Draft for consultation

Screening for Autism Spectrum Disorders in Children below the age of 5 years

A draft report
for the UK National Screening Committee

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Introduction

1. This paper reviews screening for autism spectrum disorders (ASD) in children below the age of five years against the UK National Screening Committee criteria for appraising the viability, effectiveness and appropriateness of a screening programme (UK National Screening Committee 2003). The appraisal stops short of most of the criteria for appraising the programme as a whole, because gaps in the evidence regarding the test and the treatment suggest that implementation of a screening programme would be premature. This paper is based on a literature search conducted by the National Screening Committee in November 2010. Full details of the search strategy are set out in Appendix A.

2. Autism spectrum disorders (ASD) are complex developmental disorders, behaviourally defined, that include a range of possible developmental impairments in reciprocal social interaction and communication, and also a stereotyped, repetitive or limited, behavioural repertoire. Classical autism was described by Kanner in 1944 (Matson et al 2007). In 1980 the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM III) introduced the concept of ASD, which includes people with some, but not all of the features of classical autism. ASD now includes autism, Asperger's syndrome and pervasive developmental disorders – not otherwise specified (PDD-NOS). Studies of screening and early intervention for children with ASD below the age of five years rarely include children with Asperger's syndrome, because this is not usually diagnosed till later in childhood. Table 1 (slightly modified from Levy et al 2009) summarises the main features of these three conditions.

Table 1: main features of autism, Asperger's syndrome and PDD-NOS

	Autism	Asperger's syndrome	PDD-NOS
Age of recognition (diagnosis)	yrs (3-5 yrs)	>3 yrs (6-8 yrs)	Variable
Regression?	About 25% (social or communication)	No	Variable
Sex ratio (M:F)	2:1	4:1	M>F (variable)
Socialisation	Poor	Poor	Variable
Communication	Delayed, deviant; might be non-verbal	Variable (circumscribed interests)	Variable
Behaviour	More impaired than in Asperger's syndrome or PDD-NOS (includes stereotypy)		Variable
Intellectual disability	>60%	Mild to none	Mild to severe
Cause	More likely to establish genetic or other cause than in Asperger's syndrome or PDD-NOS	Variable	Variable
Seizures	25% over lifespan	Roughly 10%	Roughly 10%
Outcome	Poor to fair	Fair to good	Fair to good

Current screening policy

3. A 2006 review of screening for ASD against the NSC criteria reported that there was no screening test suitable for use in a population setting that has been fully validated, and that there was insufficient evidence regarding the effectiveness of interventions (Williams and Brayne 2006). In July 2009 the Child Health Sub-Group of the NSC reviewed the evidence on screening for autism and decided that the introduction of screening could not be recommended to the UK NSC. The current UK National Screening Committee policy is that whole population screening for autism in children should not be offered (UK National Screening Committee 2011).

4. In the USA the U.S. Preventive Services Task Force (USPSTF) does not have any recommendation regarding screening for autism. It has considered the broader topic of screening for speech and language delay in preschool children, and concluded that the evidence is insufficient to recommend for or against routine use of brief, formal screening instruments in primary care to detect speech and language delay in children up to 5 years of age (USPSTF 2006)**.** The Centers for Disease Control and Prevention takes a different view, recommending universal screening for both developmental delays and ASD. It recommends that all children should be screened for developmental delays and disabilities during regular well-child doctor visits at ages 9 months, 18 months, and 24 or 30 months. In addition, it recommends that all children should be screened specifically for ASD during regular well-child doctor visits at ages 18 months and 24 months (Centers for Disease Control and Prevention 2011a). This endorsement of universal screening for ASD is presumably based on confidence in the effectiveness of early intervention, since the CDC webpage on treatments for ASD claims that 'research shows that early intervention treatment services can greatly improve a child's development' (Centers for Disease Control and Prevention 2011b). However, the two references cited in support of this statement (Handleman and Harris 2000, National Research Council 2001) are both a decade old and therefore predate almost all the randomised controlled trials (RCTs) of early intervention treatment services for ASD. The 'treatment' section of this review presents the findings, and limitations, of the 14 identified RCTs of early intervention for ASD.

The Condition

The condition should be an important health problem

5. Up to one per cent of children may have ASD. Most studies of the prevalence of autism and ASD include mainly school age children, with few studies measuring prevalence in children under five. There is wide variation in the prevalence estimates for autism and ASD across individual studies, and systematic reviews have produced somewhat varying estimates of prevalence. Williams et al (2006) estimated the prevalence of autism as 7.1 per 10,000 (95% CI 1.6-30.6) and the prevalence of ASD as 20.0 per 10,000 (4.9-82.1). Fombonne (2009) estimated the prevalence of autism as 20.6 per 10,000 (1.6-30.6) and the prevalence of PDD-NOS as around 30 per 10,000. In prevalence studies conducted in the UK, Chakrabarti and Fombonne (2005) estimated the prevalence of autism among 4-6 year olds in part of the Midlands as 18.9 per 10,000 (14.1–25.0), and the prevalence of ASD as 59.8 per 10,000 (50.8-69.9). Baird et al (2006) produced somewhat higher estimates for the South Thames region, with the prevalence of autism among 9-10 year olds as 38.9 per 10,000 (29.9-47.8) and the prevalence of ASD as 116.1 per 10,000 (90.4-141.8).

