

Screening tests are prone to variety of subtle types of bias [120,121]. In principle, a consensus therefore exists on the international level that controlled studies of the whole screening chain,

ideally with randomisation or other methods of fair allocation to treatment groups, are the soundest basis to assess benefits and harms.

Some comments referred to such a study design as ethically questionable. The developmental deficits of children with hearing impairment compared to those without hearing impairment, which had been observed by persons submitting comments and described in the literature, were named as the main reason for these concerns. The persons submitting comments were also convinced that the physiological theory applies that there is only a limited time window for the optimal maturation of hearing development in children. Some persons submitting comments also demanded a reversal of the burden of proof, in the sense that the benefit of newborn hearing screening should be regarded as proven as long as studies did not show the opposite.

The present evaluation also considered data from non-randomised retrospective studies. In contrast to the opinion of persons submitting comments, not all studies considered show a clear and positive association between early treatment and long-term development. This does not result in a reliable basis for the assessment of a benefit. At the same time, there is only little information available on potential harmful effects of a screening programme or early treatment. The assumption of many persons submitting comments that universal hearing screening cannot cause relevant damage is therefore not proven by robust evidence.

Regarding the issue of the appropriateness of a study in which an intervention is consciously withheld from participants, the consequences of potential advantages and disadvantages must be carefully weighed. On the side of the potential benefit, the hope exists of avoiding or at least limiting the effects of a lifelong disadvantage. It can be inferred from the prevalence of congenital hearing impairment that 1 to 3 per 1000 children investigated could have this advantage. It is a special feature of hearing screening that a later intervention may be less effective.

On the side of potential adverse effects, there is a minor burden due to unnecessary tests for the large majority (997 to 999 of 1000) of children with normal hearing and the consequences of possibly false test results. However, compared with other screening tests, the potential of universal newborn hearing screening to cause harm seems limited. The test is non-invasive, and acceptance by parents is high. False positive screening results are more relevant, which may affect up to 40 of 1000 children, insofar as the recommended referral rate of 4% is fulfilled [31,34]. With higher referral rates, the number of children with false positive screening results may also be higher. The extent of parents' anxiety caused by false results depends on the type of education and support, as well the quality of the programme (see DIMDI update [18]). Appropriate education about the relevance and limitations of a screening result must be an integral part of a programme. In unfavourable cases, a false positive result could lead to an "over-treatment" of children with normal hearing. Information could not be obtained from the studies included as to whether and how many such cases occurred. But

even if a false positive result led to unnecessary provision of a hearing aid in a child with normal hearing, this would be reversible. If the child is provided with a cochlear implant, the potential harm caused by an, in principle, appropriate but unsuccessful therapy needs to be considered, for example, due to the intervention itself. Against the background of the weighing of these factors and the fact that professional societies have already publicly supported the implementation of newborn hearing screening, it seems questionable that a sufficient number of patients would agree to randomisation.

The non-concurrent comparison favoured by the persons submitting comments must be seen as problematical – for example, the comparison of the proportion of children with hearing impairment in regular schools before and after implementation of universal newborn hearing screening or also of children with hearing impairment treated at an earlier or later stage. In particular, changes in the educational concept of the integration of children with hearing impairment into schools can have a substantial impact on this outcome parameter. For this reason, the comparison of groups within the same time period was an explicit inclusion criterion for this report (see report plan [43] and Sections 4.1.1 and 4.1.2 *Study types*). The publications by Diller 2006a [122] and 2006b [123] could not be included, as they did not fulfil this criterion.

The inclusion of these 2 publications would not have changed the conclusions of this report. The publication by Diller 2006a [122] was presented as evidence by persons submitting comments that an early provision of a cochlear implant (age: 0.1–2.11 years) improved the chance of being admitted to a regular school. However, our own analysis of the data did not show a statistically significantly difference between groups, if the proportion of children with placement in a “regular” institution (regular kindergarten, preschool, school, or vocational school) was compared with those in “non-regular” institutions (special kindergarten, school for people with hearing and/or language disabilities, early rehabilitation programmes). The publication by Diller 2006b [123] compared the schooling situation of children with hearing impairment in Germany in 2 different periods (1994 versus 2004), and concluded that a higher proportion of children were admitted to regular schools in 2004. An increase over time of the proportion of children with hearing impairment in regular schools (possibly through a changed situation regarding early rehabilitation) cannot be inferred from these data. For methodological reasons, the data from the German Professional Society of Teachers for Persons with Hearing Impairment do not provide evidence of an advantage for children provided with treatment at an earlier stage regarding cognitive development or admission to regular schools.

Procedures of the model projects on universal newborn hearing screening

A further point of criticism in the comments on the preliminary report was that the procedures specified in the various consensus papers on universal newborn hearing screening [30,33,34,38] were not described clearly in the section dealing with the German model

projects (Section 5.1.5). According to these papers, a 3-stage procedure was intended. Furthermore, uniform criteria for the age of confirmation of diagnosis (up to 3 months of age) and start of treatment (up to 6 months of age) had been defined.

However, the assessment of the reports on German model projects showed that, regarding the implementation of these specifications, substantial variability existed, which was to be presented transparently in the present report. The efforts of individual federal states and hospitals to implement universal newborn hearing screening within a tight financial framework are acknowledged. However, the reports on the model projects confirm that the way universal newborn hearing screening is implemented has a substantial impact on the various quality indicators of such a programme (see also the Section *Quality assurance measures in universal newborn hearing screening*).

Can congenital hearing impairment in children be diagnosed and treated early by the implementation of universal newborn hearing screening? (see Table 6 and Section 5.1.4)

The assumption that universal newborn hearing screening can lead to earlier diagnosis of congenital paediatric hearing impairment is supported by the 2 screening studies included (Kennedy 2006, Yoshinaga-Itano 2001) and by the model projects. The chances of early diagnostic clarification are markedly higher in screened than in unscreened children. It follows that, if the structural conditions are provided, the chances of adequately early treatment will also be increased. As far as could be seen from the reports, in the model projects included, most of the screened children whose hearing impairment was discovered during the screening were diagnosed within the first 3, or at least the first 6, months of life and then treated. Other HTA reports confirm that diagnosis and treatment after universal newborn hearing screening occur at an earlier stage [2,11,18].

However, the studies also document the partially high rates of lost to follow-up for children initially identified as abnormal in screening. In the Kennedy study (2006), the interval between diagnosis and treatment with a hearing aid was estimated as 5 months [5]. It was also reported for the Hanover model project that the start of treatment after diagnosis was delayed for some time for many children in the screening programme. This finding shows that substantial benefit from screening for the children with a hearing impairment can only be expected if the organisation ensures that there are no unnecessary delays in the chain “suspicion-diagnosis-treatment” and, most importantly, that there are no interruptions.

Overall evaluation: There are indications that universal newborn hearing screening leads to earlier diagnosis of hearing impairment.

What is the benefit of treating hearing impairment as early as possible?

(see Sections 5.1.3 and 5.2.3)

After assessing the included studies, this report found no reliable evidence that early treatment of children with hearing impairment is of benefit.

Studies with the necessary randomised design, adequate size and duration and good quality needed for this purpose have not yet been published. One reason may be that the comparison of the patient-relevant benefit of different treatment strategies for hearing impairment is much more complex and demanding than, for example, the comparison between drugs. As it is possible that there will never be definitive studies on the treatment of hearing impairment or on universal newborn hearing screening, this report has explicitly included study types which - because of their design – can only provide indications, but not reliable evidence.

The initial impression is that many published articles investigate the possible benefit of early treatment of children with hearing impairment. However, only a few of these are of adequate quality to allow reliable data interpretation. For the present report, results from 2 screening studies and 4 treatment studies could be included to answer this question. Five of the 6 studies provide indications that tend to support the idea that early intervention is of advantage for the language development of children with hearing impairment. However, the advantages of early treatment are smaller in the studies of better quality than in those with major deficiencies.

The results of these studies should generally be interpreted with caution, particularly because of possible selection mechanisms. Neither of the 2 screening studies provided explicit information on the number and characteristics of the children who were not considered in the analysis. However, this would have been necessary, for example, to assess whether and how the selection of the children could have distorted the results, on the basis of the children's language ability and comprehension. A finding in the Kennedy 2006 study is interesting. The authors evaluated the results for children with hearing impairment from 2 different perspectives. On the one hand, they compared the language development of children from the screened group with children from the unscreened group (or with children screened at a later stage). On the other hand, they compared children whose hearing impairment had been diagnosed up to the age of 9 months with children who had been diagnosed and treated later. It is noticeable that the comparison according to age at diagnosis indicates greater advantage for early diagnosis than the comparison of children whose hearing impairment was identified within or outside screening. This finding also indicates that screening should not be simply equated with early intervention.

This report includes 4 studies in which children with early and late treatment of hearing impairment were compared. These studies attempted to control adequately for confounding factors. Nevertheless, here too, the possibility cannot be excluded that factors other than the time of the start of treatment led to advantages for children who received early treatment. The question as to why early treatment was neglected for children given late (later) treatment is decisive here. For these reasons, it is difficult to distinguish between the effects of early treatment and the effects of the treatment itself.

Some studies provide indications of additional decisive confounding factors that might mask the effects of early treatment. Here too, some of the results are contradictory. Moeller 2000 [103] emphasises the value of parental involvement for language development; he considered that this was even more important than the age at intervention. In contrast, he concluded that the severity of the hearing impairment was without influence. This is contradicted by the results of a recently published prospective cohort study (Wake 2005) [104], which concluded that mainly the severity of the hearing impairment was decisive, rather than early intervention. It may be noted that only 11 of the total of 88 children investigated in Wake 2005 were treated before the postulated critical age of 6 months. It is therefore doubtful that the statistical power of the study is at all adequate to test the relevance of very early intervention.

Can an optimal age for the treatment of children with hearing impairment be identified?

