Vision screening in children aged 4-5 years

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

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Authors:
Ameenat Lola Solebo, Honorary Clinical Research Fellow[1] and Specialist Trainee in Ophthalmology

Jugnoo Sangeeta Rahi, Professor of Ophthalmic Epidemiology[1,3] and Honorary Consultant Ophthalmologist[2]

1. MRC Centre of Epidemiology for Child Health, UCL Institute of Child Health
2. Great Ormond Street Hospital NHS Foundation Trust
3. UCL Institute of Ophthalmology

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Introduction

Screening for reduced vision in children aged 4 – 5 years is primarily undertaken, as part of the NHS Healthy Child Programme, to detect individuals with amblyopia, which literally means '*blunted sight'* but is a form of cerebral visual impairment. The term describes the clinical scenario of reduced vision affecting one eye (or very rarely both eyes) caused by a disturbance to the normal developmental processes in visual neural pathways during the most vulnerable period of early childhood. The most common conditions predisposing to amblyopia are strabismus (squint) and refractive error and it is commonly defined as impaired vision that is not attributable to a structural abnormality of the eye.
Early detection of amblyopia is necessary to avoid permanent visual deficit by allowing treatment to be undertaken within the sensitive period of neuroplasticity (growth and change) in the visual system.

Rarely however, amblyopia can arise from 'form deprivation' caused by structural abnormalities such as congenital cataract.

Programmes of vision screening in childhood arose haphazardly some decades ago in the UK, with considerable heterogeneity in their content and implementation. The first major systematic review (HTA commissioned) of the evidence base for these practices was published in 1997 by Snowdon and Stewart Brown. (1;2) They concluded that *'there was a lack of good quality research into the natural history of the target condition, the associated disability, or the efficacy of available treatments',* prompting rationalization of screening practices.

The current NSC policy, last reviewed in 2005, is that all children should be screened for reduced vision between 4 and 5 years of age, with testing undertaken by orthoptists (specialists in the assessment of vision in childhood) or by other professionals in an orthoptic-led service (i.e. trained and supported by orthoptists).

We report here a systematic review of evidence published between January 1995 and July 2012 (that is, since the HTA review by Snowdon and Stewart Brown), to assess screening for reduced vision in children aged 4-5 years against the National

Screening Committee (NSC) criteria for appraising the viability, effectiveness and appropriateness of a screening programme.

A literature search was undertaken using the Medline, Embase and PsychINFO databases and the Cochrane library. The search strategy is detailed in the Appendix. Papers were selected according to the conventional hierarchy of grades of evidence (using Centre of Evidence Based Medicine, CEBM, criteria). Of the 3343 identified titles, 817 abstracts were assessed, and from these abstracts 207 full text papers were assessed independently by both authors. A total of 86 studies were included in the review (Appendix Table 1).

In this review we refer to visual acuity which is a measure of visual resolution, or the ability to discriminate between edges in visual space. The gold standard scale for acuity in ophthalmic practice is now the LogMAR (***Log****arithmic* ***M****easure of* ***A****ngle of* ***R****esolution)* system, in which each 'line' of optotypes (symbols on vision chart comprising letters or pictures) corresponds to a unit of 0.1 and represents a 10 fold difference in acuity compared to the adjacent line; we present in addition the Snellen notation equivalent as some readers may be more familiar with this older, non-logarithmic scale. 'Crowded' vision charts where each line has multiple optotypes are the gold standard for assessing acuity in subjects with amblyopia.

Appraisal against NSC criteria

These criteria are available online at http://www.screening.nhs.uk/criteria

We use the NSC review convention in relation to reporting whether a criterion is met: 'yes' (in full or in part), 'no' or 'not met because of insufficient evidence' to assess criterion.

1. The condition should be an important health problem

Normal vision requires integration of a number of visual functions. Visual acuity, the key modality, forms the basis of the classification systems that the World Health Organisation and others use to categorise individuals as non-impaired, visually impaired, severely visually impaired or blind. All these classifications are based on

acuity in the *better* eye, tested with glasses or contact lenses if required. Thus, individuals with reduced visual acuity in one eye alone, however marked this may be, are not considered visually impaired. The majority of disorders that cause bilateral visual impairment or blindness in children in the UK are present from birth or early infancy (3;4) and the vast majority (>97%) of children with significantly reduced vision affecting both eyes are diagnosed early in childhood because of the concerns of their parents or carers, or in the context of the routine universal NHS Newborn and Infant Physical Examination programme, or through other disorder-specific screening programmes.(3)

Description of the condition

All visual parameters/functions (e.g. form perception or motion perception) mature with age as a consequence of both structural and functional development of the eyes and the visual neural pathways in early childhood. There are a number of sensitive periods from birth onwards during which normal visual experience drives these structural and functional changes. Normally, healthy newborns have an average acuity of worse than 1.0 logMAR (or Snellen equivalent 6/60), maturing to an average of 0.3 logMAR (Snellen equivalent 6/12) by 24 months of age, and approaching adult levels by 5-6 years of age.(11-13)

Amblyopia is a neuro-developmental disorder, a form of cerebral visual impairment, which manifests as reduced acuity in in the absence of a structural ocular or visual pathway abnormality. Most commonly amblyopia arises through an interruption of normal visual development due to blur from defocus (*refractive amblyopia*, which may be related to *anisometropia*, or unequal refraction between the eyes), and / or a failure to maintain alignment of the eyes (*strabismic amblyopia*). Whilst refractive error and strabismus may result in reduced vision due to amblyopia, and require treatment as part of the management of amblyopia, they do not in themselves constitute an impairment of visual acuity. Much less commonly amblyopia can occur due to structural disorders of the eye, such as cataract, which obscure incoming images (*form deprivation amblyopia*). Amblyopia can also arise through a combination of factors. Rarely predisposing (‘amblyogenic’) factor(s) cannot be identified. Thus amblyopia is to some degree a diagnosis of exclusion, after a

thorough ophthalmic assessment has ruled out other structural causes of reduced vision.

Amblyopia is predominantly unilateral i.e. manifest as reduced vision in one eye.(5-8) It is often associated with impaired or absent stereoacuity (3D vision or depth perception). (9;10)

As amblyopia is a developmental disorder, affected children grow up without a comparative visual experience and are likely to be unaware of the poorer vision in their amblyopic eye. Early intervention is required to restore or achieve normal visual experience and thus maintain normal visual development trajectories. The sensitive window was thought to 'close' by the age of about 8 years in most individuals, but more recently it has been accepted that the period of plasticity extends beyond this age, as evidenced by studies of successful amblyopia treatment in late childhood. (14-18)

Disorders other than amblyopia have not been considered specifically in this review for the following reasons:
- significant bilateral visual impairment in otherwise healthy children would be expected to be detected before age 4 – 5 years due to the absence of normal visual behaviour / visual responsiveness/visual attention
-many disorders causing significant vision impairment are associated with co-morbidity such that affected children would be under the care of health professionals by age 4 – 5 years(3;4)
In addition, disorders associated with amblyopia, such as strabismus or refractive error, which are of sufficient severity as to negatively impact on visual development and require intervention, would be identified through the detection of the resultant amblyopia. Thus, the detection of childhood refractive error or strabismus in the absence of amblyopia has not been considered.

Prevalence of amblyopia

There is variation in the acuity threshold used to define amblyopia in prevalence studies (Tables 1 and 2). Nevertheless, amblyopia is a common childhood disorder and has been found to be a common disorder in adult populations, particularly those

which have not undergone childhood vision screening. (19;20) Since the 1997 HTA report, which did not identify any studies on the prevalence of amblyopia in childhood, there have been two relevant UK population based studies. In ALSPAC (Avon Longitudinal Study of Parents and Carers), amblyopia was defined as vision worse than 0.2 logMAR (or 6/9.5 Snellen) in the worse eye, or an interocular difference of at least 0.2 (2 lines on a logMAR chart). An overall prevalence (combining screened and unscreened populations) of 3.6% (95% confidence interval 3.3-4.1) was reported in 7483 children examined at age 7 years (56% of the 13988 children originally recruited to the study), with 0.6% of children bilaterally affected. An analysis of 8-9 year old children in Northern Ireland who had previously undergone screening and consequently treatment for amblyopia identified 2% of children (32/1582) with acuity worse than 0.18 or 6/9 Snellen (95% CI 1.4 – 2.9).(22)

These prevalence estimates for the UK are within the reported ranges from the diverse population based studies from other countries, with between 1% and 4% of children aged less than 6 years old affected, depending on the study methodology and amblyopia definition used and the characteristics of the study population (e.g. the existence of a national compulsory screening programme). Across the age ranges, the majority of the population based studies which use whole population sampling selection report a prevalence of approximately 2%.(8;23-25)