6. There has been a rise in the recognised prevalence of autism and ASD over time, but it remains uncertain whether this reflects an increase in the true prevalence, or other factors. Fombonne (2009) concluded that the rise is at least partly explained by broadening of the diagnostic concept and criteria for diagnosing autism and ASD. King and Bearman (2009) concluded that diagnostic substitution (from categories such as 'mental retardation' to 'autism') accounted for a quarter of the increase in the prevalence in California from 1992 to 2005. Nassar et al (2009) concluded that the rise in the incidence of ASD in Western Australia was related to changes in diagnostic practices and service provision. Age at diagnosis has also been reducing and this may also contribute to a rising prevalence in children (Parner et al 2008, Hertz-Picciotto and Delwiche 2009, Leonard et al 2010). Increased awareness amongst parents and clinicians has also been suggested as a cause of increased assessment and diagnosis of autism (Leonard et al 2010).

7. Notwithstanding these uncertainties regarding the prevalence of autism and ASD, the cost of ASD to individuals, families and society is substantial. Knapp et al (2009) estimated the cost of supporting children with ASD in the UK as £2.7 billion per year, and the cost of supporting adults with ASD as £25 billion per year. The largest costs for children with ASD are for education; the largest costs for adults are the opportunity cost of lost employment for individuals with ASD, and the cost of accommodation for those with intellectual disability.

The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage

8. The currently accepted 'gold standard' for diagnosing ASD in children under the age of five years is clinical judgement (Kleinman et al 2008a), The reliability of these clinical diagnoses could be assessed by asking different clinicians who are blind to each other's conclusions to assess a group of children with suspected ASD, either at the same time or after an interval, and comparing their diagnoses. To provide the best possible information about the natural history of 'ASD' in children who are given this diagnosis in early childhood through a population-based screening programme, studies should ideally include all the children with ASD in a defined population, including those who have been detected through a population-based screening programme, and not just those who have been referred to a clinic (Centre for Reviews and Dissemination 2009:113). This is important because cohorts of toddlers who

have been referred to a clinic may be more severely affected, and hence easier to diagnose reliably, than toddlers who have not been referred to clinic but might be detected through a population-based screening programme.

9. This review did not identify any studies that meet both the criteria described in paragraph eight i.e. that include all the children with ASD in a defined population, and use at least two clinicians who are blind to each others' diagnoses.

Stability of ASD diagnoses in screen-detected children

10. Four studies (Cox et al 1999, Sutera et al 2007, Kleinman et al 2008a, Van Daalen et al 2009) assessed the stability of diagnosis in screen-detected ASD, but in none of them were the diagnoses at follow-up made by people who were blind to the initial diagnosis. In these four studies the stability of diagnoses made around the age of two years, up to re-assessment around the age of four years, was higher for 'autism' (range of reported stability = 63% to 70%) than for 'PDD-NOS' (33% to 67%); the more inclusive category 'ASD' is naturally more stable (75% to 100%) than either 'autism' or 'PDD-NOS' (Table 2).

Table 2: Diagnostic stability of diagnoses of 'autism', PDD-NOS' and 'ASD' made at around two years of age

Reference	Screen-derived cohort?	T2 assessors blind to diagnosis at T1?	Number of children	Median age at T1 assessment (months)	Median age at T2 assessment (months)	'Autism': proportion of T1 diagnoses of that were stable till T2	'PDD-NOS': proportion of T1 diagnoses of that were stable till T2	'ASD' (includes both autism and PDD-NOS): proportion of T1 diagnoses of that were stable till T2
Cox 1999	Yes	No	12	20	42	6/9 (67%)	2/3 (67%)	12/12 (100%)
Sutera 2007	Yes	No	73	27	53	-	-	60/73 (83%)
Kleinman 2008	Yes	No	77	24	48	32/46 (70%)	5/15 (33%)	46/61 (75%)
Van Daalen 2009	Yes	No	53	23	42	25/40 (63%)	7/13 (54%)	46/53 (91%)
Lord 2005	No	Yes	130	24	108	71/84 (85%)	14/46 (30%)	124/130 (95%)
Charman 2005	No	No	26	24	84	22/26 (85%)	-	-
Turner 2006	No	No	25	31	109	16/18 (89%)	2/7 (29%)	22/25 (88%)
Turner and Stone 2007	No	No	48	29	53	20/38 (53%)	3/10 (30%)	30/48 (63%)
Chawarska 2009	No	no	61	22	47	32/43 (74%)	15/18 (83%)	61/61 (100%)

Stability of ASD diagnoses in clinic-referred children

11. Some studies of the stability of diagnoses of ASD in clinic-referred children have much longer periods of follow-up than those in screen-detected children, the longest being the cohort followed to nine years of age by Lord et al (2006). This study also has the merits of a large sample size and use of follow-up assessors who were blind to the original diagnoses. With the exception of a rather low stability for diagnoses of PDD-NOS (30%), this study reported figures for stability of diagnoses given at age two years that are slightly more favourable than those found in the four studies of screen-detected ASD described above: 85% for autistic disorder, and 95% for ASD as a whole. Diagnostic change was primarily accounted for by movement from PDD-NOS to autism.