An argument for early hearing screening is the physiological model according to which hearing mainly develops during the first 6 months of life and that largely normal acoustic stimulation is necessary for this development [2,12]. If this concept is correct, children with hearing impairment should achieve greater benefit from intervention in this phase than later.

In particular, the Moeller 2000 study provides information on this aspect, as this study investigated the age of intervention as a continuous variable. Taken together, the results indicate that there is an interaction: the earlier the intervention was, the lower the disabilities from hearing impairment. However, the differentiation of age specifically within the first months of life was inadequate, so that no adequately precise conclusion can be drawn for the postulated critical time period up to the age of 6 months.

The HTA report of the German Institute for Medical Documentation and Information (DIMDI) [2] also stated that the available studies do not allow any conclusive answer to the question of age differentiation in the evaluation of the benefits and harms of early cochlear implantation. The update of this HTA report [18] includes 2 additional studies (Wake 2005 [104], Wake 2004 [124]) and comes to a similar conclusion. Wake 2005 was also included in the present report. Wake 2004 was excluded, as the control group included children without hearing impairment (inclusion criterion I1 for treatment studies not fulfilled). According to the interpretation of the DIMDI authors, the 2 studies showed that language and psychosocial development was more affected in children with hearing impairment than in the comparator group without hearing impairment. However, the comparability of groups is questionable, as the sample originated from different birth cohorts. In addition, it is unclear whether the measurement instrument used to assess quality of life is sufficiently valid, and what the measured difference between groups means in everyday life. Finally, Wake 2004 does not answer the question as to what extent universal newborn hearing screening improves quality of life.

Is there evidence that children with a specific severity of hearing impairment have no benefit or special benefit from hearing screening?

It cannot be assumed a priori that children with hearing impairment of every severity benefit from screening to an equal extent. For example, some authors point out that relatively early provision of a hearing aid is not necessarily accompanied by better language development, if severe hearing impairment is present [125]. In principle, severe hearing impairment is treatable, for example, by provision of a cochlear implant. No exact definition exists of the lower threshold for a hearing impairment from which intervention is of benefit to the child. Many studies and screening programmes use thresholds of about 35-40 dB hearing loss. Within the framework of this report, the question remains open whether these are children who really need treatment. This also applies to the question as to whether children with monolateral hearing impairment should also be given treatment (as early as possible), which the German Society for Phoniatry and Paediatric Audiology recommends in specific cases in a consensus paper on the provision of hearing aids in children [16].

Studies on the long-term development of children with mild to moderate hearing impairment have come to the conclusion that delayed development (particularly with respect to language) and educational problems are probable for these children [126,127], as well as for children with monolateral hearing impairment [128]. The Wake 2005 study contains data from groups with different severity of hearing disorders. These data indicate that children with mild hearing impairment are mostly within the lower normal range, indicating that their development is at least mildly delayed.

In this context, the definition of “need of treatment” in the model project reports is rather imprecise. For example, in the Hesse model project, monolateral hearing impairment was to be identified, although the report states that only a small proportion of these have (as yet) been treated. In the model project report for Mecklenburg-Western Pomerania, it is stated that a “control group” was to include children with monolateral hearing impairment, without any additional explanation of what was to be done with this control group.

It remains an open question as to when an impairment or delay in development can be regarded as being of clinical relevance. This might necessitate a comparison between different areas, such as language, social aspects, and school performance. The possibility should also be considered that development may proceed differently in different individuals and that children might compensate in other areas for deficits in one area. These effects might also be age dependent. The test procedures – for example, to record language development - are not all equally reliable [129].

To help define the severity of the hearing impairment and optimal time of treatment, studies would be desirable that specifically investigate the relevant threshold values and time points. Additional factors should also be considered to help assess the relevance of these 2 factors

and other factors. For example, the quality and quantity of immediate treatment and of continuing and concomitant measures should be considered; this includes the involvement of parents, kindergarten, and junior school. It cannot be assumed without further assessment that early diagnosis leads to early therapy, which then leads automatically in the long term to a more favourable development [104].

Benefit of early diagnosis and treatment: results from other HTA reports

The number of studies included in the present report is much lower than in most other HTA reports. This is because the criteria for inclusion were stricter. Nevertheless, this stricter selection did not lead to different key conclusions.

The present report only included 4 of the studies included in the HTA reports from other institutions investigating the question of the benefit of therapy as early as possible, because only these studies permitted statements on patient-relevant outcome parameters and were of adequate quality [40,102,103,105]. The studies cited in other HTA reports that were excluded because of inadequate control for confounding factors (inclusion criterion I2 not fulfilled) were carefully scrutinised for this report, to establish to what extent they might be of practical relevance. For example, it was examined whether these studies had investigated children with very different degrees of hearing impairment, the spectrum to be expected in the target group for universal newborn hearing screening. In about half the studies, only children with high-grade hearing impairment were investigated; in one third of the studies, no information at all was provided on the severity of the hearing impairment, so that one may assume that no studies of practical relevance were overlooked. Appendix B contains a list of these studies under “Excluded studies”.

In its short report published in 2004 [26], the Swedish HTA agency SBU came to the conclusion that there was “moderately strong scientific evidence” (evidence level 2[18]) that universal newborn hearing screening with OAE or ABR led to early detection of hearing impairment. However, it was also noted that “Limited evidence exists that earlier detection and commencement of habilitation promotes improved communication and language development in the child” (evidence level 3).

The HTA report of the Australian Medicare Services Advisory Committee (MSAC) [28] primarily investigated the diagnostic quality of relevant screening procedures, but also made a statement on the benefit of early intervention. The report bases this conclusion on the English HTA report (NCCHTA [7], see below), and 5 studies from this report, as well as an additional study [105], which is also discussed in the present report. According to this, there are

[18] The SBU evidence evaluation distinguishes four levels of evidence. Level 1 = strong scientific evidence, Level 2 = moderately strong scientific evidence, Level 3 = limited scientific evidence, Level 4 = insufficient scientific evidence.

theoretical reasons to argue that early intervention could reduce the disabilities from hearing impairment. The clinical research data to support this were nevertheless reported to be relatively weak.

The report of the French HTA agency Agence Nationale d'Accréditation et d'Évaluation en Santé (ANAES [24]) – now Haute Autorité de Santé (HAS) – is based on a selection of the studies in the English HTA report and comes to similar conclusions: early intervention is linked to benefit. However, it was also noted that there was no consistent definition of "early" and, moreover, that factors other than early intervention had to be considered, such as the social environment and the parents' level of education.

The American Agency for Healthcare Research and Quality (AHRQ) [11,27] also pointed out the poor or – at best – adequate quality of the available cohort studies, and noted that therefore only limited evidence was available showing that intervention before the sixth month of life was linked to improved language abilities at the age of 2 to 5 years.

The 1997 HTA report from the English National Coordinating Centre for Health Technology Assessment (NCCHTA [7]) concludes that the evidence for the advantages of early intervention was limited and complex. However, there were clear indications that early detection of hearing impairment was of advantage for language and communication. They concluded that the introduction of universal newborn hearing screening should be considered, complemented by an additional test at the age of 7 months for those children who had not been previously screened.

The DIMDI HTA report [2] stands out in this series of HTA reports, as on the one hand, it concludes that the evidence base is poor, but on the other, regards the benefit of early intervention as "probable". This report discusses 18 studies listed in other HTA reports, together with 18 additional studies. All studies investigated the language development of children with the early intervention in comparison with the late (later) intervention. The authors point out the limitations in the methodological quality of all studies. Nevertheless they concluded it was probable that a universal newborn hearing screening programme would have a favourable effect on early intervention and thus on language development and the chances of participation in normal schooling. The 2006 update of this HTA report, which discusses 2 additional studies, comes to the same conclusion [18].

The classification of a benefit as "probable" is problematical, in particular as the DIMDI HTA report does not define "probability of a benefit". This category is not used in the international evidence scale and seems to be prone to subjective assessments. It can also be inferred from the DIMDI HTA report that the classification is also explicitly based on the evaluation of the theory on language development (citation page 7 [see also page 123]: "At the same time, an essential advantage for language development by means of early intervention, corresponding to the theory of language development, seems probable").

In principle it is problematical when an HTA report, after finding only limited supporting evidence on a theory it is to evaluate, uses the theory to be evaluated itself as an argument.

Overall evaluation: There are indications that early treatment of children with hearing impairment is of advantage regarding language development. However, the studies included do not allow any robust conclusions. Other factors may play a relevant or even more relevant role – such as parental involvement in (language) development or the severity of the hearing impairment. Other patient-relevant goals, such as social aspects, educational development or professional situation, have not been investigated. On the basis of the included studies, it is not possible to identify a maximum age at which treatment of children with hearing impairment should start. In particular, it cannot be inferred from these studies whether the time at which therapy should start depends on the severity of the hearing impairment.

How reliably can a congenital hearing impairment be identified by screening? (see Sections 5.1.4 and 5.3.3)

The test procedures used in the screening programmes should be both simple and low risk. Their results should also be as reliable and provide as meaningful results as possible. The balance between sensitivity and specificity is an important criterion. On the one hand, the screening procedure should overlook as few children with hearing impairment as possible (implying high sensitivity), while on the other hand, it should indicate as few as possible suspected cases of hearing impairment, which then turn out to be false after further clarification (implying high specificity).

Overlooked cases of hearing impairment (false negative results) may not only make the overall success of the screening programme doubtful, but could also theoretically harm the affected children. This is because signs of hearing impairment in the child may later be ignored by people in the child's environment from a feeling of false security, thus delaying the diagnosis.

False suspected cases (false positive results) can cause the parents worry and anxiety and can possibly cause long-term changes in family behaviour [130]. In addition, they considerably increase the costs of a screening programme, as they can only be identified after additional diagnostic effort.

When initiating a screening programme, it is therefore important to keep a balance between potential benefit and possible harm. A prerequisite for this is the clear definition of the medical condition to be diagnosed, for example, the specification of threshold values defining a degree of hearing impairment that requires treatment. In addition, the prevalence of the disease in the population examined should be known. The test procedure should be accepted and adequate treatment for a positive test result should be defined [131].