Table 1. Global prevalence of amblyopia in children aged under 6 years

Age at testing (yrs)	Country	Study population*	Particip'tn rate (%)	Definition of amblyopia / reduced vision using corrected vision in worse eye**	n	Preval'ce (%) (95% CI)	Additional information
0.5 - 6	Singapore (26)	Residents of public housing in Singapore 2006	72.3	>0.18 or interocular difference 0.2 with logMAR or SG test	1682	2.8 (2 - 3.6)	Inability to comply with visual testing in 67% and 23% of 30-35 month and 36-47 month old children respectively
0.5 - 6	Singapore (27)	Residents of public housing in Singapore 2010*	72.3	>0.18 or interocular difference 0.2 with logMAR or SG test, and presence of amblyogenic factor	1682	1.2 (0.1 - 1.7)	Results also reported in Dirani et al (28)
2.5 – 6	USA(24)	Whole population stratified sampling 2009* (Baltimore)	97	≥0.2 and interocular difference 0.2 on HOTV testing with Amblyopia Treatment study VA protocol	2546	1.8 (0.9 - 3.1)	Lower prevalence, 0.8% in African American population, (95% CI 0.3–1.7)
2.5 – 6	USA (23)	Whole population stratified sampling 2008* (Los Angeles)	77	>0.3 or interocular difference 0.2 on HOTV testing with Amblyopia Treatment study VA protocol	3350	1.5 (1.1 – 2)	Prevalence in African American and Hispanic children 0.5% prevalence bilateral amblyopia
2.5 - 6	Australia (8)	Whole population stratified sampling 2010*	74	≥0.2 or interocular difference 0.2 on testing with HOTV/Lea/ETDRS + amblyogenic factor	1422	1.9 (1.2 - 2.6)	Higher prevalence in children aged >3 years; 0.7% prevalence of bilateral amblyopia
3 - 6	Hong Kong (29)	Randomly selected sample of preschool children (1996/7, and 2006/7	96.5 (1996) 99.3 (2006)	≥0.3 (converted, SG chart testing)	601 (1996) 823 (2006)	3.8 (1996) (2.3 - 5.3) 2.7 (2007) (1.6 - 3.8)	Increasing prevalence of myopia (from 2.3 to 6.3%) not matched by an increasing prevalence of amblyopia
3 – 6	Iran(30)	National screening programme 2009*	66	>0.18 (converted, Snellen chart testing)	1.4 million	1.3 (1.3-1.3)	
5 - 8	Australia (5)	Whole population stratified sampling #2003/4	79	≥0.3 or interocular difference ≥0.2 on logMAR chart testing	1739	1.8 (1.2 – 2.4)	0.1% prevalence bilateral amblyopia

SG: Sheridan Gardiner (uncrowded Snellen type visual acuity test). All other non-Snellen tests mentioned use crowded optotype (multiple letters / shapes on each line) logarithmic progression charts

Particip'tn: Participation. Preval'ce: prevalence

* Publication date used where no recruitment / examination date cited by investigators

**included within these figures are children with bilateral amblyopia, in which vision in both eyes fails to meet the threshold

Table 2. Global prevalence of amblyopia in older children and adults

Age at testing (yrs)	Country	Study population *	Particip'tn rate (%)	Definition of amblyopia / reduced vision using corrected vision in worse eye**	n	Preval'ce (%) (95% CI)	Additional information
6	Iran(31)	School health check attendees 2009*	92	>0.18 or interocular difference ≥2 lines (converted, Snellen chart testing)	815	1.7 (0.8 – 2.6)	
6 – 7	Oman(32)	Random sampling of schools 1998*	92%	>0.3 (converted, Snellen chart testing)	6292	0.9 (0.7 – 1.1)	
6 - 7	Thailand (33)	School year group 2004*	Not given	Interocular acuity difference of ≥0.1	6898	1.1 (0.9 – 1.4)	7.3% of children had vision >0.18 on Snellen testing
6 - 15	China (34)	Whole population cluster sampling 2004*	Not given	>0.1	3469	1.9 (1.5 – 2.4)	0.8% prevalence of amblyopia with vision ≥0.3
6 - 21	Iran(35)	Whole population cluster sampling 2011*	86	>0.18 or interocular difference ≥0.2 lines (converted, Snellen chart testing)	2150	1.9 (1.3 – 2.5)	
7	UK (6)	Population based longitudinal cohort study 1998-2000	56	>0.18 or interocular difference 0.2	2037	3.6 (2.9 – 4.5)	0.6% prevalence bilateral impairment. Maternal smoking independently associated with amblyopia
8 - 9	UK (22)	State school children 2005*	Not given	≥0.3 (converted, Snellen chart testing)	1582	1.1 (0.6 – 1.6)	Screened and treated sample
11 - 14	Brazil (36)	Cluster sampling of state school children 2008*	86	>0.18 (converted, Snellen chart testing) ≥0.2	2441	2.2 (1.5 – 2.9) 1.0 (0.6 – 1.4)	3
12 - 13	Mexico (37)	Non random sampling 1999	78	≥0.3 and interocular difference ≥0.2	1035	2.5 (1.6 – 3.5)	
12 - 13	Sweden (38)	Non random sampling 1998	67	≥0.2	1046	1.1 (0.5 – 1.7)	Screened and treated sample
30+	China (39)	Cluster sampling of rural population 2011*	90	≥0.2	6799	2.8 (2.4 – 3.2)	1.1% prevalence bilateral amblyopia, and 1% prevalence of amblyopia with vision ≥0.3
40+	Australia(40)	Whole population cluster sampling 2000*	86	>0.18 and interocular difference ≥0.1	4744	3.1 (2.6 – 3.6)	
49+	Australia (20)	Whole population stratified sampling 1998*	82	≥0.18	3654	3.2 (2.6 - 3.8)	2.6% prevalence amblyopia when defined as ≥0.2 and interocular difference ≥0.2
50+	Iceland (19)	Whole population cluster sampling 2008	63.9	≥0.3	1045	1.9 (1.1 – 2.7)	

* publication date used where no recruitment / examination date cited by investigators
**included within these figures are individuals with bilateral amblyopia, in which vision in both eyes fails to meet the threshold

The impact of unilateral reduced vision due to amblyopia

The significant impact on development, health and quality of life of impaired vision in *both* eyes from early life is well documented. The management of amblyopia is a cornerstone of paediatric ophthalmic practice and its predominance as the main cause of reduced vision in children (most conditions that cause bilateral vision impairment are individually uncommon) may explain the hitherto limited literature on its impact.

Reduced vision in one eye might be expected to impact on an individual in various ways. It could have a functional impact on educational experience, employment or other social outcomes; or impact through visual impairment or blindness if the better seeing eye is injured or diseased; or via an impact on psychological health, well-being or quality of life, for example through anxiety engendered by having only one 'good' eye. Inconsistent associations between impaired vision in one eye and poorer mental health, general health, social functioning, and general quality of life have been reported from large population based studies of adults in the UK and Australia.(41;42) However, these studies address the impact of *acquired* loss of vision due to injury or illness in those with previously normal vision in both eyes, rather than the scenario that pertains in amblyopia, i.e. a failure to develop and use normal vision from childhood.

Snowdon and Stewart Brown's report did not identify any robust evidence of disability in individuals with unilateral amblyopia, and concluded that there was an *'urgent need for research on the functional impact of unilaterally reduced vision*'.(1) Subsequently there have been some research efforts to understand the impact and disutility of unilateral amblyopia, as described below.

- *Visual function and visual health*

Loss of vision in the *non-amblyopic* eye of individuals with unilateral amblyopia may result in visual impairment or blindness. An increased risk of visual impairment in individuals affected with amblyopia compared to the general population has been reported from three population based studies. These comprise the Blue Mountain Eye study (BMES) of Australian adults aged over 49 years; a longitudinal study of 7983 adults in Rotterdam; and a national study using active surveillance through clinicians (via the British Ophthalmic Surveillance Unit) which identified in one year in the UK 370 individuals rendered visually impaired or blind following loss of sight due to injury or disease affecting

their non-amblyopic eye. The Australian and UK studies defined visual impairment as vision in the better eye, i.e. with both eyes open, of worse than 0.3 logMAR (6/12 Snellen) a level which would preclude driving in Australia, the UK and the USA whilst the Dutch study used the WHO definition of visual impairment: vision in the better eye worse than 0.5 LogMAR (6/18 Snellen). Over a five year period, individuals with amblyopia in the Australian study had a 2.7 times higher risk (95% CI 1.6 – 4.6) of visual impairment when compared to non-amblyopes(43) whilst the relative risk was 2.6 (95% CI 1.4 – 4.5) in the Rotterdam study (44). The lifetime risk (cumulative incidence) of visual impairment due to illness or injury affecting the non-amblyopic eye was estimated to be to be at least 1.2% for those with amblyopia in the UK.(45)

Failure to develop normal vision in one eye may also result in the failure to develop stereopsis (depth perception). Depth is perceived through slight differences between the images from either eye, but visual cues such as shade and relative size can also be of use. It is recognised that acquired loss of stereopsis later in life due to injury or disease in previously normally sighted eyes can be limiting.(41;42) However, whilst reduced stereopsis due to amblyopia has been shown to have some negative impact on fine motor tasks in experimental settings (such as placing pegs in a board, threading beads or pouring water from one container into another) (46;47), the 'real life' functional impact of impaired stereopsis for individuals growing up and living with amblyopia remains unclear.

- *Quality of life*

Assessing self-reported vision-related quality of life in children is challenging and this is reflected in the dearth of appropriate instruments. There is therefore a limited literature on the impact of amblyopia on quality of life during childhood. (48) In one study, using a parent proxy instrument (the PedsQL, a generic health related quality of life measure) no significant difference was found in the quality of life in North American children aged 2 – 6 years with (n=71) and without (n=3247) amblyopia although the limitations of proxy versus self-report were acknowledged.(49)

We were unable to find robust evidence showing an impact of amblyopia *per se* on self-reported quality of life in adulthood.