12. Across the group of studies conducted with clinic-referred children who received their initial diagnosis around the age of two years, the ranges of estimates of the stability of diagnoses overlaps with those reported for screen-detected children: 53% to 89% for 'autism'; 29% to 83% for 'PDD-NOS'; and 63% to 100% for 'ASD'.

13. If one relies only on the data obtained from screen-detected cohorts, and overlooking the problem that none of them used blind assessment at follow-up, it is probably safe to conclude that about a third of children who are given a diagnosis of 'autism' at 20-23 months of age as a result of a screening programme, and up to a quarter of those identified as being within the broader category of 'ASD', are likely to lose these diagnoses by the age of four years.

14. These figures could reflect either the impact of early intervention, assuming it is effective, or over-diagnosis at age two. Whether early intervention can account for the movement of a third of two year olds out of the category of 'autism' depends on evidence from RCTs of the effectiveness of such intervention (see the section on 'treatment' below).

Risk of missed diagnoses during screening

15. This is addressed more fully in the section on the 'test' below, where the performance characteristics of various approaches to screening are reviewed. In the context of reviewing the natural history of ASD it is noteworthy that two prospective studies of children at high risk of ASDs suggest that there are several different onset patterns of ASD. In some children multiple signs of ASD, particularly impairments in social functioning and communication, are present by 14 months of age to such a degree that an expert might consider a diagnosis of ASD (Landa and Garrett-Mayer 2006). In other children, however, clear signs of ASDs are not present until later in the second year of life, or even until the third year (Landa et al 2007). This implies that screening around the age of two years would inevitably miss some cases, which has led some authors to call for screening for ASDs to begin by 18 months of age and be repeated at 24 and 36 months of age (Landa 2008).

Variability of prognosis within diagnostic category

16. Within diagnostic category, prognosis is very variable. Anderson et al (2009) assessed the development of adaptive social skills in 192 children who were diagnosed at age 2 years with autism, PDD-NOS or non-ASD developmental disabilities. They found that children with autism had the weakest social skills, but in all diagnostic categories improvement in social skills ranged from minimal to very dramatic. Strong expressive language skills were associated with better outcome in the autism group, and strong receptive language skills were associated with better outcome in the PDD-NOS group. The authors claimed that 'children with autism most at risk for problems with social adaptive abilities later in life can be identified with considerable accuracy at a very young age', but this conclusion is premature until the performance of these predictors of outcome has been validated in an independent sample of children with ASD.

All the cost-effective primary prevention interventions should have been implemented as far as practicable

17. Opportunities for primary prevention of ASDs are constrained by limited knowledge of their causes. About 10-15% of cases of ASD are associated with known genetic causes, such as fragile X syndrome and tuberous sclerosis (Levy et al 2009), but this knowledge does not lend itself to primary prevention strategies.

If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

18. Not relevant to screening for autism.

The Test

There should be a simple, safe, precise and validated screening test and The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed

19. Table 3 summarises the findings of studies that have assessed a variety of approaches to general population screening for ASD in early childhood. Most studies have assessed a specific screening tool, but two (Tebrugge et al 2004, Barbaro et al 2010) have evaluated routine child surveillance by health professionals. Tebrugge et al (2004) used community medical files to conduct a retrospective study of children aged 9-10 years in one district. This design allowed accurate assessment of the sensitivity of surveillance for detecting ASD (64% at the 2-year check, 94% at the 3.5-year check), but the authors did not describe any data from which positive predictive value might be estimated. Barbaro et al (2010) conducted a prospective study with limited follow-up, from which the positive predictive value of screening can be estimated (81%), but not sensitivity.

The following abbreviations are used for screening tools in Table 3:

CESDD	Checklist for Early Signs of Developmental Disorders
CHAT	CHecklist for Autism in Toddlers
ESAT	Early Screening of Autistic Traits questionnaire
M-CHAT	Modified CHecklist for Autism in Toddlers
YACHT-18	Young Autism and other developmental disorders CHeckup Tool

Table 3: Studies of screening tools or child surveillance for ASD

Ref	Screening tool	Users of the tool	Setting	Number screened	Mean months of age (range) at screen	Age in months up to which false negatives could be identified	Number of screen-positive cases of ASD	Sens	PPV	Comments
Tebrugge 2004	Routine Child Surveillance	Health professionals	UK	2,536	24 and 42	96-108	20	63% 94%	?	• Sensitivity data are for 'concerns noted at surveillance check'. Sensitivity lower at 2yr check than at 3.5yr check.
Dietz 2006	ESAT, then psychological assessment	Physicians, then psychologists	Nether-lands	31,724	15 (13-23)	42 (further follow-up due at age 6yrs)	18	?	25%	• Only 1.2% of children failed the initial screen with ESAT. • 31% refused psychological assessment, and another 27% refused clinical evaluation. • ASD diagnosis was dropped for 2/16 children who were available for assessment at 42 months.
Van Den Heuvel 2007	CHAT (2 rounds)	Public health nurses	Ireland	2,117	18?	?	3	?	43%	• Parents of 10 / 29 children who 'failed' first screen refused a second screen.
Kleinman 2008 (low-risk group)	M-CHAT, then phone interview for 'failures'	Caregivers, then phone interview by investigator	USA	3,309	21 (16-30)	59 (48-88)	20	?	65%	• USA lacks a good surveillance system to detect missed cases of ASD
Pandey 2008 (low-risk only, young group)	M-CHAT, then phone interview for 'failures'	Caregivers, then phone interview by investigator	USA	4,265	19	59?	10	?	28%	• Update on Kleinman 2008. • 11% refused phone interview or could not be contacted, another 37% refused clinical evaluation after interview or could not be contacted,
Pandey 2008 (low-risk only, older group)	M-CHAT, then phone interview for 'failures'	Caregivers, then phone interview by investigator	USA	1,785	25	59?	19	?	61%	• Update on Kleinman 2008. • 15% refused phone interview or could not be contacted, another 21% refused clinical evaluation after interview or could not be contacted,