The accuracy and reliability of a test procedure can be expressed with various parameters. Sensitivity and specificity are of clinical relevance, as is the positive predictive value, meaning the proportion of children with a positive finding who actually suffer from a hearing impairment.

A multistage concept (combination of several screening tests in sequence) has been suggested for newborn hearing screening. According to this, hearing screening should proceed in 3 stages as a rule. In primary screening (stage 1, mostly OAE), if the initial finding is abnormal, this should be confirmed by a retest. If the finding is still abnormal, a rescreening is performed a few weeks later (stage 2). If the findings are still abnormal, final diagnostic clarification is performed (stage 3). There is apparently no consensus for the retest in primary screening and for rescreening. Both renewed measurement of otoacoustic emissions and automated brain stem audiometry (A-ABR) are employed. If only the OAE test is repeated, it should be noted that this test (if conducted under similar conditions as in the primary test), does not in principle provide an additional gain in information and ultimately can only increase specificity at the expense of sensitivity (with a strategy that trusts the negative test result: “believe the negative”). If A-ABR is used as the retest in primary screening, rescreening is dispensed with in some cases.

As the probability of auditory neuropathy is increased in neonates with risk factors for hearing impairment, screening with A-ABR alone has been discussed for this target group [48,57,61,66]. In auditory neuropathy, the function of the outer hair cells is intact and otoacoustic emissions can be recorded, but not acoustically evoked potentials [132,133].

There are 2 possible approaches to evaluate the sensitivity and specificity of a screening method. The first is comparison with a suitable gold standard. It is essential for a comparison of this sort that all persons in the selected population are investigated with both methods, particularly those persons who have given negative results with the screening method. This is the only way in which the proportion of false negative results can be assessed. The second approach, in which the comparison with the gold standard can be dispensed with, consists of following up the screened population until the medical condition to be identified is manifest in all affected patients.

In the German model projects, neonates with normal findings were not followed up over an extended period. It is therefore unknown whether or how often children with hearing impairment were overlooked by the screening programme. For this reason, adequate estimates of the sensitivity of the test procedures cannot be made on the basis of the model project reports. Because of the low prevalence of congenital hearing impairment, the distortion of estimates of specificity is negligible and can be indirectly inferred from the number of abnormal findings (the “referral rate”). However, this assumes that the definition of “abnormal” is clear and consistent (e.g. monolateral versus bilateral), as is that of “need of

treatment", accompanied by a clear relationship to primary screening or the rescreening. This was not the case in most reports.

The Hesse model project report [57] states that the sensitivity was 100%; but this is based on the assumption that the hearing of all children with normal screening findings was in fact normal. However, this assumption is contradicted by the Wessex study (Kennedy 2005 [77]). This study is distinguished by a series of methodological features that justify it being given special consideration in the evaluation of the benefits and harms of universal newborn hearing screening. All children in this study were offered not only 2-stage newborn hearing screening with OAE and A-ABR, but also an additional screening test at the age of about 8 months with visually conditioned distraction audiometry. In addition, in the course of several years the authors repeatedly contacted the local centres in the study region to identify children with hearing impairment ("audiology services"). With this approach, the authors considered that they had succeeded in identifying almost all the children in this region with congenital hearing impairment over a period of 8 years. Children with postnatally acquired hearing impairment were excluded. Taken together, the results show that the neonatal screening had only identified about 71% of the children exhibiting congenital hearing impairment at the age of 7 to 9 years. However, most (78%) of the overlooked cases had not participated in the screening: 7 of 9 children with "undetected" hearing impairment had not participated. The children who were actually false negatives in the screening test only corresponded to about 8% of the children with actual hearing impairment (2 of 24 children). Two of the 6 German model projects (Hanover and Upper Palatinate) also reported on children with hearing impairment with false negative screening results. In both cases, these were children with a 35delG mutation in the *gjb2* gene coding for connexin 26 - a gene deficiency which has been reported elsewhere to lead to false negative (screening) findings [67]. A further study (Almenar Latorre 2002 [54]), in which a 2-stage screening with OAE and ABR in 1532 newborns was investigated, reported no false negative screening results. Due to the incomplete follow-up of children with a negative screening result, this study was excluded from the present evaluation.

The specificity in the Wessex study was about 98.5%, i.e., 1.5% of the children without hearing impairment gave abnormal findings (false positive results) in screening. The specificity permits an estimate of the additional effort that has to be expended in screening. With rare medical conditions, this is also the essential determinant of the positive predictive value, i.e. the proportion of those with a positive (pathological) screening test who are in fact affected. In the case of the Wessex study, this was 22 out of 342 children (6.5 %).

The referral rates reported in the German model projects suggest that the values for specificity for sequential primary screening (combination of OAE and A-ABR) will be similar to those in the Wessex study. If the screening is with OAE alone, the referral rates are about twice as

high, so that lower specificity and a much less favourable positive predictive value can be expected in this case.

The negative predictive value, i.e. the proportion of those with a negative (non-pathological) screening test who are not affected, is of only secondary interest in rare medical conditions, as the probability of the absence of the condition is very high anyway (even without a negative screening test).

In the context of the present report, no other study could be identified that adequately investigated the quality of a sequential procedure (i.e. the combination of measurements of otoacoustic emissions and brain stem audiometry). In this context, the AHRQ HTA report only mentions one study of good quality (Norton 2000 [118]). This study covered children in an at-risk group whose screening findings at the age of 8-12 months of life were compared with visual enhancement audiometry as the gold standard. The OAE procedure exhibited high sensitivity (98%) in the detection of profound hearing impairment or deafness, but was less sensitive in the diagnosis of moderate or severe hearing impairment (80%, specificity 80%). Comparable values were measured for ABR (sensitivity 84%, specificity 90%). The sensitivity of the sequential procedure (OAE, ABR) was calculated to be 89%. According to these data, screening in this manner gives a false negative finding in about 1 in 10 children with a hearing impairment – essentially in agreement with the Wessex study.

This study was not included in the present report, as it investigated 3000 children from a high risk group that did not correspond to the general target population for early screening. As a consequence of this selection, the prevalence of hearing impairment in Norton 2000 is 10 to 20-fold higher than in the everyday screening population. As the prevalence also has a direct effect on the ratio of correct positive to false positive findings, results from high risk groups can only serve as orientation, but cannot be transferred to a general screening programme. Moreover, studies that do not consider the diagnostic quality in the actual target population can also lead to a biased estimate of sensitivity and specificity (“spectrum bias” [120,121]). In the DIMDI HTA report [2], 2 other studies were discussed that investigated sequential screening strategies [134,135]. However, these studies did not fulfil the inclusion criteria of the present report, as they contained no information on diagnostic quality criteria or on the population investigated (proportion of at-risk children).

The diagnostic studies included in this report only allow very limited conclusions about the quality of the OAE measurements in comparison to ABR. The sensitivity of the OAE relative to abnormal findings in ABR lay between 50% and 100% and the specificity between 49% and 97%. For methodological reasons, a quantitative summary of these values was not meaningful. For example, the evaluation unit in half the studies (mainly in older ones) was the ear rather than the child, which makes interpretation difficult.

The large variation in the values found for sensitivity and specificity is very striking. This may be due to several factors: differences in the stringency of the test criteria (e.g. stimulus level, signal to noise separation, reproducibility, threshold), different instruments (e.g. diagnostic or screening instruments, generation of screening instruments), the age of the children, environmental noise, the type of hearing impairment, the accuracy of the reference test itself, or the experience of the test operator and evaluator. Except in one study, no information on the qualification or the professional background of the test operators could be obtained from the studies included. Abbott Gabbard 1999 reports that experienced audiologists and trained or specialist staff were involved. In the hearing screening model projects, the screening was mainly performed by trained (non-physician) staff (midwives, nurses, and medical-technical assistants for functional diagnostics) and sometimes performed by ENT specialists.

Diagnostic quality of the screening procedure: results from other HTA reports

Other reports [2,18,27,28] have selected other inclusion and exclusion criteria for the studies included on the diagnostic quality of the screening tests. As a consequence, there are differences in both the number and selection of the studies included. Thus other reports also usually consider studies in at-risk populations and studies based on the assumption (without control) that all negatively tested neonates correspond to genuinely negative diagnoses (see Sections 4.1.4 and 4.1.5). In spite of the differences in study selection, other HTA reports give similar values for sensitivity and specificity regarding the measurement of otoacoustic emissions (with similarly large ranges).

In the context of the present report, no statement can be made on the quality of brain stem audiometry alone (ABR), as no study fulfilled the inclusion criteria. The DIMDI HTA report [2] reports that the recording of auditory brain stem potentials with ABR gave much greater and more homogeneous values than the measurement of otoacoustic emissions. The sensitivity was said to vary between 89 and 100% and the specificity between 96 and 98%. If one also considers the update [18], the lower limit for specificity is 86% due to the inclusion of an additional study (Schönweiler 2002 [74]).

Overall evaluation: No overall reliable evaluation of the diagnostic quality of OAE and A-ABR as single screening tests is possible, as there has been no systematic evaluation on an adequately large group of children without risk factors. However, the Wessex study indicates that sequential screening (first OAE and then, if finding abnormal, A-ABR) in practical use can achieve acceptable sensitivity of over 90%, with specificity of over 98%. However, this finding should be confirmed, as it is based on a relatively small number of children with hearing impairment; the 95% CI for sensitivity extends from 74 to 98%. In addition, it must be considered that the proportion of unidentified children markedly increases if the children not participating in screening are included in the evaluation.

What are the possible adverse effects of universal newborn hearing screening? (see Section 5.1.3.7)

In general, screening always has the potential to cause harm. Two types of harm must be distinguished: (a) direct harm, caused by the investigation itself, and (b) indirect harm, as a consequence of a screening finding. The consequences of false positive and false negative findings are then of special relevance, as are the consequences of possible over-diagnosis and over-treatment of children with findings that do not actually need treatment.