- *Utility and general and mental health outcomes*

Evidence from the 1958 British birth cohort study, comprising all subjects born within 1 week in 1958 who were followed longitudinally from infancy with biomedical examinations, suggests that amblyopia is not associated with any impact on general health outcomes, although moderate / severe amblyopia (vision >0.5 logMAR) was associated with a higher risk of road traffic accidents between the age of 17 and 33.(50)

One group of investigators has attempted to directly measure the disutility (patient reported assessment of overall health status compared to 'perfect' health) of amblyopia in adulthood. A retrospectively identified group of individuals within the Netherlands (n=145) were asked to report on their perceptions of the impact of their amblyopia.(51) Utility was found to be slightly lower in amblyopic individuals (0.99 utility score versus 1 for 'perfect health') and 70% of individuals with amblyopia reported they would sacrifice 1 year of life for 'perfect vision' (51)

- *Socioeconomic outcomes*

There are statutory occupational vision requirements in many countries. For example, in the UK vision of worse than 0.18 logMAR in the worse eye precludes employment in the Royal Air Force, worse than 0.3 precludes occupation as a pilot, and worse than 0.4 precludes occupation in the other armed forces, police or jobs necessitating the driving of large vehicles.(50) However, there is a limited robust evidence base for these recommendations. Within the 1958 British birth cohort, amblyopia was not associated with achieved educational level, employment, occupation type (including any of the 'prohibited' occupations), social mobility, socialisation or behavioural problems.(50)

Summary

Amblyopia is a common disorder of childhood with a prevalence of between 1% and 5% depending on the amblyopia definition, case ascertainment methodology, study population and whether population screening exists. There remains a surprisingly limited literature which currently points to a relatively mild disutility associated with amblyopia *per se* or with associated impaired stereopsis either in childhood or beyond into adult life. Based on the current literature, the major impact of amblyopia in population terms lies in

its importance as a preventable risk factor for subsequent visual impairment or blindness due to loss of vision in the non-amblyopic eye through injury and disease.

- Criterion 1 met? **YES, PARTLY (INCOMPLETE EVIDENCE)**

2. The epidemiology and natural history of the condition should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage

Frequency

The 1997 HTA report on childhood vision screening concluded that whilst the reported prevalence of childhood visual deficits depended on taxonomy and study methodology, the prevalence of childhood visual disorders comprising reduced vision, amblyopia and associated disorders specifically strabismus and refractive error, stayed consistently between 2% and 6%.(1)

We have not identified any incidence studies of amblyopia in the UK or in similar populations.

As described earlier, the UK prevalence of amblyopia amongst children aged 4-5 years is likely to be within the range of 1% to 4%. Prevalence of amblyopia appears to increase in early childhood. One cross-sectional study of age-group specific prevalence in 119,311 children reported an increase in prevalence between the ages of 1 and 4 years but stable rates thereafter(52), echoing other studies.(23;24) At 1 year, 15% of affected children had anisometropia and 32% had strabismus associated with their amblyopia compared to 71% and 41% respectively at age 7 years.

Natural history

- The development of amblyopia

As described earlier, amblyopia develops if normal visual development in childhood is interrupted due to blur, defocus, form/stimulus deprivation or loss of binocularity during the ‘developmental windows’ during which visual experience is required for initial neural pathway formation (the ‘sensitive’ period for an insult) and for subsequent modification (the ‘critical’ period for amelioration), as evidenced by a strong body of mammalian animal research. (53).

Clinical studies have established that the severity of amblyopia is related to the severity of the ‘insult’ and its timing. Thus, the profound form deprivation in infancy caused by ocular diseases such as congenital cataract will result in dense amblyopia: population based

studies of outcomes following congenital cataract surgery report that delays in surgery in infants of as little as a week result in meaningful reduction in functional visual outcome. (54) In humans amblyopia does not appear to develop for the first time after the age of 8 years(55) but since clinical trials would be unethical, there is no high level evidence on the duration of the 'sensitive period' in the developmental window.

Given long established clinical practices of screening and treatment, and the animal and human research supporting the notion of sensitive periods, it is unsurprising that there is a limited literature on the natural history of untreated amblyopia. Clinically, the lack of equipoise amongst practitioners is such that it is extremely unlikely that a randomized clinical trial would be conducted in which any children were randomized to receive no treatment. Since the 1997 HTA report, one study of eighteen 4-5 year olds with failed concordance to prescribed amblyopia treatment (occlusion) has reported that all children remained amblyopic (vision in worse eye worse than or equal to 0.3, 6/12) 1 year after diagnosis; 1 of the children (who received some sporadic occlusion) had better vision and seven of the children (40%) exhibited worse vision in their amblyopic eyes 1 year after diagnosis, (56)

There has been some investigation of the question of whether *residual* neurological plasticity exists i.e. outside the classical developmental window of the first 8 years of life. Rahi et al described improvement in acuity in the amblyopic eye in 31% of individuals (with known childhood onset amblyopia) one year after loss of vision in their better eye, and notably, with a greater likelihood of improvement in those who had previously undergone any amblyopia treatment in childhood (45). Chua et al described 1 in 10 individuals with known childhood amblyopia noting visual improvement of more than 2 lines in the amblyopic eye five years after onset of sight loss affecting their better eye.(43) Whether these changes in acuity in adult life in amblyopic eyes under the conditions that are simulated by occlusion treatment (i.e. penalization of the non-amblyopic eye to allow the amblyopic eye to dominate) represent true neuroplasticity or simply a reactivation of latent vision is not known. Whilst this question is intriguing and merits further exploration, the focus of amblyopia treatment should remain intervention within the critical period in childhood so as to avoid permanent visual deficit in the amblyopic eye. As such, screening for reduced vision at 4 -5 years enables those with established amblyopia to be detected at a sufficiently early stage to allow effective treatment to be provided.

- Criterion 2 met? **YES**

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

This criterion is not applicable to vision screening in children aged between 4 and 5 years as there are no effective interventions for primary prevention of amblyopia.

4. 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

This criterion is not applicable to vision screening in children aged between 4 and 5 years.

5. There should be a simple, safe, precise and validated screening test

Whilst the diagnosis of amblyopia is made after a full clinical examination to exclude other conditions, screening relies on testing visual acuity. Vision testing is children is a safe, relatively simple procedure which can be performed by suitably trained non-specialist staff, though testing requires appropriately sized and illuminated space which is free of distraction. With regards to the precision and validation of the test, the 1997 HTA report did not address the question of which visual testing method to use. The 2005 NSC policy update concluded that each eye should be tested separately with a crowded (lines of letters / shapes rather than a single letter / shape on each line) visual acuity chart and testing using crowded logMAR charts is also recommended by the Royal College of Ophthalmologists (http://www.rcophth.ac.uk/page.asp?section=637&sectionTitle=Current+issues+and+opportunities+-+Vision+screening+for+children). However there is currently no UK recommendation as to the specific crowded logMAR based test to be used for vision screening.

Several different logMAR based crowded letter / picture (or optotype) charts exist. Those most commonly assessed in the literature on childhood vision testing are the:

- ETDRS (Early Treatment Diabetic Retinopathy Study) charts, which present letter optotypes in linear arrangements. ETDRS charts were designed for use in adults and they remain the gold standard measure of visual acuity in adults and in older children (optimal in those older than 8 years)

- HOTV charts, in which separate lines of letters or picture optotypes are presented on individual cards. All HOTV optotypes exhibit internal vertical symmetry (e.g., ‘H’ rather than ‘E’ which is changed on mirror image)
- Lea charts / cards, in which linear arrangements or separate cards with symbol optotypes are presented, all with internal vertical symmetry.
- Kay charts in which separate lines of picture optotypes are presented on individual cards. Whilst the HOTV and Lea picture optotypes are simple geometric shapes, the more complex Kay pictures are more designed to be recognizable ‘real life’ images (cat, duck, windowed house) and exhibit no internal symmetry

Whilst these individual tests have reliable testability indices in experimental settings, with regards to their precision, the majority of studies have examined the sensitivity or specificity of these different vision tests using, as a reference point, the detection of amblyogenic risk factors rather than the detection of reduced vision *per se* .(57-62) We identified sources of evidence on the testability and agreement of different optotype tests in children under 6 years old (thereby including the target population of children 4-5 years old). Children aged 5 years were able to display a logMAR line of better visual acuity with the symmetrical optotypes used on HOTV testing in comparison to ETDRS testing,(63) which may be explained by the internal symmetry of the HOTV optotypes enabling shape recognition. In a comparison of the two tests which use internally symmetrical optotypes, the North American Vision in Preschoolers studies demonstrated that the HOTV (letter optotype) and Lea (picture optotype) tests could be successfully used in children aged 4 or 5 years, (64-66) with a fair level of agreement (69% in 4 year olds, 70% in 5 year olds, and no tendency for worse visual acuity with either test). Conversely, the Kay (complex picture optotypes) and ETDRS (letter optotype) tests have been shown to exhibit only a low level of agreement (intra-class correlation co-efficient or ICC of 0.6 in amblyopic eyes) in 3-5 year olds(67).The 2000 United States Prevention Service Task Force (USPSTF) systematic report into childhood screening concluded that the HOTV and Lea tests were the most appropriate tests for vision screening in children aged under 5 years.(60)

Summary

Whilst there is evidence for the superiority of crowded logMAR optotype testing (over uncrowded tests), there is only limited evidence on the comparable precision of the different crowded logMAR tests available for testing for reduced vision in children aged 4 – 5 years old. There remains no national guideline on which acuity test to use.

Criterion 5 met? **YES, PARTLY**

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

By definition, vision of 0.0 LogMAR or 6/6 is considered as 'normal' adult acuity. As described earlier, there is a developmental trajectory in visual acuity. From recent UK and US studies, it is estimated that the mean visual acuity at 4 – 5 years old is between 0.08 and -0.075 using crowded logMAR testing. (13;68;69)

The variable cut offs used to define amblyopia in childhood – anywhere from 0.2 to 0.4 – are a reflection of the difficulty in defining a level of vision that can, with certainty, be expected to be clinically and functionally meaningful. Within the UK, the NSC guidelines on vision screening state that children 'should be referred to specialist services for further assessment if they do not achieve 0.2 in both eyes (roughly equivalent to 6/9 on a Snellen based linear chart), despite good cooperation.

- Criterion 6 met? **YES**

7. The test should be acceptable to the population

Vision testing is a non-invasive procedure carried out in routine clinical practice. It is therefore unsurprising that there has been very little robust research on acceptability, and consequently no direct evidence that the test is acceptable to the population.
It is therefore assumed that vision testing is acceptable to children and their families but there is no robust evidence (such as studies of uptake to screening) to support this.