Ref	Screening tool	Users of the tool	Setting	Number screened	Mean months of age (range) at screen	Age in months up to which false negatives could be identified	Number of screen-positive cases of ASD	Sens	PPV	Comments
Robins 2008	M-CHAT, then phone interview for 'failures'	Parents, then phone interview by investigator	USA	4,797	24 (17-34)	?	21	?	57%	• 22% refused phone interview or could not be contacted, another 39% refused clinical evaluation after interview. • Authors are still in the process of rescreening this cohort, to determine sensitivity.
Wetherby 2008	Infant-Toddler Checklist	Families	USA	5,385	6-24 (repeated)	48?	56	≤93%	6%	• Infant-Toddler Checklist does not screen specifically for ASD, so 18% of children were screen-positive.
Honda 2009	YACHT-18, then phone call, home visit, psychological consultation and weekly group for 'failures'	Public health nurses	Japan	2,814	18	?	11	79%	3% for YACHT-18	• 'Screening' involves a lot of follow-up assessment for children who turn out not to have a problem. • PPV of 100% was only achieved after 17 months of further assessment.
Barbaro 2010	Developmental surveillance	Maternal and Child Health nurses	Australia	20,770	8-24 (repeated)	24	89	?	81%	• Only 1.0% of children were considered 'at risk' by the developmental surveillance programme and referred. • 49% refused assessment after being referred. • True sensitivity is unknown.
Dereu 2010	CESDD	Childcare workers	Flanders	6,808	17 (3-39)	?	27	?	?	• Authors' claims for test performance are invalid because true number of false negatives is unknown. • Second step of screening (parent questionnaire) failed for two-thirds of screen-positive children because parents did not complete the questionnaire.

20. Among studies that have assessed a specific screening tool, the approach that has yielded the highest positive predictive values for ASD (around 60%) involves parents or caregivers using the Modified Checklist for Autism in Toddlers (M-CHAT), followed by a phone interview for those who fail this initial screen (Kleinman et al 2008, Pandey et al 2008, Robins et al 2008). Pandey et al (2008) found that the positive predictive value was much better when the M-CHAT was used at 25 months rather than 19 months of age (61% vs 28%). Dietz (2006) attempted screening at an even younger age (15 months) using the Early Screening of Autistic Traits (ESAT) questionnaire and found a similarly low positive predictive value at this age (25%). These positive predictive values are for confirmation of diagnosis shortly after screening; up to a quarter of children who are counted as true positives shortly after screening will lose their diagnosis of 'ASD' by the age of four years (see sections 10-14 above).

21. Few studies of specific screening tools for ASD have attempted to estimate sensitivity, because detection of missed cases requires excellent surveillance systems and several years' follow-up of the screened cohort. Such surveillance systems are not widely available in the USA, where most of the population-based screening studies have been performed. None of the papers on M-CHAT have data from which sensitivity in the general population can be estimated. The sensitivity of ESAT is also unknown, though by comparing the number of cases detected in their study with recent prevalence figures in the literature Dietz (2006) concluded that it is probably 'low'.

22. Approaches to screening for which authors have claimed high levels of sensitivity have used the Young Autism and other developmental disorders CHeckup Tool (YACHT-18) (Honda et al 2009) and the Infant-Toddler Checklist (Wetherby et al 2008). However, these levels of sensitivity (79-93%) were only obtained by using approaches to screening that had very low initial positive predictive values (3-6%), and children who failed the initial screen required multiple follow-up assessments over about 18 months before the outcome of screening was decided and sensitivity estimates were made.

23. Boyd (2010) reports that two other screening tools are undergoing testing: a revision of the original CHAT tool, called the Quantitative Checklist for Autism in Toddlers (QCHAT) designed for use in toddlers aged 18-24 months; and the First Year Inventory, which focuses on screening infants at 12 months of age.

24. In summary, it is possible that routine surveillance of child development by health professionals may offer the best trade-off between sensitivity and positive predictive value, though no study has reported both these measures. Among screening tools that can be used by parents or caregivers, M-CHAT seems to be the most promising, in that it offers reasonable positive predictive values (provided the screened children are aged at least two years). However, the sensitivity of M-CHAT in a general population sample has not yet been reported.