In the case of universal newborn hearing screening, the frequency and severity of harmful effects were not systematically investigated in the studies included in this report. Only the screening study by Kennedy 2006 contained an attempt of this sort. However, the results can hardly be interpreted, because of the unclear selection mechanisms and the lack of control groups (without screening).

Direct harm from the screening procedure

The studies included provide no indications of direct negative consequences from the screening test. As the OAE and A-ABR test procedures are both non-invasive, direct harm seems to be improbable anyway.

Indirect harm from screening findings

False positive findings are an inevitable effect of neonatal hearing screening. The rate is highly dependent on the definition of the hearing threshold and on whether hearing impairment is to be identified and assessed in one or both ears (Kennedy 2000). With a referral rate of 2%, it can be assumed that a hearing impairment is only actually present in about 1 of 20 children with abnormal findings and in only 1 in 40 children, if the referral rate is 4%. These children can only be distinguished by additional diagnostic tests. When evaluating the possible consequences of false positive findings, the procedure used for additional diagnosis therefore plays a role. In this case, clarification of a positive screening finding is also usually performed with non-invasive procedures. The interval between positive findings and diagnostic clarification is also important, as a false positive finding can trigger anxiety in parents. It is a characteristic of a quality-assured screening programme that these intervals are defined. According to the quality criteria (which are currently being revised) of the neonatal hearing screening programme that was introduced throughout England in March 2006, audiological diagnosis must be performed immediately after an abnormal finding has been recorded [136,137].

There is an extensive discussion of some potentially negative consequences of universal newborn hearing screening in the systematic review paper by the group investigating outcomes of Early Hearing Detection and Intervention (EHDI) Programs [138]. This group is made up of representatives of different research institutions and professional societies in the

"International Working Group on Childhood Hearing" (IGCH). The aim of this review was to assess the causes and consequences of neonatal hearing screening programmes on parental anxiety and the resulting psychological consequences for the affected children.

The review comes to the conclusion that there are in principle no indications that neonatal hearing screening programmes have any major effect on parental anxiety; however, interpretation of the available evidence was difficult, because of the low return rate of the anxiety questionnaires, the absence of adequate control groups and the differences between the instruments used to measure anxiety. There was a degree of anxiety, but this was not above average and could not be assigned to the type of screening finding (positive or negative) or to the screening as such.

There is a theory that the anxieties of the mother have a particularly negative effect on the mother-child bond within the first days of life – especially after a positive screening finding. However, Hyde 2004 et al. do not consider that this idea is supported by the available studies [138]. It is rather the case that the authors emphasise the value of a correct positive screening finding. In some cases, the behaviour of the parents towards the child may change, but this is evident in a change in the manner of attention and should be seen positively. One example of this is pacifying a crying child by non-auditory methods, such as touch and/or visual stimulation. It was also noted, however, that no suitable studies investigating specific aspects of the early bond in specific situations were currently available (e.g. screening as such, a positive screening finding, type of treatment) and that other positive effects of anxiety should also be considered, such as increased motivation to participate in follow-up investigations. Evaluation of the relation between risk and benefit would in general be difficult in practice.

Another aspect is that a false negative screening finding might have medical consequences. If a child with a congenital hearing impairment is not identified in the screening test, this may lead to a false sense of security, so that the child is diagnosed and treated (even) later than would have been the case without screening. Cases of this sort are not described in the studies included in this report.

Over-diagnosis and over-therapy

As part of the discussion on possible negative consequences of a screening programme, it must also be considered whether hearing screening can lead to over-diagnosis and over-therapy. To express it more exactly, are there children who are treated because of a correct positive finding, but who have no benefit from this treatment? A variant of this question, adapted to neonatal hearing screening, would be: How often, if at all, are children given early treatment who gain no benefit from it? It should also be asked what the possible disadvantages would be for children in whom a hearing impairment is detected early, although this detection would have had no direct consequences (as reported in some of the model projects).

The questions regarding the disadvantages of too-early treatment or over-therapy or early detection without immediate consequences have not yet been properly examined in studies. Treatment strategies have been a much more controversial issue. Advocates of the dominant theory of a sensitive phase of maturation of the auditory pathways and language acquisition emphasise the advantage of intervention, with the goal of allowing children adequate language development by improving their hearing. Opponents emphasise possible harm from increased or exclusive focus on language development: this orientation towards deficits (rather than orientation towards resources) would have the effect that (other) resources of the child would not be adequately exhausted and that other factors might be neglected that might have a more important influence on language acquisition (such as social exchange, shared attention and experiences, mutual understanding) [11]. It is therefore possible that the advantages of treatment might be linked to disadvantages in other areas. As regards cochlear implantation, it must not be forgotten that there is a potential risk, as with any surgical operation requiring general anaesthesia. It may be more difficult to assess to what extent provision of a hearing aid or treatment not aimed at improving hearing, but at enhancing non-verbal communication, may also have negative consequences. Because of the lack of studies comparing different types of treatment, no statement can be made on the validity of the opinions outlined above.

Overall evaluation: Because of the lack of reliable studies, possible harm from neonatal hearing screening cannot be evaluated. The potential exists, particularly from false positive findings. The frequency and consequences of these are primarily dependent on the quality regulations and quality assurance measures in a screening programme, as well as on the information given to parents.

Different screening strategies

The alternatives to UNHS include no screening at all, screening at a later time point, for example at the age of 8 months (as in England between 1960 and 2006 and in Finland) or selective screening of at-risk children. All children in the Kennedy 2006 study, including those in the UNHS group, were offered the opportunity of screening at 8 months. It follows that a direct comparison of UNHS alone with screening at a later age cannot be deduced, but rather the value of UNHS as an “add-on”. The results are thus of only limited value for the comparison between UNHS and no UNHS.

No studies were found that compared UNHS with the screening of only at-risk children. If a series of assumptions were made (e.g. that about 50% of children with hearing impairment exhibit risk factors for hearing impairment), indirect conclusions could be possible about the comparative efficiency of the 2 strategies. For example, it can be assumed that the positive predictive value of the tests would be greatly increased if only at-risk children were screened, as the prevalence of hearing impairment in this at-risk population would be substantially greater than in the overall birth cohort. (This depends on the proportion of at-risk children in

the total cohort and on differences in the test quality criteria between children with and without risk factors). This would greatly reduce the expenditure for screening, although children not identified at an early age would lose out. However, the uncertainties seem to be too great to allow reliable statements without comparative studies. In this context, a result of the Wessex study is interesting [77]: Whereas 65% of the children during the UNHS screening period belonged to the at-risk group, the corresponding figure for the period without UNHS was only 43% ($p = 0.09$, exact Fisher test). It is possible that the UNHS contributed to increased screening of at-risk children.

Summary of the conclusions of other HTA reports

Taken together, almost all HTA reports in this area [7,25-29] come to the conclusion that – in spite of some plausible theoretical arguments – there is only limited evidence that universal newborn hearing screening is of benefit to the short or long-term development of children with hearing impairment. The literature searches performed for these reports were in part designed to be highly sensitive and led to the identification of many studies on all 3 aspects (screening, treatment, and diagnosis). There were, however, not enough studies of good to adequate quality to provide the basis for a reliable statement.

The Finnish short report [25] concludes that the benefit of universal newborn hearing screening has not been demonstrated, in particular with respect to the social and professional development as adults. This type of screening was not regarded as an alternative to screening at 8 months, as has been performed in Finland.

The English HTA report [7] undertakes a highly comprehensive evaluation. For various screening strategies, a comparative evaluation was made of the costs, number of identified children, acceptance and aspects of equitability and fairness, as well of the specific challenges. There was said to be only limited evidence of the benefit of universal newborn hearing screening, although a favourable effect of early detection of hearing impairment was to be assumed. This statement was essentially based on 4 retrospective studies in which children with hearing impairment were compared with children with normal hearing with respect to various parameters such as type of school visited, unemployment, and quality of life. However, there is currently no unambiguous answer to the question as to what extent the outcome parameter of language development, as usually recorded in the studies, is also valid with regard to the long-term quality of life, psychosocial and mental well-being and possibilities for independent professional choices [104]. Sequential universal newborn hearing screening (S-OAE, A-ABR), which had already been implemented in pilot regions since 2000, was nevertheless established by law throughout England and Wales in March 2006 as a service provided by the National Health Service (NHS) [136]. It is exemplary that the procedures and the details of the programme are determined by centrally defined quality standards and extensive documentation of strict quality indicators. Relevant data from the

participating children are recorded in a joint central database, so that regular assessment of the programme is possible.

The DIMDI HTA report 2004 [2] and update 2006 [18] noted deficits in research and a lack of data, but came, however, to the conclusion that a benefit of universal newborn hearing screening was probable. This was also the case in comparison with at-risk children. After viewing the available evidence, we can neither confirm nor disprove this statement.

For reasons of redundancy, further systematic reviews and HTA reports are only presented briefly here: (a) The report of the regional Basque HTA organisation [139] does not evaluate the benefit of a screening programme to identify paediatric hearing impairment, but assumes such a benefit and aims to compare different screening strategies. The authors regard a combined screening with OAE and ABR to be an adequate screening strategy and support this statement (among other things) with other HTA reports: (b) the Cochrane Review [20], comparing universal with selective newborn hearing screening, did not find studies on this topic and concluded that the long-term benefit of universal newborn hearing screening had so far not been investigated adequately; and (c) the systematic review on newborn hearing screening in Hong Kong [140] concluded that there is increasing evidence of the benefit of universal newborn hearing screening, but refers to the results of individual studies, without considering their quality.

Quality assurance measures in universal newborn hearing screening

Quality standards to be fulfilled in universal newborn hearing screening programmes were already described in 2 German consensus papers in 2001 [34,38]. In principle, a quality-assured screening programme should assess the whole screening programme (from early detection to diagnostic clarification to the initiation of treatment).