- Criterion 7 met? **YES, partly (indirect evidence)**

8. 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

Making a diagnosis of amblyopia requires an expert clinical examination to rule out other causes of reduced vision and to identify the underlying associated amblyogenic factors. It may also be necessary to undertake electrodiagnostic testing, neuroimaging or other specialised evaluations to assess the higher visual processing system. Whilst actual clinical practices are likely to be similar, there is a need for uniformity through a national policy and care pathway for the further investigation of children who fail the screening test at age 4 – 5 years.

- Criterion 8 met? **NO**

9. 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

This criterion is not applicable to vision screening in children aged between 4 and 5 years.

10. 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

Effectiveness of treatment

Since the 1997 HTA report which concluded that there was no robust high level evidence that treatment for amblyopia was effective, three Cochrane systematic reviews have been undertaken to assess the effectiveness of treatment for strabismic,(70) refractive(71) and stimulus deprivation amblyopia, respectively.(72) The review of stimulus deprivation amblyopia was unable to find any randomized controlled trials on the impact of treatment: this may be because of the lack of equipoise amongst clinicians regarding treatment for this group of children, in whom amblyopia is generally severe, due to a specific ocular disorder which requires treatment of itself, and in whom response is only seen with

intensive treatment. (54;73) The other Cochrane reviews concluded that there was some benefit seen with refractive correction (glasses) for purely refractive amblyopia, and that occlusion was associated with improved vision in strabismic amblyopia. (70;71) The systematic review of vision screening in children aged 1 to 5 years by the United States Preventive Services Task Force concluded that there was adequate evidence that 'early treatment for amblyopia, including the use of cycloplegic agents (to paralyse the focusing mechanism of the eye), occlusion, and glasses, for children 3 to 5 years of age leads to improved visual outcomes'.(74)

There have been three randomized controlled trials (RCTs) in children aged less than 6 years on the effectiveness of treatment which had a delayed treatment arm. Owing to the lack of equipoise amongst clinicians it is highly unlikely that any future trials would include a non-treatment arm in randomized controlled trials of interventions for amblyopia in young children.

Clarke et al recruited 177 children aged 3 – 5 years who had been identified as having unilateral amblyopia of any cause (vision in the worse eye of 0.18 to 0.78 logMAR, or 6/9 to 6/36 Snellen) at vision screening in the UK. In this pragmatic, single masked randomized control trial children were randomized to no initial treatment (n=59), glasses only (n=59), or full treatment with glasses and occlusion therapy (n=59). At 52 weeks, children in the full treatment group had moderately but statistically significantly better vision than the non-treatment group. Fewer children in the full treatment group had vision of less than 0.3 (4% versus 27%). At 78 weeks, following institution of full treatment for all children there was no statistically significant difference in visual outcome between the two groups overall. The authors concluded that a one year delay in treatment for amblyopia had no significant negative impact at this age.(73) However, amongst those with moderate or severe amblyopia, a (statistically) significantly larger proportion in the 'delayed' treatment group still had acuity worse than 0.3 logMAR (4% of children in the full treatment group compared with 27% in the 'delayed treatment' group): it is this group with more severe amblyopia who are most at risk of blindness through visual loss affecting their non-amblyopic eye. Interestingly, at 52 weeks, 44% of children who had been randomized to the delayed/non-treatment group were no longer categorized as amblyopic. This is most likely accounted for by physiological age-related maturation of vision and/or improved reliability of vision testing, giving the impression of 'improved'

acuity, although resolution of amblyopia in these children between the ages of 4 and 5 cannot be excluded. The existing natural history data are insufficient to be able to reliably distinguish between these two scenarios. The findings nevertheless support the current screening threshold of vision worse than 0.2 logMAR for 4-5 year olds, so as to minimize the number of 'false positive' referrals.

Awan et al undertook a RCT comparing no occlusion (patching) versus 3 hours/day of occlusion versus 6 hours/day of occlusion in a UK group of 60 children aged 3 – 5 years with amblyopia of all causes (vision worse than 6/9) which had failed to respond to a period of glasses wear alone (attrition 8/60). The amount (dose) of occlusion was assessed objectively. Despite a prior period of refractive adaption i.e. improving vision through use of glasses alone, mean acuity of children receiving *no* occlusion still improved by 0.24 logMAR (over 2 lines) over a 12 week period from initial referral. Mean acuity in children receiving 3 and 6 hours of occlusion improved by 0.29 and 0.34 logMAR respectively; thus there was a small but statistically significant treatment effect of between half and one full line on the logMAR chart that was attributable to occlusion itself. The association between visual outcome and actual (as opposed to prescribed) dose of daily occlusion was stronger, with children who achieved 3-6 hours/day achieving significantly better visual results at 12 weeks.(75)

The North American Pediatric Eye Disease Investigator Group (PEDIG) has published extensively on the various treatment modalities for amblyopia. In one study, 2 hours of occlusion/day was compared to no occlusion in a trial of 180 children aged 3 – 7 years with anisometropic amblyopia, showing that after 5 weeks vision improvement in the occlusion group was half a logMAR line greater than the non-treatment group. However, all children who needed refractive correction received it during the 16 weeks leading up to the trial, so there were no completely untreated children in this trial. (76)

Due to the differing methodologies of these randomized controlled trials, meta-analysis is inappropriate. However together they provide evidence that occlusion treatment is, on average, associated with a gain of at least 1 line of logMAR acuity in amblyopic children treated at age 3-5 years.

We identified 19 randomized controlled trials comparing different types/regimens of

treatments for amblyopia (after removing 5 duplicate reports) as summarized in Table 3. Broadly speaking, there is no evidence for the superiority of any particular occlusion regimen for moderate or severe amblyopia; but there is some evidence that older children and children with severe amblyopia are most likely to benefit from a greater ‘dosage’ of occlusion. Constant chemical penalization with atropine (to paralyze the focusing mechanism of the eye) instilled twice weekly can show equivalent
results to occlusion regimens in moderate amblyopia, but carries the potential risk of ocular and systemic side effects as well as the risk of causing amblyopia in the good eye through ‘over’ occlusion. However, it is argued that this may be offset by the greater personal and social impact of cosmetically obvious occlusion.

Table 3. Summary of randomized controlled trials comparing different treatments for amblyopia.

Age (yrs), *(n)*	Study population	Treatment arms	Loss to follow up	Findings	Adverse events
Different regimens of patching					
3 – 8, *(80)* (2)	Mild to severe vision worse than 0.1, and interocular difference >0.1	6hrs patching V 12 hrs patching Both groups: 18 weeks of refractive adaptation for children with refractive error	0	No statistically significant difference between treatment groups However, objective assessment of actual dose of occlusion received revealed association with better visual outcome	
3 – 7, *(189)* (77)	Moderate amblyopia 0.3 – 0.6	2 hrs patching V 6 hrs patching Both groups – 1 hr near work	4% (3 2hr, 5 in 6hrs group)	No sign diff At 5 weeks, 1.8 in 2hr V 1.9 in 6hr group At 4 months, >2 lines improvement in 75& V 76%	Social stigma questionnaire score worse in 6hr group
3 -7, *(175)* (78)	Severe amblyopia 0.7 – 1.3	6 hrs patching V Full time patching Both groups – 1 hr near work Patching at least 8 hrs 6 days a week V patching 8hrs alternate days	10% (6 full time, 12 in 6hr group)	No sign difference At 4 months, mean improvement 4.8 6 hr and 4.7 in full time group	No difference in tolerance / social stigma score
4 – 5, *(40)* (79)	Moderate to severe amblyopia 0.5 – 1.3		5% (1 each group)	'No sign diff in visual improvement or time to improvement Mean change 0.6 log in daily patching V 0.8 alternate patching – 2 line difference	Not given
5 – 26, *(53)* (14)	Moderate to severe amblyopia 0.4 and worse	Full time occlusion V alternating patching sound eye 1:age child in years	Not given	No sign diff in outcome at follow up (mean 16 months) 52% of children aged over 9yrs gained two lines of acuity	Not given
Patching versus chemical penalization with atropine					
3 – 7, *(419)* (80)	Moderate amblyopia 0.3 – 0.7	Daily atropine V At least 6 hrs patching (reviewed at 4 months)	4% (7 patching, 10 atropine group)	No sign diff (2.8 atropine V 3.2 lines gained in patching group, 74% atropine V 79% success in patching group) Patients prescribed >10hrs patching gained more vision than atropine group / patients receiving less patching	Not given
7 – 12,(*193*) (81)	Moderate to severe amblyopia 0.3 – 1.3	Weekend atropine V 2 hrs patching	5% (8 atropine group, 2 patching) buy	No sign diff (mean improvement 1.5 lines atropine and 1.7 lines patching group) at 17 weeks	Ocular side effects 16%, systemic side effects 3% atropine group Skin irritation 5% patching group
7 – 12, (*40*) (82)	Severe amblyopia 0.7 – 1.3 Nested within the above study	Weekend atropine V 2 hrs patching	18% (2 atropine, 5 patching group)	No sign diff at 17 weeks (mean improvement 1.4 V 1.8 lines)	Reverse amblyopia 5%, light sensitivity 15%, systemic side effects 15% atropine group
7 – 17, (*507*) (18)	Moderate to severe amblyopia 0.3 – 1.3	Daily atropine for 7 – 12 plus 2 – 6 hrs patching V Optical correction alone	8% (10 optical, 19 treatment group)	>2 lines improvement in acuity amblyopic eye in 53% treatment group versus 25% optical treatment group ($p<0.001$) at 24 weeks, and in 47% versus 20% for those aged 13-17 with no previous history of amblyopia treatment	4% children under 12 discontinued atropine due to difficulty with near work
3 – 10, (*55*) (83)	Residual amblyopia 0.2 – 0.5	Intense treatment 6hrs patching and daily atropine V Weaning group	0	No sign diff with intensive treatment. >2 lines gained in 11% intensive versus 22% weaning group	Not given
4 – 10,(*120*) (84)	Moderate amblyopia 0.3 – 0.7	Twice weekly atropine V 2hrs patching	0	No sign diff: >2lines improvement in 74% V 76% patching, vision better than 20/25 in 50% by 2 years follow up	Not given
8 – 20, (*63*) (15)	Anisometropic amblyopia only, Moderate to severe amblyopia 0.5- 1	Daily atropine V Full time patching with sound eye patched for 1 day every week	9% (3 each group)	No diff in improvement in vision at 6 months (mean improvement 2.4 lines) but faster improvement and greater improvement in near acuity in patching group	Eye redness: one patient discontinued atropine

Table 3 cont. Summary of randomized controlled trials comparing different treatments for amblyopia.