The test should be acceptable to the population

25. This review did not find any studies that directly assessed acceptability. However, studies of screening for ASD in the general population typically report that parents of between one third and one half of all children who fail the initial screening test drop out of the screening process before it has completed (Dietz et al 2006, Van Den Heuvel et al 2007, Kleinman, Robins et al 2008, Pandey et al 2008, Robins et al 2008, Barbaro et al 2010). Approaches to screening for ASD used in recent studies are clearly not accepted by a substantial proportion of parents.

There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals

26. The National Institute of Health and Clinical Excellence (NICE) is due to publish a clinical guideline with the title 'Autism spectrum disorders in children and young people: recognition, referral and diagnosis' in September 2011. In November 2010 the Department of Health requested NICE to produce a clinical guideline in collaboration with the Social Care Institute for Excellence on the management of ASD in children and young people. The publication date is not yet confirmed.

If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out.

27. Not relevant to screening for autism.

The Treatment

There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment

28. This section deals exclusively with RCTs, for the following reasons. Screening differs from routine clinical care because the process is initiated by the state or professionals, not by patients or parents. In the context of routine clinical care it is appropriate for professionals to use the best evidence available, even if it is of questionable validity, to guide their response. In the context of screening, it is not appropriate for professionals or the state to initiate contact with the public unless there is very strong evidence that available treatments are effective. RCTs are the gold standard for assessing effectiveness; the only context in which non-randomised designs can produce very strong evidence of effectiveness is when the effect of treatment is large in relation to the effects of all the possible biases, and that is not the case with treatments for ASD.

29. Hundreds of studies have attempted to assess the effectiveness of various treatments for ASD, but this review identified only 14 RCTs of interventions for children under the age of 5 years with ASD. Three were for Early Intensive Behavioural Intervention / Applied Behaviour Analysis (EIBI / ABA) (Table 4) and 11 were for focused behavioural interventions (Table 5). No RCTs were found for pharmacological interventions in children under 5 years with ASD. Most of these RCTs have reported some changes in response to early intervention. Whether such changes lead to significant improvements in adulthood, in terms of greater independence and vocational and social functioning, is unknown (Rogers and Vismara 2008).

Early Intensive Behavioural Intervention / Applied Behaviour Analysis

30. Interventions under this heading seek to address multiple core deficits in ASD, including linguistic, social, and cognitive problems (Vismara and Rogers 2010). The three RCTs of EIBI / ABA all involved intensive treatment (at least 25 hours per week) over a long period (at least two years) and periods of follow-up of at least two years. A total of 100 children with ASD have been studied in these three RCTs. The first RCT (Smith 2000) concluded that EIBI was effective, the second (Sallows and Graupner 2005) concluded that it made no difference. A systematic review that incorporated these two RCTs and nine non-randomised studies concluded that 'overall, the quality and consistency of this body of evidence are weak. Consequently, no conclusions can be drawn from this literature about how well EIBI works' (Blue Cross and Blue Shield Association 2009). The authors recommended that RCTs with larger sample sizes and longer follow-up should be done. A review by Spreckley and Boyd (2009) reached similar conclusions.

Table 4: RCTs of Early Intensive Behavioural Intervention / Applied Behaviour Analysis

Reference	Number of children	Median age (range) at baseline in months	Case mix	Test intervention	Control intervention	Duration of intervention (months	Length of follow up (months)	Results
Smith 2000	28	36	Autism, PDD-NOS	Intensive behavioural treatment at home for 25 hrs/wk	Parent training: 5 hrs/wk for 3-9 months, plus 10-15 hrs/wk in public school special education classes	24-36	57	Improvement in IQ, visual-spatial skills, language & academics, but not adaptive functioning or behaviour problems. Those with autism improved less than those with PDD
Sallows 2005	24	34	Autism	Intensive behavioural treatment: 38 hrs/wk of direct treatment, 6-10 hrs/wk of in-home therapist supervision	32 hrs/wk of direct treatment, 1.5-2.5 hrs/wk of in-home therapist supervision	48	48	No effect on any measure (cognitive, language, adaptive, social, or academic). Control intervention may have been too similar to test intervention.
Dawson 2010	48	24	Autism PDD-NOS	Intensive behavioural treatment (Early Start Denver Model): 15 hrs/wk of treatment by trained therapist, 16 hrs/wk of treatment by parents	Routine community care: 9 hrs/wk of individual therapy, 9 hrs/wk of group therapy	24	≥24	Improvement in IQ and adaptive behaviour. After including parental ratings, proportion with diagnosis of 'autism' improved, but ADOS severity scores and repetitive behaviour scores did not improve. Parents had invested a great deal of themselves in delivering the treatment for two years, so they might have been very keen to see a change in diagnostic severity and unconsciously biased their outcome assessments in favour of the intervention being effective.

31. Other reviewers have been more generous in their interpretation of the evidence base. For example, although Howlin et al (2009) concluded that 'there is strong evidence that EIBI is effective for some, but not all, children with ASD', though they also acknowledged that 'there remains a dearth of RCTs, which are needed in order to provide unbiased evidence of efficacy'.