The evaluation of data from German model projects on universal newborn hearing screening shows that the way such a programme is implemented has a substantial impact on the quality.

In both German consensus papers on universal newborn hearing screening, individual quality indicators are named which, for example, were assessed in the model projects, and in part provided with specific standard values.

- Decisive factors for the effectiveness of the screening programme are the preferably complete tracking of the children who had abnormal results in the screening test and were diagnosed with a hearing impairment, as well the identification of all children with congenital hearing impairment at a later suitable time. The coverage rate of the children with abnormal test results in the first stage of screening should be at least 95%.

- The screening expenditure is mainly determined by the proportion of children with abnormal screening results in the first stage of screening. The maximum rate of abnormal

test results should be 4% at the most; this corresponds to a specificity of about 96%, assuming a low prevalence of the disorder.

- In order to achieve a great an impact as possible, at least 95% of newborns should be included in the region where the screening is to take place.
- Diagnostic measures, i.e., confirmatory diagnostics to clarify an abnormal screening result, should take place within the first 3 months of life, in order to ensure the initiation of an intervention within the first 6 months of life.

Regarding the design of the German programme, in addition to considering the experiences in the German model projects, it is also recommended to consider international experience, for example, in Great Britain. The design of the programme should include a system that follows the development of children at least until junior school age and can identify deficits in the provision of care and allocate them to a specific level of care.

Medical necessity

The assessment of medical necessity is problematical in screening tests. On the one hand, it depends on the question as to whether the reason for the investigation is an infectious disease; a screening test after infections could potentially be medically necessary for reasons of public health protection. However, the aim of screening tests is mainly to identify individual diseases that do not necessarily endanger or present a burden to others. In this situation, there is no medical necessity to protect others.

The decisive factor for the introduction of a screening programme is then the answer to the question as to whether there is sufficient evidence of a benefit of the programme and whether the population-based weighing of potential benefits and harms leads to a positive result. Both the frequency of events and their severity are relevant to both the benefit and harm of a screening programme. It is an assessment in which, for example, the reduction in morbidity and mortality have to be considered against the necessary expenditure and potential disadvantages, such as over-diagnoses and an increased demand for tests to clarify findings.

The following estimate could be made for universal newborn hearing screening in Germany: According to the Federal Office of Statistics, a total of 686000 children were born in 2005 (see also http://www.destatis.de/presse/deutsch/pm2006/p3300023.htm). With a prevalence of hearing impairment of 0.12%, one would expect 823 children with hearing impairment. Assuming a sensitivity of 90% and an acceptance of the screening programme of 95%, 704 of 823 of these children would be identified in UNHS (correct positive results), 119 children (15%) would not be identified.

For children with no hearing impairment, the programme would have the following consequences: With a participation rate of 95%, a test would be performed in 645183

children with normal hearing from which they had no benefit. With a specificity of 98%, 12 904 would receive a false positive result.

Overall, 13 608 (12 904 plus 704) children with a positive result would undergo further diagnostic clarification to identify the 704 children with hearing impairment.

Even if a screening test has been introduced, the assessment of the individual medical necessity is a subjective decision regarding the individual case. By definition, the target group of screening tests are symptom-free persons for whom there is precisely no specifically-founded necessity to apply a measure. The reason for a screening test is usually a theoretical and rare risk, which always leave the individual the free choice of deciding against the test. Because the large majority of persons to be investigated are healthy, from the point of view of the individual, small disadvantages of the test can also be relevant for the decision, if they endanger the person’s health.

As described above, the hope to prevent or at least limit a life-long disadvantage belongs to the benefits of UNHS. However, this hope has not been reliably demonstrated. On the side of potential harm, there are inconveniences caused by unnecessary tests and diagnostic clarifications, although the assessment of these harmful effects also remains uncertain. However, compared with other screening tests, the potential of UNHS to cause harm is limited.

Ultimately, the assessment of this balance is not a question of medical necessity, but a societal and individual consideration of values.

7 CONCLUSION

There are indications that children with hearing impairment identified in UNHS programmes have advantages with respect to language development. Other patient-relevant outcomes, such as social aspects, quality of life, educational development and, finally, professional situation, have not been adequately investigated for evaluation.

If the Federal Joint Committee decides to introduce UNHS in Germany, it is recommended that suitable concomitant measures should be implemented at the same time to provide quality assurance. These measures should comprise the following factors: unambiguous case definitions; specification of clear quality standards (minimal coverage rate, maximum rate of abnormal tests in the first step, time of confirmatory diagnostic procedures, time of the start of provision of treatment); as complete a tracking as possible of children with abnormal test results and children diagnosed with congenital hearing impairment; and identification of all children with congenital hearing impairment (including those from periods or regions without screening) at a suitable point later in time.

8 LIST OF THE STUDIES INCLUDED IN THE EVALUATION

8.1 Screening studies included*

Other intervention studies (Ic)

Kennedy 2006 [5,77-83]**

- Kennedy CR, McCann DC, Campbell MJ, Law CM, Mullee M, Petrou S et al. Language ability after early detection of permanent childhood hearing impairment. N Engl J Med 2006; 354(20): 2131-2141.
- Kennedy C, McCann DC, Campbell MJ, Kimm L, Thornton R. Universal newborn screening for permanent childhood hearing impairment: an 8-year-follow-up of a controlled trial. Research Letter. Lancet 2005; 366(9486): 660-662.
- Mutton P, Peacock K. Neonatal hearing screens: Wessex re-visited. Comment. Lancet 2005; 366: 612-613.
- Kennedy C, Kimm L, Thornton R, Davis A. False positives in universal neonatal screening for permanent childhood hearing impairment. Lancet 2000; 356(9245): 1903-1904.
- Kennedy CR (Wessex Universal Neonatal Hearing Screening Trial Group). Controlled trial of universal neonatal screening for early identification of permanent childhood hearing impairment: coverage, positive predictive value, effect on mothers and incremental yield. Acta Paediatr Suppl 1999; 88(432): 73-75.
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- Watkin PM, Baldwin M, Dixon R, Beckman A. Maternal anxiety and attitudes to universal neonatal hearing screening. Br J Audiol 1998; 32(1): 27-37.
- Wessex Universal Neonatal Hearing Screening Trial Group. Controlled trial of universal neonatal screening for early identification of permanent childhood hearing impairment. Lancet 1998; 352(9145): 1957-1964.

* Classification of the evidence level according to the Code of Procedure of the Federal Joint Committee. Code of Procedure of the Federal Joint Committee §18 Classification and Evaluation of the Documents (2005) [Online text] [Access on 3.01.2007]. Accessed under http://www.g-ba.de/cms/upload/pdf/abs2/beschluesse/2005-09-20-VO-BANZ.pdf; Evidence Classification of Screening Studies Following the Classification of Therapeutic Methods (unless otherwise stated).
** Evidence classification of the subpopulation I (Wessex study) following the classification of diagnostic methods, as a corresponding category for the classification of therapeutic methods is not available; for subpopulation II: prospective comparative cohort study (IIb).

Retrospective comparative studies (III)

Yoshinaga-Itano 2001 [40,41]

- Yoshinaga-Itano C, Coulter D, Thomson V. Developmental outcomes of children with hearing loss born in Colorado hospitals with and without universal newborn hearing screening programs. Semin Neonatol 2001; 6(6): 521-529.
- Yoshinaga-Itano C, Coulter D, Thomson V. The Colorado Newborn Hearing Screening Project: effects on speech and language development for children with hearing loss. J Perinatol 2000; 20: S132-S137.

8.2 Treatment studies included

Retrospective comparative studies (III)

Markides 1986 [102]

- Markides A. Age at fitting of hearing aids and speech intelligibility. Br J Audiol 1986; 20(2): 165-167.

Moeller 2000 [103]

- Moeller MP. Early Intervention and Language Development in Children Who Are Deaf and Hard of Hearing. Pediatrics 2000; 106(3): e43.

Wake 2005 [104]

- Wake M, Poulakis Z, Hughes EK, Carey-Sargeant C, Rickards FW. Hearing impairment: a population study of age at diagnosis, severity, and language outcomes at 7-8 years. Arch Dis Child 2005; 90(3): 238-244.

Yoshinaga-Itano 1998 [105]

- Yoshinaga-Itano C, Sedey AL, Coulter DK, Mehl AL. Language of early- and later-identified children with hearing loss. Pediatrics 1998; 102(5): 1161-1171.

8.3 Diagnostic studies included

8.3.1 Studies that evaluated a 2-stage screening

Cross-sectional and cohort studies (IIb)

Kennedy 2005 (Wessex study) [77,79,80,83]

1. Kennedy C, McCann DC, Campbell MJ, Kimm L, Thornton R. Universal newborn screening for permanent childhood hearing impairment: an 8-year-follow-up of a controlled trial. Research Letter. Lancet 2005; 366(9486): 660-662.
2. Kennedy C, Kimm L, Thornton R, Davis A. False positives in universal neonatal screening for permanent childhood hearing impairment. Lancet 2000; 356(9245): 1903-1904.

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4. Wessex Universal Neonatal Hearing Screening Trial Group. Controlled trial of universal neonatal screening for early identification of permanent childhood hearing impairment. Lancet 1998; 352(9145): 1957-1964.

8.3.2 Studies that compared OAE with ABR

Cross-sectional and cohort studies (IIb)

Abbott Gabbard 1999 [106]

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Dort 2000 [107]

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Liao 1999 [111]

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Luppari 1999 [112]

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Reuter 1998 [113]

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APPENDIX A: Search strategies

SCREENING STUDIES

Regarding screening studies, the search strategies for the databases of the Cochrane Library, as well as EMBASE, CINAHL, PsycINFO, are missing (problems saving data); the search strategies are orientated towards the other searches performed for screening studies.