Age (yrs), *(n)*	Study population	Treatment arms	Loss to follow up	Findings	Adverse events
Different regimens of chemical penalization					
3 – 7, (*168*) (85)	Moderate amblyopia 0.3 – 0.6	Daily atropine V Weekend atropine	5% (6 daily, 2 weekend)	No sign diff at 5 weeks (1.6 V 1.7 weekend) or at 4 months (2.6 lines both groups)	Reverse amblyopia 6 in daily, 4 in weekend group (total 6%)
Other					
3 – 7, (*425*) (86)	Moderate to severe amblyopia 0.3 – 1.3	2 hours patching with near vision tasks (adherence 87%) V 2 hours patching with distance tasks at 6 feet (adherence 89%)	7% (14 near, 16 distance group)	No sign diff at 6 weeks (2.6 V 2.5 line gained) or at 17 weeks (3.6 lines both groups)	
4 – 5.5, (*76*) (87)	Anisometropic amblyopia only, moderate to severe amblyopia 0.18 – 1.18	Refractive correction V Refractive correction with Bangerter occlusion filter over sound eye	13% (10 each group)	No diff at 1 year (4 lines gained)	
3 – 10, (*186*) (88)	Moderate amblyopia 0.3 – 0.6	Occlusion with Bangerter filter V Occlusion with patching	9% (8 Bangerter, 9 patching group)	No sign diff but 0.4 line difference favouring patching at 24 weeks	Vision worse in sound eye in 1% Bangerter group and 6% patching group
2 – 10, (*70*) (89)	Mild to moderate amblyopia vision better than 0.5	Atropine 2xweek V Defocusing lens sound eye	10% (4 atropine, 3 defocusing group)	Significantly greater improvement in patching group: 81% versus 26% gaining 2 lines vision at 6 months	Reverse amblyopia in 1 child in atropine group
3 – 7, (*180*) (90)	Moderate amblyopia 0.3 – 0.7	Weekend atropine V Weekend atropine plus defocusing with plano lens	5% (6 atropine, 2 atropine + plano group)	No sign diff at 18 weeks (2.4 V 2.8 lines plano lens)	Facial flushing in 4% children, ocular symptoms in 7%
3 – 6, (*60*) (82)	Severe amblyopia 0.7 – 1.3	Weekend atropine V Weekend atropine plus plan lens defocus sound eye	7% (4 daily, 2 weekend)	No sign diff but mean outcome in atropine and plano lens group half a line better at 18 weeks (5.1 V 4.5 lines gained)	Reverse amblyopia in 4% atropine only and 19% atropine with plano lens Ocular side effects 11% Facial flushing 1 patient

For completeness, studies involving children >5 years old have been included to provide evidence of the neuroplasticity of visual development past the classical sensitive period

The UK study by Stewart et al (Table 3) which enrolled all children with any form of amblyopia (vision worse than 0.1LogMAR) used dose-occlusion monitors to objectively measure the achieved dose of occlusion, and reported that children randomized to receive 6 or 12 hours of occlusion a day were receiving on average 66% (4 hours) and 50% (6 hours) of their prescribed dose respectively. Mean starting visual acuity was the same in all three groups, thus poor concordance was not explained by lesser severity of disease. This poor concordance highlighted the burden of intensive amblyopia treatment for children and their families, and the importance of fully informing, involving and supporting the family during amblyopia treatment. Whilst this finding suggests that *intensive* treatment per se has low levels of acceptability amongst the target population, it is important to note that the great majority (97%) of parents adhered to treatment at some level, albeit within the artificial environment of a RCT.(2)

There is, at present, no evidence from RCTs that stereoacuity improves with amblyopia treatment, although one randomized trial (of 177 amblyopic and non-strabismic UK children) reported a trend towards better stereoacuity over a 1 year period for children treated with refractive correction or with occlusion treatment.(9) This finding is consistent with a non-comparative study pooled from six different PEDIG RCTs.(10)

Benefits of early treatment

We found no direct evidence from randomised controlled trials of the benefit of screening and treating at 4-5 years versus intervention at either at older or younger ages.

As discussed earlier, the RCT by Clarke et al reported that for children with moderate amblyopia, delayed treatment led to a poorer visual outcome.(91) The trial by Stewart et al reported that younger children responded more rapidly to treatment with less occlusion: 3 to 6 hours of daily occlusion was sufficient for children aged 4 to 6 years, but over 6 hours of occlusion was required to achieve the same response in children over 6 years old.(2) In addition, a report using pooled data from 966 children recruited to various PEDIG RCTs suggested that children aged less than 7 years were more responsive to treatment than older subjects, with the effect of age being stronger in children with severe amblyopia.(92)

Stability of outcome

The long term stability of visual acuity in children treated for amblyopia is unclear. It has been reported that in up to 25% of children visual acuity can 'slip' to varying degrees from best final acuity achieved in the first year following cessation of treatment.(93;94) We have not identified any long term follow up studies on visual outcome into adulthood.

Summary

The current evidence base suggests that occlusion treatment is, on average, associated with a gain of at least 1 line of logMAR acuity in amblyopic children treated at age 3-5 years. There is also evidence that, *overall*, treatment undertaken before 4 years of age does not confer significantly better vision in either the short or long term than treatment started between 4 and 6 years. However a delay in treatment for children aged 4-5 years old with more severe amblyopia may lead to worse outcomes for children. Importantly, it is these children who have the greater risk of disabling bilateral visual impairment should visual loss occur in the better seeing eye in later life.

- Criterion 10 met? **YES, partly**

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

The 2010 Royal College of Ophthalmologists guidelines on the management of amblyopia provide a summary of the recommended age and cause dependent treatments for amblyopia (www.rcophth.ac.uk/core/core_picker/download.asp?id=939).

- Criterion 11 met? **YES**

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

There have been no national audits of the management or outcomes of the screening and treatment of amblyopia from which variations in practice can be assessed or addressed. This is a significant gap in the current evidence base.

Criterion 12 met? **NOT MET AS INSUFFICIENT EVIDENCE TO ASSESS CRITERION**

13. There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened

There are no randomized controlled trials of the effectiveness of childhood vision screening at ages 4-5 years in reducing morbidity. The recent systematic reviews of the effectiveness of childhood vision screening all conclude that there is no good evidence on the impact of screening in reducing morbidity, and that there is a need for more research.(61;95-98). Recent population based studies from Israel and Sweden report that populations which have undergone screening for amblyopia have a lower prevalence of amblyopia than those which have not.(99;100)

A randomized trial embedded within ALSPAC (Avon Longitudinal Study of Parents and Children) showed that intensive repeated vision screening between 6 months and 3 years old compared to one-off screening at age 3 years resulted in a small difference in visual acuity at 7.5 years old for children with amblyopia (0.14 versus 0.2 or half a line of logMAR, p=0.002) although 45% of recruited children were lost to follow up, and there was no difference between the two groups in the intention to screen analyses.(101;102) Notably, families from lower socioeconomic status groups (as determined by parental occupation) were more likely to have children with an eye disorder (predominantly hypermetropia as well as amblyopia) but were significantly less likely to seek out and see an eye care specialist (OR 0.65, 95% CI 0.43 – 0.98)(103). This highlights the potential value of universal screening of a ‘captive’ population at school entry in addressing inequities in access or provision.

- Criteria 13 met? **NOT MET AS INSUFFICIENT EVIDENCE TO ASSESS CRITERION**

14. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public

We were unable to identify UK population based studies which directly examined the acceptability of the programme to the public. However, recent observational studies on issues relating to screening report high levels of uptake / participation (71) and there is consistent support for universal screening from lay / voluntary sector organizations. This contrasts with the evidence of moderate / poor levels of concordance with occlusion (discussed earlier) and the adverse psychosocial impact of occlusion (discussed below).

- Criterion 14 met? **NOT MET AS INSUFFICIENT EVIDENCE TO ASSESS CRITERION**

15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment)

The 1997 HTA report and the 2005 NSC policy update concluded that occlusion treatment of amblyopia may not be free of harm and that children who wear glasses may be teased, but overall the benefits outweighed this negative impact where there was significantly reduced vision.