32. It is important to point out that the claim in a 2009 Lancet review article that EIBI / ABA is 'highly effective for up to half of children enrolled in about ten randomised clinical trials done in the past 20 years' (Levy et al 2009) is incorrect. The authors of this statement (Mandell et al 2010) claimed that a previous publication (Rogers 1998) had reviewed five randomised trials. In fact, no RCTs of these interventions had been published by 1998, and none are cited in the article by Rogers (1998). Dawson and Gernsbacher (2010) were therefore correct in writing that 'the claims made by Levy and colleagues, with respect to intensive Applied Behaviour Analysis programmes for autistic children, have no basis'.

33. Dawson and Gernsbacher (2010) were mistaken, however, in stating that the intended comparison between randomised groups in the RCT reported by Sallows and Graupner (2005) was not done. The comparison was done, and the authors found no benefit from Applied Behavioural Analysis. Although the authors took the unusual step of combining data from the two arms of the trial for many of their analyses, data from the two arms were also analysed separately and the abstract of their paper states that 'outcome after 4 years of treatment, including cognitive, language, adaptive, social, and academic measures, was similar for both groups'. Although the study by Sallows and Graupner (2005) is an RCT, some authors of systematic reviews of EIBI (for example Eldevik et al 2009) have excluded it from their analyses on the grounds that children in both arms of the trial received a form of EIBI. They argue that the negative result does not therefore imply that EIBI/ABA is ineffective.

34. The third RCT of EIBI / ABA (Dawson et al 2010), published after all the systematic reviews cited above, found that intervention produced significant improvements in IQ and adaptive behaviour. Diagnostic severity improved when parental assessments were taken into account, but not when assessment was based solely on objective rating scales. Given that the parents had invested a great deal of themselves in delivering the treatment for two years, they might have been very keen to see a change in diagnostic severity and unconsciously biased their outcome assessments in favour of the intervention being effective.

Focused behavioural interventions

35. Focused behavioural interventions are specific teaching procedures that practitioners or parents use to promote children's learning and development in specific areas, or to decrease challenging behaviours. Service providers select specific focused interventions to address individual objectives for children and their families (Boyd et al 2010). These interventions are less intensive than EIBI / ABA.

36. This review identified 11 RCTs of various types of focused behavioural interventions for young children with autism or ASD. They all reported some beneficial effects, though in the trial by Yoder (2006) these had disappeared by 12 months. However, only one of these studies involved more than 60 children, and most of them followed up the children for only a year or less (Table 5). The one larger study, with 152 children, found no effect of treatment on autism symptoms (Green et al 2010). The authors noted that larger trial sizes generally produce smaller effects (see McMahon et al 2008), and suggested that the optimistic results from other studies should be reassessed. In the one trial with longer follow up (two years), a third of the included children had diagnoses of global developmental delay or language delay, not ASD, and the published data do not permit an assessment of whether there were significant benefits for children with ASD (Rickards et al 2009).

Table 5: RCTs of focused behavioural interventions

Reference	Number of children	Median age (range) at baseline in months	Case mix	Test intervention	Control intervention	Duration of intervention (months)	Length of follow up (months)	Results
Field 1997	22	54	Autism	Touch therapy from a volunteer student for 15 minutes per day, 2 days per week	A volunteer student sat with the child on her lap and engaged the child in a game	1	1	Reduction in stereotypic behaviours, increase in initiative behaviours
Jocelyn 1998	35	43 (24-72)	Autism, PDD	Day care plus parent-focused intervention: 5 weekly 3-hr classes; on-site consultation 3 hrs/wk for 10 weeks; 3 case conferences	Day care only	3	3	Improvement in language age score (5.3 vs 1.1 months)
Drew 2002	24	23	Autism	Train parents to develop joint attention skills and action routines; speech and language therapist visited parents at home for 3hrs ever 6/52	Standard local services (but 3 children started intensive behavioural intervention)	12	12	Marginal improvement in words understood
Aldred 2004	28	48 (29-60)	Autism	Social communication intervention targeting parental communication; regular monthly therapist contact for 6 months with a further 6 months of 2-monthly consolidation sessions	Routine care	12	12	Improvement in ADOS score
Yoder 2006	36	33 (21-54)	Autism, PDD-NOS	Communication intervention: Picture Exchange Communication System (PECS)	Communication intervention: Responsive Education & Prelinguistic Milieu Teaching.	6	12	No difference between treatments at 12 months
Kasari 2008	58	43	Autism	Joint attention or symbolic play for 30 min/day from educational psychologists experienced in autism, plus the (substantial) control intervention	30 hrs/wk at an applied- behavioural-analysis- based day hospital	1.5	12	Improvement in expressive language (mod to large effect size). Controls were receiving other intensive therapies, so uncertain whether children would benefit from this test while receiving standard community care.