Overview of the electronic databases searched (screening studies)

	Date of primary search	Date of search update
MEDLINE	29.11.2005	01.06.2006
EMBASE	02.12.2005	01.06.2006
Clinical Trials	12.12.2005	29.08.2006
ERIC	12.12.2005	29.08.2006
CINAHL	02.12.2005	01.06.2006
PsycINFO	02.12.2005	01.06.2006
PSYNDEX	12.12.2005	29.08.2006
CDSR	12.12.2005	29.08.2006
Other Reviews	12.12.2005	29.08.2006
Economic Evaluations	12.12.2005	29.08.2006
Technology Assessments	12.12.2005	29.08.2006

Search strategies (screening studies)

	MEDLINE – Screening studies
1	child$.ti,ab,hw.
2	infant$.ti,ab,hw.
3	(newborn$ or (new adj1 born)).ti,ab,hw.
4	neonat$.ti,ab,hw.
5	(paediatri$ or pediatri$).ti,ab,hw.
6	exp CHILD/
7	exp INFANT/
8	or/1-7
9	exp Hearing Disorders/
10	(hearing adj (disorder$ or los$ or impair$)).ti,ab,hw.
11	9 or 10
12	exp MASS SCREENING/

13	screen$.ti,ab,hw.
14	((newborn$ or neonat$ or auditor$ or hearing) adj (screen$ or assess$)).ti,ab,hw.
15	or/12-14
16	8 and 11 and 15

	ERIC – Screening studies
1	screen$
2	hearing
3	1 AND 2
4	NEONAT$
5	newborn$
6	infant$
7	paediatr$
8	pediatr$
9	4 OR 5 OR 6 OR 7 OR 8
10	3 AND 9

	PSYNDEX – Screening studies
1	child* or infant* or newborn* or neonat* or paediatric or pediatric
2	hear*
3	oae or eoae or toae or teoae or dpoae or otoacoustic emission* or (oto adj acoustic emission*) or abr or aabr or dabr or bera or bear or eabr or (brainstem adj audiometry) or (brainstem adj audiometry adj response) or (brainstem adj auditory adj response) or (brainstem evoked response audiometry) or (evoked brainstem auditory response)
4	screen*
5	1 and 2 and 3 and 4

TREATMENT STUDIES

Regarding treatment studies, the search strategies for the databases of the Cochrane Library are missing (problems saving data); the search strategies are orientated towards the other searches performed for treatment studies.

Overview of the electronic databases searched (treatment studies)

	Date of the primary search	Date of the search update
MEDLINE	29.11.2005	01.06.2006
EMBASE	12.12.2005	01.06.2006
Clinical Trials	12.12.2005	29.08.2006
ERIC	12.12.2005	29.08.2006
CINAHL	12.12.2005	01.06.2006
PsycINFO	12.12.2005	01.06.2006
PSYNDEX	12.12.2005	29.08.2006
CDSR	12.12.2005	29.08.2006
Other Reviews	12.12.2005	29.08.2006
Economic Evaluations	12.12.2005	29.08.2006
Technology Assessments	12.12.2005	29.08.2006

Search strategies (treatment studies)

	MEDLINE – Treatment studies
1	child$.ti,ab,hw.
2	infant$.ti,ab,hw.
3	(newborn$ or (new adj1 born)).ti,ab,hw.
4	neonat$.ti,ab,hw.
5	(paediatri$ or pediatri$).ti,ab,hw.
6	exp child/
7	exp infant/
8	or/1-7
9	exp hearing disorders/
10	exp hearing impaired persons/
11	(hearing adj (disorder$ or los$ or impair$)).ti,ab,hw.

12	hearing.ti,ab,hw
13	or/9-12
14	exp “rehabilitation of hearing impaired”/
15	exp hearing aids/
16	exp Cochlea implantation/
17	cochlea$ implant$.ti,ab,hw.
18	(hearing adj (aid$ or device$ or prosthes$)).ti,ab,hw.
19	or/14-18
20	exp clinical trials/
21	exp research design/
22	exp treatment outcome/
23	exp double-blind method/
24	exp single-blind method/
25	((single or double or triple) adj3 blind$3).ti,ab,hw.
26	random$.ti,ab,hw.
27	controlled clinical trial.pt
28	practice guideline.pt
29	clinical trial.pt
30	(clinical adj trial$1).ti,ab,hw.
31	exp epidemiological research design/
32	(control$3 adj trial$1).ti,ab,hw.
33	randomi#ed controlled trial.pt
34	comparative study/
35	pla#ebo$.ti,ab,hw.
36	or/20-35
37	8 and 13 and 19 and 36

	EMBASE – Treatment studies
1	child$.ti,ab,hw.
2	infant$.ti,ab,hw.
3	(newborn$ or (new adj1 born)).ti,ab,hw.
4	neonat$.ti,ab,hw.
5	(paediatri$ or pediatri$).ti,ab,hw.
6	or/1-5
7	exp Auditory Rehabilitation/
8	exp hearing aid/
9	exp cochlea prosthesis/
10	exp implantation/

11	cochlea$ implant$.ti,ab,hw.
12	(hearing adj (aid$ or device$ or prosthes$)).ti,ab,hw.
13	or/7-12
14	Clinical Trial/
15	Double Blind Procedure/
16	Single Blind Procedure/
17	((single or double or triple) adj3 blind$3).ti,ab,hw.
18	random$.ti,ab,hw.
19	(clinical adj trial$1).ti,ab,hw.
20	(control$3 adj trial$1).ti,ab,hw.
21	Randomized Controlled Trial/
22	exp comparative study/
23	pla#ebo$.ti,ab,hw.
24	or/14-23
25	6 and 13 and 24

	ERIC – Treatment studies
1	hearing ADJ los$
2	hearing ADJ impair$
3	hearing ADJ disorder$
4	1 OR 2 OR 3
5	hearing ADJ aid$
6	cochlea$
7	rehabilitation
8	hearing ADJ device$
9	5 OR 6 OR 7 OR 8
10	therap$
11	treatment$
12	random$
13	10 OR 11 OR 12
14	4 AND 9 AND 13

	CINAHL – Treatment studies
1	child$.ti,ab,hw.
2	infant$.ti,ab,hw.
3	(newborn$ or (new adj1 born)).ti,ab,hw.
4	neonat$.ti,ab,hw.

5	(paediatri$ or pediatri$).ti,ab,hw.
6	or/1-5
7	exp hearing aid/
8	exp "Rehabilitation of Hearing Impaired"/
9	exp Cochlea Implant/
10	cochlea$ implant$.ti,ab,hw.
11	(hearing adj (aid$ or device$ or prosthes$)).ti,ab,hw.
12	or/7-11
13	exp Clinical Trials/
14	exp Study Design/
15	exp Double-Blind Studies/
16	exp Single-Blind Studies/
17	((single or double or triple) adj3 blind$3).ti,ab,hw.
18	random$.ti,ab,hw.
19	(clinical adj trial$1).ti,ab,hw.
20	(control$3 adj trial$1).ti,ab,hw.
21	Randomized Controlled Trial/
22	exp comparative study/
23	pla#ebo$.ti,ab,hw.
24	or/13-23
25	6 and 12 and 24

	PsycINFO – Treatment studies
1	child$.ti,ab,hw.
2	infant$.ti,ab,hw.
3	(newborn$ or (new adj1 born)).ti,ab,hw.
4	neonat$.ti,ab,hw.
5	(paediatri$ or pediatri$).ti,ab,hw.
6	or/1-5
7	exp hearing aid/
8	exp Cochlea Implant/
9	cochlea$ implant$.ti,ab,hw.
10	(hearing adj (aid$ or device$ or prosthes$)).ti,ab,hw.
11	or/7-10
12	exp Clinical Trials/
13	((single or double or triple) adj3 blind$3).ti,ab,hw.
14	random$.ti,ab,hw.
15	(clinical adj trial$1).ti,ab,hw.

16	(control$3 adj trial$1).ti,ab,hw.
17	pla#ebo$.ti,ab,hw.
18	exp Treatment Outcomes/
19	or/12-18
20	6 and 11 and 19

	PSYNDEX – Treatment studies
1	child* or infant* or newborn* or neonat* or paediatric or pediatric
2	hear*
3	Cochlea implant* or (rehabilitation adj hear*) or (hear* adj aid*)
4	1 and 2 and 3

DIAGNOSTIC STUDIES

Regarding diagnostic studies, the search strategies for the databases of the Cochrane Library are missing (problems saving data); the search strategies are orientated towards the other searches performed for diagnostic studies.

Overview of the electronic databases searched (diagnostic studies)

	Date of the primary search	Date of the search update
MEDLINE	15.11.2005	01.06.2006
EMBASE	12.12.2005	01.06.2006
Clinical Trials	12.12.2005	29.08.2006
ERIC	12.12.2005	29.08.2006
CINAHL	12.12.2005	01.06.2006
PsycINFO	12.12.2005	01.06.2006
PSYNDEX	12.12.2005	29.08.2006
CDSR	12.12.2005	29.08.2006
Other Reviews	12.12.2005	29.08.2006
Economic Evaluations	12.12.2005	29.08.2006
Technology Assessments	12.12.2005	29.08.2006

Search strategies (diagnostic studies)

	MEDLINE – Diagnostic test procedures
1	exp Hearing Disorders/
2	(deaf or deafness).ti,ab,hw.
3	(hearing adj (disorder$ or los$ or impair$)).ti,ab,hw.
4	or/1-3
5	exp CHILD/
6	exp infant/
7	child$.ti,ab,hw.
8	infant$.ti,ab,hw.
9	neonat$.ti,ab,hw.
10	newborn$.ti,ab,hw.
11	(paediatri$ or pediatri$).ti,ab,hw.
12	or/5-11