We were unable to identify any studies on harms caused by the screening test or subsequent diagnostic procedures. However, there is a body of evidence on the negative impact of treatment (both glasses and occlusion), on child and parent proxy report of quality of life, specifically in relation to a child's perception of self, relationship with carers and with peers (104-111) Lower self-esteem was reported by 10 to 12 year olds (N=47) who had previously undergone occlusion or refractive correction for amblyopia compared to age matched controls. (107) Within ALSPAC, reports of peer verbal and physical bullying of children were 35% more common amongst children who wore patches or glasses for amblyopia.(104) In a multidisciplinary qualitative study of the psychosocial impact of amblyopia, through interviews with 41 children and young people aged 3-18 years and their families, it was found that that although some children (usually those with good parental and peer support systems) were able to maintain a positive perception of their treatment,

for others initiation of amblyopia treatment resulted in a ‘spoiling’ of self -identity, feelings of stigma, and withdrawal from peers.(110) Conversely, in a prospective study using parental proxy reports from carers of children aged 4 – 6 years old, whilst there was a more negative perception towards the child following the initiation of treatment, there was no evidence of an association between occlusion and the carer’s perception of stress or perception of the child’s well-being.(111) Hrisos et al also failed to find an association between parent proxy measures of childhood well-being and occlusion therapy.(109)

The physical harms of amblyopia treatment include skin irritation with wearing of occlusive patches, which although rarely discussed, affected 5% of children in one randomised controlled trial(81). Adverse systemic and topical drug reactions following use of topical atropine for chemical penalisation have also been described in several of the PEDIG randomised controlled trials (Table 3).

Summary

Overall, from studies which directly measured the child’s experience and perceptions there is evidence of some negative impact of amblyopia therapy in some children. It is difficult to quantify and compare the psychological harm of amblyopia treatment with the negative impact and disutility of amblyopia *per se*. Population based longitudinal studies of quality of life, socioeconomic outcomes and patient perceived disutility are needed, using robust, age-group specific instruments or outcome measures and of sufficient size to enable ‘adjusted’ multivariable analysis. The significant challenges to conducting such studies may explain the dearth of such research so far.

- Criterion 15 met? **NOT MET AS INSUFFICIENT EVIDENCE TO ASSESS CRITERION,**

16. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money). Assessment against this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource

A series of economic evaluations of the cost effectiveness of vision screening at 3 years of

age in Germany, led by Konig,(112-114) has identified the critical influence of the costs of examinations, disorder prevalence, test sensitivity and specificity on the overall costs of a screening programme. The estimated cost-effectiveness ratio of screening (programme costs per each detected case) varied from 242 to 3641 Euro depending on the parameters used within the model (which were drawn in part from primary research). Despite this, the authors concluded that screening was cost effective. Researchers in North America have also concluded that visual acuity screening in childhood is cost effective practice, based on models drawing on estimates from the literature..(115) These models of screening include testing for potentially amblyogenic conditions (refractive error and strabismus) rather than for reduced vision per se, and so are not directly applicable to current practice in the UK.

In a recent UK HTA commissioned report(96) the cost-effectiveness of screening, again for both amblyopia and amblyogenic factors, by orthoptists at ages 3-5 years was modeled using parameter values from the literature. The lowest estimated cost per quality-adjusted life-year (QALY) gained through screening was £134, 963, significantly higher than the £20,000 - £30,000 per QALY considered by NICE to be a cost-effective use of resources. These models used a higher prevalence of amblyopia (4.8%) than would be expected in the UK using the NSC/RCOphth screening threshold of LogMAR worse than 0.2, which may have resulted in an over statement of cost effectiveness. However, this estimate was highly sensitive to the key unknown factor of the disutility value of amblyopia per se and was also very sensitive to the risk and disutility of visual impairment due to loss of vision in the non-amblyopic eye: a theoretical 2% reduction in utility due to amblyopia resulted in the estimated QALY cost falling to £17,000.(96)

- Criterion 16 met? **NOT MET AS INSUFFICIENT EVIDENCE TO ASSESS CRITERION**

17. All other options for managing the condition should have been considered (e.g. improving treatment, providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available

This criterion is not applicable to vision screening in children aged between 4 and 5 years.

18. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assessment standards.

There is no national guidance on how screening programmes should be managed or monitored, and there are no high quality studies in this area.

- Criteria 18 met? **NO**

19. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme

Although recent surveys by voluntary sector and consumer groups have suggested that screening is undertaken by the vast majority of Primary Care Trusts, there has been no national mapping of facilities or manpower or assessment of their adequacy. This is significant gap in the evidence base.

- Criterion 19 met? **NOT MET AS INSUFFICIENT EVIDENCE TO ASSESS CRITERION**

20. Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice

Information for parents and children /young people is available through the Healthy Child Programme, the National Screening Committee and the NHS. However, there is no guidance as to how the information about screening should be made available to potential participants.

Of related interest, a survey of UK orthoptists reported that 25% of clinicians never, and

36% only sometimes gave written information on occlusion to parents of children with amblyopia when embarking on treatment.(116) This is of particular importance as lack of information to parents has been found to be associated with poor concordance (and thus poor response to) amblyopia treatment in one randomized trial(117) and several non-controlled studies.(108;118)

- Criteria 20 met? **YES, PARTLY - INCOMPLETE EVIDENCE**

21. Public pressure for widening the eligibility criteria, for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public

There is pressure from some lay groups and some professional bodies to widen the eligibility criteria to include other ocular conditions such as strabismus or refractive error even where these are not associated with amblyopia. However we found no high quality evidence to support changes to the current programme.

- Criterion 21 met: **YES** - **THERE ARE NO SCIENTIFICALLY JUSTIFIABLE INDICATIONS FOR CHANGING THE ELIGIBILITY CRITERIA**

22. If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members

This criterion is not applicable to vision screening in children aged between 4 and 5 years.

Conclusion

Since the 1997 HTA report on childhood vision screening, considerable primary research and a number of systematic reviews have been undertaken to address gaps in the evidence base.

Nevertheless, several questions remain unanswered, of which the most important is the nature and magnitude of the impact of amblyopia *per se*. This is partly attributable to the predominance of amblyopia as the main cause of reduced vision in children managed in hospital eye services. The increased risk for individuals with amblyopia of vision impairment or blindness due to subsequent loss of vision in their non-amblyopic eye is of significance, especially as a preventable cause of visual disability, although at a population level this degree of visual loss is an uncommon event. The 'real life' correlates of amblyopia and its disutility (in conventional health economic terms) remain unclear, despite the fact that these are the most important parameters in assessing value and cost-effectiveness of screening.

There is no direct evidence that the overall benefits (outcomes) of screening a 'captive' population of children aged 4-5 years at school entry are outweighed by the benefits of screening at earlier ages. By contrast, there is good evidence that screening at ages under 4 years may increase the proportion of children with normal vision who, because of their developmental status, 'fail' vision screening necessitating further examination to accurately assess their vision and rule out amblyopia, thus increasing opportunity and economic costs. Screening later than the age of 4-5 years is likely to result in poorer outcomes in children with moderate and severe amblyopia, and is unlikely to confer benefit in terms of increased reliability of testing.

LogMAR-based crowded visual acuity tests are the most appropriate tests for vision screening to detect amblyopia, but there is presently insufficient evidence to guide the precise choice from the different crowded logMAR tests available for use in children aged 4-5 years.

Implications for policy and practice

We have found no robust evidence to support significant changes to the content of the current NSC recommended vision screening programme of children aged 4 – 5 years in the UK. These NSC recommendations are fully in line with the most recent equivalent major national policy review in the USA, where screening at younger ages has previously been strongly advocated. There is some evidence of variation in implementation in the UK and thus there is a need for those commissioning and providing screening services to promote adoption of existing national guidance on the content of the programme. In order to standardize and optimize the programme, there is a pressing need for further national guidance from the NSC and Royal College of Ophthalmologists in relation to

- Specific choice of crowded LogMAR acuity test for screening
- Diagnostic pathways following detection of reduced vision at screening
- Audit and governance of the screening service,

Standardisation of approaches would provide the context for a well-designed evaluation to address areas of incomplete evidence such as acceptability of vision testing to children/their families, stability and long term visual outcomes in both treated and untreated children.

Implications for research

Whilst attempts have been made to fill the knowledge gaps identified by the 1997 HTA report and other literature reviews, there remains a need for primary research in a number of areas.

More precise estimates of the prevalence and incidence of amblyopia (acuity worse than 0.2 logMAR, 6/9.5 Snellen) amongst children aged 4 – 5 years in the UK would be valuable for programme planning.

A significant gap remains in relation to our understanding of the ‘real-life’ adverse impact of amblyopia across the life course, and the extent to which the disutility due to amblyopia is permanently reduced by screening and treatment. The latter questions require, in particular, robust population based assessment of long term outcome after treatment, ideally through longitudinal studies of quality of life, socioeconomic status, behaviours and patient perceived disutility. Such research will be challenging but without it, our understanding of the value and effectiveness of screening will remain incomplete, being based on indirect evidence.

The lack of equipoise amongst clinicians in relation to the effectiveness of treatment is likely to continue to prevent any trials in which children are randomized to receive no treatment. However with standardisation of provision and introduction of standards relating to audit and governance, the current programme could provide the context for evaluations of long term visual outcomes of treatment and their stability.

APPENDIX

Literature search and review methodology

Sources searched: Medline (OvidSP), Embase, PsychINFO and the Cochrane library.