Reference	Number of children	Median age (range) at baseline in months	Case mix	Test intervention	Control intervention	Duration of intervention (months)	Length of follow up (months)	Results
Rickards 2009	54	45	Autism, PDD-NOS, global dev. Delay, language delay	Home visits from specialist pre-school teacher for one hr/wk during school terms, plus control intervention	5 hrs/wk at multi-disciplinary centre	12	24	Less deterioration in mean IQ, but no effect on behaviour.
Green 2010	152	45 (24-60)	Autism	Parent-mediated communication-focused intervention (PACT): 18 x 2 hr therapist-parent sessions, 0.5 hr/day practice at home	Routine care	12	13	No improvement in primary outcome (ADOS-G score). Improvement in parent-child social communication.
Ingersoll 2010	21	39 (24-47)	Autism	Reciprocal Imitation Training (RIT) for 3 hrs/wk, to teach children with autism to imitate during play	Routine care	2.5	2.5	Improvement in elicited and spontaneous imitation
Kasari 2010	38	31 (21-36)	Autism	Caregiver-mediated joint attention: 24 couching sessions delivered by graduate students	Delayed test intervention	2	12	Improvement in joint attention and diversity of functional play
Wong 2010	17	26 (17-36)	Autism	Teach parents to train children in eye-contact, gestures and words: 0.5 hr session x 10	Routine care	0.5	2	Improvement in language & communication, reciprocal social interaction and symbolic play

There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered

37. The Scottish Intercollegiate Guidelines Network guideline 98 (SIGN 2007) includes recommendations on clinical interventions for children and young people with ASD. Treatment is not covered in the forthcoming NICE Clinical Guideline on ASD in children and young people.

38. Not surprisingly, given the limited evidence available from RCTs, all but one of the recommendations in favour of specific treatments in the 2007 SIGN guideline are based on non-analytic studies, expert opinion or clinical experience, rather than scientific studies of effectiveness. The exception is a grade B recommendation that 'behavioural interventions should be considered to address a wide range of specific behaviours in children and young people with ASD, both to reduce symptom frequency and to increase the development of adaptive skills'.

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

39. This review did not identify any literature that informs appraisal against this criterion.

The Programme

There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity

40. This review did not identify any RCTs of screening for ASD in the general population. A Dutch general population screening study with a geographic control area (Oosterling et al 2010) found that a screening programme based on the ESAT tool reduced the mean age at diagnosis of ASD from 84 to 64 months, but the study did not assess whether there was any impact on morbidity or mortality.

41. An RCT of screening and early intervention among siblings of children with ASD is being conducted at the University of Washington and is due to complete in July 2012 (King 2009). The children will be screened from age 6 months and followed up to age 24 months, with assessment of the impact of early intervention on autism symptoms, language, communication and symbolic behaviour. Judgement will be required to assess the extent to which the results of this RCT can be generalised to whole population screening, because there may be genetic differences between ASD in single-incidence families compared with multiple-incidence families (Zwaigenbaum 2010).

Conclusion

This review has identified the following reasons for caution regarding a national screening programme for autism and autism spectrum disorder (ASD) in children aged less than five years:

1. Studies of the natural history of these conditions indicate that about a third of children who are given a diagnosis of 'autism' at 20-23 months of age as a result of a screening programme, and up to a quarter of those identified as being within the broader category of 'ASD', are likely to lose these diagnostic labels by the age of four years. It is not clear whether these figures reflect the impact of early intervention (assuming it is effective) or over-diagnosis at 20-23 months of age.

2. No approach to screening for ASD has demonstrated acceptable performance, in terms of both sensitivity and positive predictive value, in a general population screening study.

3. Approaches to screening for ASD used in recent studies are not accepted by a substantial proportion of parents. Parents of between one third and one half of all children who failed the initial screening test dropped out of the screening process before it had completed.

4. This review identified only three RCTs of Early Intensive Behavioural Intervention / Applied Behaviour Analysis, in which a total of 100 children have been studied. The claim made in a 2009 Lancet review article that EIBI/ABA is 'highly effective for up to half of children enrolled in about ten randomised clinical trials done in the past 20 years' (Levy 2009) is incorrect. The authors' conclusion that 'screening strategies for early identification could enable early treatment and improved outcomes' therefore lacks an adequate foundation.

5. The effect of EIBI/ABA on outcomes varied across the three identified RCTs. The most consistent effect (in two RCTs) was an improvement in IQ. The duration of follow-up in the largest trial (Dawson et al 2010) was limited to two years.

6. The review identified 11 RCTs of various focused behavioural interventions, most of which reported some benefit from intervention. However, only one of these studies involved more than 60 children, and in most of them the children were followed up for only one year or less.

7. Whether the short-term effects reported in these RCTs lead to significant improvements later in childhood, or greater independence and improved vocational and social functioning in adulthood, is unknown.

Key research questions on screening for ASD

1. Can any approach to screening for ASD demonstrate acceptable performance, in terms of both sensitivity and positive predictive value, in a general population based study?

2. Why do so many parents of children who fail initial screening tests for ASD drop out of the screening process before it has completed, and can the process be refined so that the drop-out rate is reduced?

3. Does early intervention lead to significant improvements later in childhood, or greater independence and improved vocational and social functioning in adulthood?

Appendix A

Knowledge update on screening for autism
Paula Coles, Information Scientist
20 December 2010

BACKGROUND: The previous policy decision not to screen for autism in children under the age of five years is outlined in *Health for all children*. Fourth edition. Edited by David MB Hall and David Elliman. 2003.