13	exp Diagnostic Techniques, Otological/
14	exp Otoacoustic Emissions, spontaneous/
15	(oae or eoae or toae or teoae or dpoae).ti,ab,hw.
16	(otoacoustic emission$ or (oto adj1 acoustic emission$)).ti,ab,hw.
17	exp Evoked Potentials, Auditory/
18	(abr or aabr or dabr).ti,ab,hw.
19	(bera or bear or eabr).ti,ab,hw.
20	((brainstem adj audiometry) or (brainstem adj (audiometry or auditory) adj response)).ti,ab,hw.
21	(brainstem evoked response audiometry or evoked brainstem auditory response).ti,ab,hw.
22	(auditory adj3 (brainstem or brain stem) adj3 response$).ti,ab,hw.
23	or/13-22
24	exp "Sensitivity and Specificity"/
25	DIAGNOSIS/
26	diagnos$.ti,ab,hw.
27	sensitiv$.ti,ab,hw.
28	predict$.ti,ab,hw.
29	accura$.ti,ab,hw.
30	or/24-29
31	4 and 12 and 23 and 30

	EMBASE – Diagnostic test procedures
1	exp Hearing Disorder/
2	(deaf or Deafness).ti,ab,hw.
3	(hearing adj (disorder$ or los$ or impair$)).ti,ab,hw.
4	or/1-3
5	Child/
6	Infant/
7	child$.ti,ab,hw.
8	infant$.ti,ab,hw.
9	neonat$.ti,ab,hw.
10	newborn$.ti,ab,hw.
11	(paediatri$ or pediatri$).ti,ab,hw.
12	or/5-11
13	exp otoacoustic emission/
14	(oae or eoae or toae or teoae or dpoae).ti,ab,hw.
15	(otoacoustic emission$ or (oto adj1 acoustic emission$)).ti,ab,hw.
16	exp evoked response/
17	(abr or aabr or dabr).ti,ab,hw.

18	(bera or bear or eabr).ti,ab,hw.
19	((brainstem adj audiometry) or (brainstem adj (audiometry or auditory) adj response)).ti,ab,hw.
20	(brainstem evoked response audiometry or evoked brainstem auditory response).ti,ab,hw.
21	(auditory adj3 (brainstem or brain stem) adj3 response$).ti,ab,hw.
22	or/13-21
23	exp diagnostic accuracy/
24	exp "Sensitivity and Specificity"/
25	sensitiv$.ti,ab,hw.
26	diagnos$.ti,ab,hw.
27	predict$.ti,ab,hw.
28	accura$.ti,ab,hw.
29	detect$.ti,ab,hw.
30	or/23-29
31	4 and 12 and 22 and 30

	ERIC – Diagnostic test procedures
1	oae OR eoae OR toae OR teoae OR dpoae
2	otoacoustic ADJ emission$
3	abr OR aabr OR dabr
4	auditory ADJ evoked ADJ potentials
5	bera OR eabr
6	1 OR 2 OR 3 OR 4 OR 5

	CINAHL – Diagnostic test procedures
1	exp Hearing Disorders/
2	(deaf or deafness).ti,ab,hw.
3	(hearing adj (disorder$ or los$ or impair$)).ti,ab,hw.
4	or/1-3
5	exp CHILD/
6	exp INFANT/
7	child$.ti,ab,hw.
8	infant$.ti,ab,hw.
9	neonat$.ti,ab,hw.
10	newborn$.ti,ab,hw.
11	(paediatri$ or pediatri$).ti,ab,hw.
12	or/5-11
13	exp Otoacoustic Emissions, Spontaneous/
14	(oae or eoae or toae or teoae or dpoae).ti,ab,hw.
15	(otoacoustic emission$ or (oto adj1 acoustic emission$)).ti,ab,hw.

16	exp Evoked Potentials, Auditory/
17	(abr or aabr or dabr).ti,ab,hw.
18	(bera or bear or eabr).ti,ab,hw.
19	((brainstem adj audiometry) or (brainstem adj (audiometry or auditory) adj response)).ti,ab,hw.
20	(brainstem evoked response audiometry or evoked brainstem auditory response).ti,ab,hw.
21	(auditory adj3 (brainstem or brain stem) adj3 response$).ti,ab,hw.
22	or/13-21
23	exp "Sensitivity and Specificity"/
24	DIAGNOSIS/
25	diagnos$.ti,ab,hw.
26	sensitiv$.ti,ab,hw.
27	predict$.ti,ab,hw.
28	accura$.ti,ab,hw.
29	detect$.ti,ab,hw.
30	or/23-29
31	4 and 12 and 22 and 30

	PsycINFO – Diagnostic test procedures
1	exp Hearing Disorders/
2	(deaf or deafness).ti,ab,hw.
3	(hearing adj (disorder$ or los$ or impair$)).ti,ab,hw.
4	or/1-3
5	child$.ti,ab,hw.
6	infant$.ti,ab,hw.
7	neonat$.ti,ab,hw.
8	newborn$.ti,ab,hw.
9	(paediatri$ or pediatri$).ti,ab,hw.
10	or/5-9
11	exp Auditory Evoked Potentials/
12	(oae or eoae or toae or teoae or dpoae).ti,ab,hw.
13	(otoacoustic emission$ or (oto adj1 acoustic emission$)).ti,ab,hw.
14	(abr or aabr or dabr).ti,ab,hw.
15	(bera or bear or eabr).ti,ab,hw.
16	((brainstem adj audiometry) or (brainstem adj (audiometry or auditory) adj response)).ti,ab,hw.
17	(brainstem evoked response audiometry or evoked brainstem auditory response).ti,ab,hw.
18	(auditory adj3 (brainstem or brain stem) adj3 response$).ti,ab,hw.
19	or/11-18
20	DIAGNOSIS/

21	sensitiv$.ti,ab,hw.
22	specificit$.ti,ab,hw.
23	diagnos$.ti,ab,hw.
24	predict$.ti,ab,hw.
25	accura$.ti,ab,hw.
26	detect$.ti,ab,hw.
27	or/20-26
28	4 and 10 and 19 and 27

	PSYNDEX – Diagnostic test procedures
1	child* or infant* or newborn* or neonat* or paediatric or pediatric
2	hear* or deaf or deafness or (hearing adj impair*) or (hearing adj los*) or (hearing adj disorder*)
3	oae or eoae or toae or teoae or dpoae or otoacoustic emission* or (oto adj acoustic emission*) or abr or aabr or dabr or bera or bear or eabr or (brainstem adj audiometry) or (brainstem adj audiometry adj response) or (brainstem adj auditory adj response) or (brainstem evoked response audiometry) or (evoked brainstem auditory response)
4	sensitiv* or specifi* or diagnos* or predict* or accura*
5	1 and 2 and 3 and 4

APPENDIX B.1: List of studies reviewed in full text and excluded (listed by reasons for exclusion)

Publications that were identified in the process of the literature search and were initially regarded as potentially relevant are listed here. These publications were excluded after review of the full texts, as they did not fulfil the inclusion criteria or fulfilled the exclusion criteria. An overview of studies that in principle fulfilled the inclusion criteria but were not included in the evaluation, as well as an overview of the publications reviewed within the framework of the submission of comments on the preliminary report, can be found in Appendix B.2 and Appendix G.

Screening (N = 63)

Inclusion criterion I1 not fulfilled

None

Inclusion criterion I2 not fulfilled

None

Inclusion criterion I3 not fulfilled

1. Abbott Gabbard S, Northern JL, Yoshinaga-Itano C. Hearing screening in newborns under 24 hours of age. Semin Hear 1999; 20(4): 291-305.
2. Allen RL, Stuart A, Everett D, Elangovan S. Preschool hearing screening: pass/refer rates for children enrolled in a head start program in eastern North Carolina. Am J Audiol 2004; 13(1): 29-38.
3. Boshuizen HC, van der Lem GJ, Kauffman-de Boer MA, van Zanten GA, Oudesluys-Murphy AM, Verkerk PH. Costs of different strategies for neonatal hearing screening: a modelling approach. Arch Dis Child Fetal Neonatal Ed 2001; 85(3): 177-181.
4. Bubbico L, Bartolucci MA, Broglio D. The newborn hearing screening in Italy. Riv Ital Pediatr 2005; 31(5): 290-292.
5. Buser K, Bietenduwel A, Krauth C, Jalilvand N, Meyer S, Reuter G et al. Modellprojekt Neugeborenen-Hörscreening in Hannover (Zwischenergebnisse). Gesundheitswesen 2003; 65(3): 200-203.
6. Clarke P, Iqbal M, Mitchell S. A comparison of transient-evoked otoacoustic emissions and automated auditory brainstem responses for pre-discharge neonatal hearing screening. Int J Audiol 2003; 42(8): 443-447.
7. Delb W, Gortner L, Hohenberg G. Konzept eines kombinierten Neugeborenenhör- und Stoffwechselscreenings im Saarland. Universitätskliniken des Saarlandes; Homburg/Saar: Universitätskliniken des Saarlandes/Scientific Learning Systems 2006.
8. Delb W, Merkel D, Pilorget K, Schmitt J, Plinkert PK. Effectiveness of a TEOAE-based screening program. Can a patient-tracking system effectively be organized using

modern information technology and central data management? Eur Arch Otorhinolaryngol 2004; 261(4): 191-196.

9. Finitzo T, Albright K, O'Neal J. The newborn with hearing loss: detection in the nursery. Pediatrics 1998;102(6): 1452-1460.

10. Gonzalez de Dios J, Mollar Mageres J, Rebagliato Russo M. [Evaluation of a universal screening program for hypacusia in neonates]. An Pediatr (Barc) 2005; 62(2): 135-140.

11. Gonzalez de DJ, Mollar MJ. [Neonatal hypoacusis global screening: tests assessment against program assessment]. Acta Otorrinolaringol Esp 2005; 56(7): 331-334.

12. Gorga MP, Preissler K, Simmons J, Walker L, Hoover B. Some issues relevant to establishing a universal newborn hearing screening program. J Am Acad Audiol 2001; 12(2): 101-112.

13. Gravel J, Berg A, Bradley M, Cacace A, Campbell D, Dalzell L et al. New York State universal newborn hearing screening demonstration project: effects of screening protocol on inpatient outcome measures. Ear Hear 2000; 21(2): 131-140.