Dates of search: As this report is an update to the 1997 HTA report, the search period covers January 1995 July 2012

Search 26/07/2012 (all databases on OVID)

1. (randomi?ed or randomi?ed control* trial*).tw. (894219)
2. Cohort/ or cohort.tw. (566571)
3. (case-control or longitudinal).tw. (520865)
4. Randomized Controlled Trials as Topic/ (100160)
5. 1 or 2 or 3 or 4 (1888351)
6. child/ or child, preschool/ (2956957)
7. (Treatment or Therapy or Management).tw. (9715796)
8. 6 and 7 (689547)
9. (Amblyopia or Refraction or Refractive or Strabismus or Squint or Hypermetropia or Myopia or Anisometropia).tw. (115490)
10. 5 and 8 and 9 (642)
11. (Amblyopia or Refraction or Refractive or Strabismus or Squint or Vision or Blindness).tw. (357146)
12. Mass Screening/ (124599)
13. screen*.ti. (249559)
14. exp Vision Tests/ (104466)
15. 12 or 13 or 14 (416162)
16. 5 and 6 and 11 and 15 (754)
17. Refractive Errors/ (15536)
18. Amblyopia/ or amblyopia.tw. (19451)
19. exp Strabismus/ or squint.tw. (36118)
20. Hyperopia/ or hypermetropia.tw. (7828)
21. Myopia/ or myopia.tw. (40971)

22. Anisometropia/ or anisometropia.tw. (4251)
23. Eyeglasses/ or (spectacles or glasses).tw. (34745)
24. Blindness/ (45160)
25. (visual* adj impair*).tw. (20444)
26. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 (185604)
27. 5 and 6 and 26 (2051)
28. 5 and 18 (1119)
29. (prevalence or surveillance).tw (1243689))
30. 29 and 18 (1171)
31. Cost Effectiveness/ or Cost Effective.tw (267531)
32. 31 and (18 or 16) (197)
33. Quality of Life.tw (422194)
34. 33 and 18 (248)
35. 10 or 16 or 27 or 28 or 30 (4200)
36. limit 31 to yr="1995 -Current" (**3732**)

Once duplicates removed: 2971

Cochrane search (all databases)

1. Amblyopia (340)
2. (Prevalence OR surveillance):ti,ab,kw (11827)
3. Treatment OR Therapy OR Management (419090)
4. Quality of Life (33957)
5. #1 AND #2 (21)
6. #1 AND #3 (252)
7. #1 AND #4 (35)
8. Vision screening (842)
9. Child (76146)
10. Cost Effectiveness (24127)
11. #8 AND #9 (381)
12. #8 AND #10 (313)
13. #5 OR #6 OR #7 OR #11 OR #12 (755)
14. (#13), from 1995 to 2012 **(701)**

After removal duplicates: 512
3343 in total

Of the 3343 titles, 817 abstracts have been assessed, and from these abstracts 207 full texts have been assessed. 82 of these studies were formally included within the review. (Table 4).

In addition, 14 studies which were identified from the reference list of selected papers but which had not been identified by the search were also considered for inclusion: 4 were included.

Quality

Two reviewers worked independently. We performed a first pass appraisal of each abstract followed by a retrieval of selected full text papers. Systematic reviews, randomized controlled trials and population based observational studies were prioritized. Studies which were identified from the reference list of selected papers but which had not been identified

by the search were also included within this review. We excluded narrative reviews, and conference abstracts. Papers that were not in English were not included as we did not have resource for full text translation.

Appendix Table 1 Studied included in the review

Systematic reviews and meta-analysis	**6**
• The condition (1)	
• The screening programme (4)	
• Cost effectiveness (1)	
The condition	**37**
• Prevalence/incidence	
Population based studies (23)	
UK based population studies (2)	
• Impact	
Visual function and health (5)	
Quality of life (1)	
General and mental health and socioeconomic outcome (3)	
• Natural history (3)	
The test	**12**
The treatment	**24**
• Efficacy and effectiveness of treatment	
Randomised controlled trials (3)	
• Impact of age on treatment (2)	
• Long terms outcomes (0)	
• Comparisons of different treatments (19)	
• Treatment harm (8)	
The screening programme	**7**
• Effectiveness of screening (3)	
• Cost-effectiveness (4)	
Total	**86**

References

Reference List

(1) Snowdon SK, Stewart-Brown SL. Preschool vision screening. Health Technol Assess 1997;1:i-iv.

(2) Stewart CE, Stephens DA, Fielder AR, Moseley MJ, Cooperative R. Objectively monitored patching regimens for treatment of amblyopia: randomised trial. Bmj 2007;335:707.

(3) Rahi JS, Cumberland PM, Peckham CS, British Childhood Visual Impairment Interest G. Improving detection of blindness in childhood: the British Childhood Vision Impairment study. Pediatrics 2010;126:e895-e903.

(4) Rahi JS, Dezateux C. Epidemiology of visual impairment in Britain. Arch Dis Child 1998;78:381-6.

(5) Robaei D, Rose KA, Ojaimi E, Kifley A, Martin FJ, Mitchell P. Causes and associations of amblyopia in a population-based sample of 6-year-old Australian children. Archives of Ophthalmology 2006;124(6):2006-884.

(6) Williams C, Northstone K, Howard M, Harvey I, Harrad RA, Sparrow JM. Prevalence and risk factors for common vision problems in children: data from the ALSPAC study. British Journal of Ophthalmology 2008 July;92(7):959-64.

(7) Robaei D, Huynh SC, Kifley A, Mitchell P. Correctable and Non-Correctable Visual Impairment in a Population-Based Sample of 12-Year-Old Australian Children. American Journal of Ophthalmology 2006;142(1):July-118.

(8) Pai A, Mitchell P. Prevalence of amblyopia and strabismus. Ophthalmology 2010;117(10):October-2044.

(9) Richardson SR, Wright CM, Hrisos S, Buck D, Clarke MP. Stereoacuity in unilateral visual impairment detected at preschool screening: outcomes from a randomized controlled trial. Invest Ophthalmol Vis Sci 2005;46:150-4.

(10) Wallace DK, Lazar EL, Melia M, Birch EE, Holmes JM, Hopkins KB et al. Stereoacuity in children with anisometropic amblyopia. J Aapos 2011;15:455-61.

(11) Salomao SR, Ventura DF. Large sample population age norms for visual acuities obtained with Vistech-Teller Acuity Cards. Invest Ophthalmol Vis Sci 1995 March;36(3):657-70.

(12) Mayer DL, Beiser AS, Warner AF, Pratt EM, Raye KN, Lang JM. Monocular acuity norms for the Teller Acuity Cards between ages one month and four years. Invest Ophthalmol Vis Sci 1995 March;36(3):671-85.

(13) Pan Y, Tarczy-Hornoch K, Cotter SA, Wen G, Borchert MS, Azen SP et al. Visual acuity norms in pre-school children: The multi-ethnic pediatric eye disease study. Optometry and Vision Science 2009;86(6):June-612.

(14) Stankovic B, Milenkovic S. Continuous full-time occlusion of the sound eye vs full-time occlusion of the sound eye periodically alternating with occlusion of the amblyopic eye in treatment of amblyopia: a prospective randomized study. Eur J Ophthalmol 2007;17:11-9.

(15) Menon V, Shailesh G, Sharma P, Saxena R. Clinical trial of patching versus atropine penalization for the treatment of anisometropic amblyopia in older children. Journal of AAPOS 2008;12(5):October-497.

(16) Hertle RW, Scheiman MM, Beck RW, Chandler DL, Bacal DA, Birch E et al. Stability of visual acuity improvement following discontinuation of amblyopia treatment in children aged 7 to 12 years. Arch Ophthalmol 2007;125:655-9.

(17) Singh I, Sachdev N, Brar GS, Kaushik S. Part-time occlusion therapy for amblyopia in older children. Indian J Ophthalmol 2008;56:459-63.

(18) Scheiman MM. Randomized trial of treatment of amblyopia in children aged 7 to 17 years. Archives of Ophthalmology 2005;123(4):April-447.

(19) Gunnlaugsdottir E, Arnarsson A, Jonasson F. Prevalence and causes of visual impairment and blindness in Icelanders aged 50 years and older: the Reykjavik Eye Study. Acta Opthalmologica 2008 November;86(7):778-85.

(20) Attebo K, Mitchell P, Cumming R, Smith W, Jolly N, Sparkes R. Prevalence and causes of amblyopia in an adult population. Ophthalmology 1998;105(1):Jan-159.

(21) Williams C, Northstone K, Howard M, Harvey I, Harrad RA, Sparrow JM. Prevalence and risk factors for common vision problems in children: data from the ALSPAC study. British Journal of Ophthalmology 2008 July;92(7):959-64.

(22) Donnelly UM, Stewart NM, Hollinger M. Prevalence and outcomes of childhood visual disorders. Ophthalmic Epidemiology 2005;12(4):Aug-250.

(23) Multi-Ethnic Pediatric Eye Disease Study Group. Prevalence of amblyopia and strabismus in African American and Hispanic children ages 6 to 72 months the multi-ethnic pediatric eye disease study. Ophthalmology 2008 July;115(7):1229-36.

(24) Friedman DS, Repka MX, Katz J, Giordano L, Ibironke J, Hawse P et al. Prevalence of Amblyopia and Strabismus in White and African American Children Aged 6 through 71 Months. The Baltimore Pediatric Eye Disease Study. Ophthalmology 2009;116(11):November-2134.

(25) Robaei D, Kifley A, Rose KA, Mitchell P. Impact of amblyopia on vision at age 12 years: Findings from a population-based study. Eye 2008;22(4):April-502.

(26) Pi LH, Chen L, Liu Q, Ke N, Fang J, Zhang S et al. Prevalence of eye diseases and causes of visual impairment in school-aged children in Western China. Journal of Epidemiology 2012;22(1):37-44.

(27) Chia A, Dirani M, Chan Y-H, Gazzard G, Au EKG, Selvaraj P et al. Prevalence of amblyopia and strabismus in young singaporean chinese children. Investigative Ophthalmology and Visual Science 2010;51(7):July-3417.

(28) Dirani M, Zhou B, Hornbeak D, Chang BC, Gazzard G, Chia A et al. Prevalence and causes of decreased visual acuity in Singaporean Chinese preschoolers. British Journal of Ophthalmology 2010;94(12):December-1565.

(29) Fan DS, Lai C, Lau HH, Cheung EY, Lam DS. Change in vision disorders among Hong Kong preschoolers in 10 years. Clinical & experimental ophthalmology 2011 July;39(5):398-403.