In 2006, the following systematic review was carried out:
Mawle E and Griffiths P. Screening for autism in pre-school children in primary care: systematic review of English language screening tools. *International Journal of Nursing Studies* 2006; 43:623-36

This review was used as the starting point for the current knowledge update on screening for autism in children against the UK NSC criteria and so the searches were carried out from 2005 onwards.

SOURCES SEARCHED: Medline (OvidSP), Embase, PsychINFO, Cinahl, Web of Science and the Cochrane Library.

DATES OF SEARCH: January 2005 – November 22 2010

SEARCH STRATEGY:
1. Autistic Disorder/ (13444)
2. autis$.tw. (15249)
3. 1 or 2 (17317)
4. exp Child/ (1366585)
5. exp Infant/ (836642)
6. child$.tw. (819174)
7. toddler$.tw. (4286)
8. infant$.tw. (260608)
9. 4 or 5 or 6 or 7 or 8 (2000964)
10. 3 and 9 (12728)
11. Mass Screening/ (69980)
12. screen$3.tw. (354345)
13. detect$3.tw. (1218198)
14. (test ot tests or testing).tw. (266878)
15. tool.tw. (190205)
16. checklist.tw. (12472)
17. inventory.tw. (34761)
18. instrument.tw. (60214)
19. 19 assessment.tw. (428217)
20. scale.tw. (273762)
21. question$.tw. (445238)
22. observation.tw. (184068)
23. interview.tw. (76652)
24. (parent adj report).tw. (925)
25. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 (2936357)
26. exp "Sensitivity and specificity"/ (327671)
27. (sensitiv$ or specific$).tw. (2314267)
28. (false positive$ or false negative$).tw. (46377)
29. 26 or 27 or 28 (2517163)

30. 25 and 29 (782673)
31. exp Morbidity/ (291563)
32. (prevalen$ or inciden$).tw. (774245)
33. 31 or 32 (885810)
34. Early diagnosis/ (6893)
35. "Early Intervention (Education)"/ (1182)
36. early intervention$.tw. (7410)37. 34 or 35 or 36 (14929)
37. 34 or 35 or 36 (14929)
38. 30 or 33 or 37 (1615072)
39. 10 and 38 (2373)
40. limit 39 to yr="2005 -Current" (1412)

All searches carried out on 22 November 2010

RESULTS

Database	**Results**
Medline	1412
Embase	1615
Cochrane Library	43
PsycINFO	1649
Cinahl	552
Web of Science	1507
Total	**6778**

Inclusions and exclusions

The above search strategies retrieved 6778 references in total. After duplicate references were removed a total of 3557 potentially relevant references were left. The title and abstracts of the remaining citations were scanned for relevance to screening for autism in children under the age of five years using the NSC criteria:

- the condition
- the screening test
- the intervention and treatments
- the screening programme

563 references were deemed to be relevant and are classified in to the categories below according to the NSC criteria. There will inevitably be some overlap between categories.

In addition, a simple search (autism AND intervention) of the metaRegister of Controlled Trials (http://www.controlled-trials.com/mrct was also carried out, which yielded 267 results. Of these 22 were deemed to be relevant to the review and have been included in the references below.

Therefore, a total of 585 references have been included in this knowledge update.

Systematic reviews and meta-analyses **The condition (1)** **Prevalence (1)** **Interventions (22)** • *Behavioural (13)* • *Parent/family-mediated (2)* • *Social stories (1)* • *Picture Exchange Communication System (1)* • *Music/sound therapy (2)* • *Pharmacotherapy (3)*	24
Guidelines	11
Non-systematic reviews	47
The condition Epidemiology (92) • *UK (10)* • *Europe (12)* • *USA (28)* • *Canada (4)* • *Caribbean (1)* • *South America (1)* • *Australia (2)* • *Asia (7)* • *Middle East (3)* • *Worldwide (1)* • *Reviews (17)* • *Effect of changes to diagnostic criteria (6)* Condition characteristics (18) Comorbidity reviews (10) Early signs/concerns (32) Diagnostic validity/stability (17) Experiences of diagnosis (7) Late vs. early diagnosis (2) Outcomes (32) Outcome predictors (4)	214
The test M-CHAT (7) CARS (4) ADOS (5) BISCUIT (5) A-TAC (2) ABC (2) CBCL (2) Developmental surveillance (2) SCQ/ASQ (7) ASD-DC (2) GARS (2) STAT (2) ESAT (2) ECI-4 (2) AQ (3) Miscellaneous (27) Comparisons (23) Reviews (5) Biological markers (1)	105
The treatment Interventions (148)	164

• *'Early' (12)* • *Behavioural (27)* • *Parent/family-mediated (26)* • *Communication/social interaction (10)* • *Social stories (2)* • *Project DATA (2)* • *Joint attention (2)* • *Imitation training (2)* • *Play (2)* • *Picture Exchange Communication System (2)* • *TEACCH (3)* • *Keyhole (2)* • *Early Start Denver Model (3)* • *THOMAS (2)* • *Music (1)* • *BCRI (1)* • *Combined (1)* • *Comparisons (10)* • *Pharmacotherapy (21)* • *General overviews (17)* Services (11) Costs (5) • *UK (2)* • *USA (3)*	
The screening programme	20
Total	**585**

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