14. Gravel JS, White KR, Johnson JL, Widen JE, Vohr BR, James M et al. A multisite study to examine the efficacy of the otoacoustic emission/automated auditory brainstem response newborn hearing screening protocol: recommendations for policy, practice, and research. Am J Audiol 2005; 14(2): 217-S228.

15. Grill E, Hessel F, Siebert U, Schnell-Inderst P, Kunze S, Nickisch A et al. Comparing the clinical effectiveness of different new-born hearing screening strategies: A decision analysis. BMC Public Health 2005; 5(12): 1-10.

16. Gross M, Buser K, Freitag U, Hess MM, Hesse V, Hildmann A et al. Universelles Hörscreening bei Neugeborenen – Empfehlungen zu Organisation und Durchführung des universellen Neugeborenen-Screenings auf angeborene Hörstörungen in Deutschland. Z Geburtshilfe Neonatol 2004; 208(6): 239-245.

17. Hahn M, Lamprecht-Dinnesen A, Heinecke A, Hartmann S, Bülbül S, Schröder G et al. Hearing screening in healthy newborns: feasibility of different methods with regard to test time. Int J Pediatr Otorhinolaryngol 1999; 51(2): 83-89.

18. Hatzopoulos S, Pelosi G, Petruccelli J, Rossi M, Vigi V, Chierici R et al. Efficient otoacoustic emission protocols employed in a hospital-based neonatal screening program. Acta Otolaryngol 2001; 121(2): 269-273.

19. Hayes D. Screening methods: Current status. Ment Retard Dev Disabil Res Rev 2003; 9(2): 65-72.

20. Helfand M, Thompson DC, Davis R, McPhillips H, Homer CJ, Lieu TL. Newborn hearing screening. Rockville: Agency for Healthcare Research and Quality, 2001.

21. Hess M, Wiesner T, von der Wense A, Hamburger Arbeitskreis für Hörscreening bei Neugeborenen H.A.H.N.e.V. Datenanalyse des Hamburger Hörscreening-Projektes: Auswertungszeitraum 01. August 2002 bis 31. Juli 2005. Hamburg: H.A.H.N. e.V.; 2006. (Unveröffentlichter Bericht: kann bei Bedarf im IQWiG eingesehen werden.)

22. Hyde ML. Newborn hearing screening programs: overview. J Otolaryngol 2005; 34(Suppl 2): S70-S80.

23. Interdisziplinäre Konsensus-Konferenz für das Neugeborenen-Hörscreening. Universelles Hörscreening bei Neugeborenen: Empfehlungen zu Organisation und Durchführung des universellen Neugeborenen-Screenings auf angeborene Hörstörungen in Deutschland. HNO 2004; 52(11): 1020-1027.

24. Johnson JL, White KR, Widen JE, Gravel J, Vohr BR, James M et al. A multisite study to examine the efficacy of the otoacoustic emission/automated auditory brainstem response newborn hearing screening protocol: introduction and overview of the study. Am J Audiol 2005; 14(2): 178-185.

25. Joseph R, Tan HK, Low KT, Ng PG, Tunnel J, Mathew S. Mass newborn screening for hearing impairment. Southeast Asian J Trop Med Public Health 2003; 34(Suppl 3): 229-230.

26. Kaldestad RH, Wingaard L, Hansen TW. [Screening for congenital hearing loss: a pilot project]. Tidsskr Nor Laegeforen 2002; 122(22): 2190-2193.

27. Kemper AR, Downs SM. A cost-effectiveness analysis of newborn hearing screening strategies. Arch Pediatr Adolesc Med 2000; 154(5): 484-488.

28. Kennedy CR. Controlled trial of universal neonatal screening for early identification of permanent childhood hearing impairment: coverage, positive predictive value, effect on mothers and incremental yield. Wessex Universal Neonatal Screening Trial Group. Acta Paediatr Suppl 1999; 88(432): 73-75.

29. Kennedy CR. Neonatal screening for hearing impairment. Arch Dis Child 2000; 83(5): 377-383.

30. Kerschner JE, Meurer JR, Conway AE, Fleischfresser S, Cowell MH, Seeliger E et al. Voluntary progress toward universal newborn hearing screening. Int J Pediatr Otorhinolaryngol 2004; 68(2): 165-174.

31. Kerschner JE. Neonatal hearing screening: to do or not to do. Pediatr Clin North Am 2004; 51(3): 725-736.

32. Law J, Boyle J, Harris F, Harkness A, Nye C. Screening for speech and language delay: a systematic review of the literature. Health Technol Assess 1998; 2(9): 1-184.

33. Lemons J, Fanaroff A, Stewart EJ, Bentkover JD, Murray G, Diefendorf A. Newborn hearing screening: costs of establishing a program. J Perinatol 2002; 22(2): 120-124.

34. Low WK, Pang KY, Ho LY, Lim SB, Joseph R. Universal newborn hearing screening in Singapore: the need, implementation and challenges. Ann Acad Med Singapore 2005; 34(4): 301-306.

35. McNellis EL, Klein AJ. Pass/fail rates for repeated click-evoked otoacoustic emission and auditory brain stem response screenings in newborns. Otolaryngol Head Neck Surg 1997; 116(4): 431-437.

36. Mehl AL, Thomson V. The Colorado newborn hearing screening project, 1992-1999: on the threshold of effective population-based universal newborn hearing screening. Pediatrics 2002; 109(1): E7.

37. Molini E, Ricci G, Baroni S, Ciorba A, Bellocci A, Simoncelli C. [Identifying congenital hearing impairment. Personal experience based on selective hearing screening]. Acta Otorhinolaryngol Ital 2004; 24(3): 109-116.

38. Molloy J, Kei J, Smyth V, McPherson B, Young J, Tudehope D et al. Distortion product otoacoustic emissions in neonates and two-month-old infants. Austral J Audiol 1999; 21(2): 65-76.

39. Murray G, Ormson MC, Loh MH, Ninan B, Ninan D, Dockery L et al. Evaluation of the Natus ALGO 3 Newborn Hearing Screener. J Obstet Gynecol Neonatal Nurs 2004; 33(2): 183-190.

40. Nawka T. Das Universelle Neugeborenen-Hörscreening in Mecklenburg-Vorpommern nach 3 Jahren. Ernst Moritz Universität Greifswald, Klinik für HNO, Kopf- und Halschirurgie, Abteilung Phoniatrie und Pädaudiologie; 2006. (Unveröffentlichter Bericht: kann bei Bedarf im IQWiG eingesehen werden.)

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50. Russ SA, Kuo AA, Poulakis Z, Barker M, Rickards F, Saunders K et al. Qualitative analysis of parents' experience with early detection of hearing loss. Arch Dis Child 2004; 89(4): 353-8.

51. Saiz VG, Ramirez R, Benavides M, Mateos M, Morera C. [Validity of hand-held systems for otoacoustic emissions in hearing screening]. Acta Otorrinolaringol Esp 2001; 52(1): 3-6.

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Inclusion criterion I4 not fulfilled

None

Exclusion criterion E1 fulfilled

None

Exclusion criterion E2 fulfilled

None

Treatment (N = 53)

Not suited for a direct comparison

Inclusion criterion I1 not fulfilled

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Inclusion criterion I2 not fulfilled

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Inclusion criterion I3 not fulfilled

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Inclusion criterion I4a not fulfilled

None

Inclusion criterion I4b not fulfilled

None

Exclusion criterion E1 fulfilled

None

Exclusion criterion E2 fulfilled

None

Diagnostics (N = 140)

Inclusion criterion I2 not fulfilled

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Inclusion criterion I2a not fulfilled

None

Inclusion criterion I2b not fulfilled

None

Inclusion criterion I3 not fulfilled

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Inclusion criterion I4 not fulfilled

None

Exclusion criterion E1a fulfilled

None

Exclusion criterion E1b fulfilled

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Exclusion criterion E2 fulfilled

None

Exclusion criterion E3 fulfilled

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APPENDIX B.2: List of studies reviewed in full text and not included in the evaluation

Treatment (N = 15)

Not suited for an indirect comparison (see explanation in Section 5.2.3.1)

1. Geers AE, Tobey EA. Longitudinal comparison of the benefits of cochlear implants and tactile aids in a controlled educational setting. 1995; 166: S328-S329.
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Diagnostics (N = 3)

Studies that compared OAE with OAE

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APPENDIX C: List of screened systematic reviews

1. Agence Nationale d'Accréditation et d'Évaluation en Santé. Évaluation clinique et économique du dépistage néonatal de la surdité permanente par les otoémissions acoustiques. Paris: ANAES; 1999.
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APPENDIX D: Enquiries about studies and responses from authors

Available in German only under:

http://www.iqwig.de/download/S05-01_Abschlussbericht_Frueherkennungsuntersuchung_von_Hoerstoerungen_bei_Neugeborenen.pdf

APPENDIX E: German Professional Society of Special Teachers for Persons with Hearing Impairment – Data on Early Rehabilitation and on School Placement of Children with Hearing Impairment in the Federal State of Hesse

Available in German only under:

http://www.iqwig.de/download/S05-01_Abschlussbericht_Frueherkennungsuntersuchung_von_Hoerstoerungen_bei_Neugeborenen.pdf

APPENDIX F: Meeting minutes of the scientific debate

Available in German only under:

http://www.iqwig.de/download/S05-01_Abschlussbericht_Frueherkennungsuntersuchung_von_Hoerstoerungen_bei_Neugeborenen.pdf

APPENDIX G: List of the literature named in the comments on the preliminary report

Except for English-language references, available in German only under:

http://www.iqwig.de/download/S05-01_Abschlussbericht_Frueherkennungsuntersuchung_von_Hoerstoerungen_bei_Neugeborenen.pdf

APPENDIX H: Comments on the preliminary report

Available in German only under:

http://www.iqwig.de/download/S05-01_Abschlussbericht_Frueherkennungsuntersuchung_von_Hoerstoerungen_bei_Neugeborenen.pdf