(30) Khandekar R, Parast N, Arabi A. Evaluation of 'vision screening' program for three to six-year-old children in the Republic of Iran. Indian Journal of Ophthalmology 2009;57(6):01-442.

(31) Jamali P, Fotouhi A, Hashemi H, Younesian M, Jafari A. Refractive errors and amblyopia in children entering school: Shahrood, Iran. Optometry & Vision Science 2009 April;86(4):364-9.

(32) Lithander J. Prevalence of amblyopia with anisometropia or strabismus among schoolchildren in the Sultanate of Oman. Acta Ophthalmologica Scandinavica 1998;76(6):December-662.

(33) Tananuvat N, Manassakorn A, Worapong A, Kupat J, Chuwuttayakorn J, Wattananikorn S. Vision screening in schoolchildren: Two years results. Journal of the Medical Association of Thailand 2004;87(6):June-684.

(34) He M, Zeng J, Liu Y, Xu J, Pokharel GP, Ellwein LB. Refractive error and visual impairment in urban children in southern China. Investigative Ophthalmology and Visual Science 2004;45(3):March-799.

(35) Faghihi M, Ostadimoghaddam H, Yekta AA. Amblyopia and strabismus in Iranian schoolchildren, Mashhad. Strabismus 2011;19(4):December-152.

(36) Salomao SR, Cinoto RW, Berezovsky A, Mendieta L, Nakanami CR, Lipener C et al. Prevalence and causes of visual impairment in low-middle income school children in Sao Paulo, Brazil. Investigative Ophthalmology and Visual Science 2008;49(10):October-4313.

(37) Ohlsson J, Villarreal G, Sjostrom A, Cavazos H, Abrahamsson M, Sjostrand J. Visual acuity, amblyopia, and ocular pathology in 12- to 13-year-old children in Northern Mexico. Journal of AAPOS 2003;7(1):February-53.

(38) Ohlsson J, Villarreal G, Sjostrom A, Abrahamsson M, Sjostrand J. Visual acuity, residual amblyopia and ocular pathology in a screened population of 12-13-year-old children in Sweden. Acta Ophthalmologica Scandinavica 2001;79(6):2001-595.

(39) Wang Y, Liang YB, Sun LP, Duan XR, Yuan RZ, Wong TY et al. Prevalence and causes of amblyopia in a rural adult population of Chinese: The Handan Eye Study. Ophthalmology 2011;118(2):February-283.

(40) Brown SA, Weih LM, Fu CL, Dimitrov P, Taylor HR, McCarty CA. Prevalence of amblyopia and associated refractive errors in an adult population in Victoria, Australia. Ophthalmic Epidemiology 2000;7(4):Dec-258.

(41) Chia EM, Mitchell P, Ojaimi E, Rochtchina E, Wang JJ. Assessment of vision-related quality of life in an older population subsample: The Blue Mountains Eye Study. Ophthalmic Epidemiol 2006 December;13(6):371-7.

(42) Rahi JS, Cumberland PM, Peckham CS. Visual impairment and vision-related quality of life in working-age adults: findings in the 1958 British birth cohort. Ophthalmology 2009 February;116(2):270-4.

(43) Chua B, Mitchell P. Consequences of amblyopia on education, occupation, and long term vision loss. British Journal of Ophthalmology 2004;88(9):September-1121.

(44) Van LR, Eijkemans MJC, Vingerling JR, Hofman A, De Jong PTVM, Simonsz HJ. Risk of bilateral visual impairment in individuals with amblyopia: The Rotterdam study. British Journal of Ophthalmology 2007;91(11):November-1451.

(45) Rahi J, Logan S, Timms C, Russell-Eggitt I, Taylor D. Risk, causes, and outcomes of visual impairment after loss of vision in the non-amblyopic eye: a population-based study. Lancet 2002;360:597-602.

(46) O'Connor AR, Birch EE, Anderson S, Draper H. Relationship between Binocular Vision, Visual Acuity, and Fine Motor Skills. [Article]. Optometry & Vision Science December 2010;87(12):942-947(12):942-7.

(47) O'Connor AR, Birch EE, Anderson S, Draper H. The functional significance of stereopsis. Invest Ophthalmol Vis Sci 2010 April;51(4):2019-23.

(48) Carlton J, Kaltenthaler E. Health-related quality of life measures (HRQoL) in patients with amblyopia and strabismus: a systematic review. Br J Ophthalmol 2011 March;95(3):325-30.

(49) Wen G, McKean-Cowdin R, Varma R, Tarczy-Hornoch K, Cotter SA, Borchert M et al. General health-related quality of life in preschool children with strabismus or amblyopia. Ophthalmology 2011 March;118(3):574-80.

(50) Rahi JS, Cumberland PM, Peckham CS. Does amblyopia affect educational, health, and social outcomes? Findings from 1958 British birth cohort. Bmj 2006 April 8;332(7545):820-5.

(51) van de Graaf ES, van Kempen-du SH, Looman CWN, Simonsz HJ. Utility analysis of disability caused by amblyopia and/or strabismus in a population-based, historic cohort. Graefe's Archive for Clinical and Experimental Ophthalmology 2010;248(12):December-1807.

(52) Donahue SP. Relationship Between Anisometropia, Patient Age, and the Development of Amblyopia. American Journal of Ophthalmology 2006;142(1):July-140.

(53) Hubel DH, Wiesel TN. The period of susceptibility to the physiological effects of unilateral eye closure in kittens. J Physiol 1970 February;206(2):419-36.

(54) Chak M, Wade A, Rahi JS. Long-term visual acuity and its predictors after surgery for congenital cataract: findings of the British congenital cataract study. Invest Ophthalmol Vis Sci 2006 October;47(10):4262-9.

(55) Levi DM. Prentice Award Lecture 2011: Removing the Brakes on Plasticity in the Amblyopic Brain. [Review]. Optometry & Vision Science June 2012;89(6):827-838(6):827-38.

(56) Simons K, Preslan M. Natural history of amblyopia untreated owing to lack of compliance. Br J Ophthalmol 1999;83:582-7.

(57) Bertuzzi F, Orsoni JG, Porta MR, Paliaga GP, Miglior S. Sensitivity and specificity of a visual acuity screening protocol performed with the Lea Symbols 15-line folding distance chart in preschool children. Acta Ophthalmol Scand 2006 December;84(6):807-11.

(58) HOWARD CM, FIRTH AYM. Is the Cardiff Acuity Test Effective in Detecting Refractive Errors in Children? [Article]. Optometry & Vision Science August 2006;83(8):E577-E582(8):E577-E582.

(59) Schmucker C, Grosselfinger R, Riemsma R, Antes G, Lange S, Lagreze W et al. Diagnostic accuracy of vision screening tests for the detection of amblyopia and its risk factors: a systematic review. Graefes Arch Clin Exp Ophthalmol 2009;247:1441-54.

(60) Chou R, Dana T, Bougatsos C. Screening for visual impairment in children ages 1-5 years: update for the USPSTF. Pediatrics 2011;127:e442-e479.

(61) Mathers M, Keyes M, Wright M. A review of the evidence on the effectiveness of children's vision screening. Child Care Health Dev 2010;36:756-80.

(62) Vision in Preschoolers (VIP) Study Group. Effect of Age Using Lea Symbols or HOTV for Preschool Vision Screening. [Article]. Optometry & Vision Science February 2010;87(2):87-95(2):87-95.

(63) Leone JF, Gole GA, Mitchell P, Kifley A, Pai AS, Rose KA. Visual acuity testability and comparability in Australian preschool children: the Sydney Paediatric Eye Disease Study. Eye (Lond) 2012 July;26(7):925-32.

(64) VISION IN PRESCHOOLERS STUDY GROUP. Preschool Visual Acuity Screening with HOTV and Lea Symbols: Testability and Between-Test Agreement. [Article]. Optometry & Vision Science September 2004;81(9):678-683(9):678-83.

(65) Vision in Preschoolers (VIP) Study Group. Effect of Age Using Lea Symbols or HOTV for Preschool Vision Screening. [Article]. Optometry & Vision Science February 2010;87(2):87-95(2):87-95.

(66) Hered RW, Murphy S, Clancy M. Comparison of the HOTV and Lea Symbols charts for preschool vision screening. J Pediatr Ophthalmol Strabismus 1997;34:24-8.

(67) Jones D, Westall C, Enssle M. A comparison of two visual acuity tests in pediatric partients with amblyopia. 2002.

(68) Sonksen PM, Wade AM, Proffitt R, Heavens S, Salt AT. The Sonksen logMAR test of visual acuity: II. Age norms from 2 years 9 months to 8 years. J AAPOS 2008 February;12(1):18-22.

(69) Drover JR, Felius J, Cheng CS, Morale SE, Wyatt L, Birch EE. Normative pediatric visual acuity using single surrounded HOTV optotypes on the Electronic Visual Acuity Tester following the Amblyopia Treatment Study protocol. J AAPOS 2008 April;12(2):145-9.

(70) Taylor K, Elliott S. Interventions for strabismic amblyopia. Cochrane Database Syst Rev 2011;CD006461.

(71) Taylor K, Powell C, Hatt Sarah R, Stewart C. Interventions for unilateral and bilateral refractive amblyopia. 2012.

(72) Hatt S, Antonio-Santos A, Powell C, Vedula SS. Interventions for stimulus deprivation amblyopia. Cochrane Database Syst Rev 2006;CD005136.

(73) Lambert SR, Wilson ME, Plager DA, Morrison DG, VanderVeen DK, Freedman SF. Findings of the infant aphakia treatment study. 2011;Conference: 37th Annual Meeting of the American Association for Pediatric Ophthalmology and Strabismus San Diego, CA United States. Conference Start: 20110330 Conference End: 20110403. Conference Publication: (var.pagings). 15 (1):e37.

(74) US Preventive Services Task Force. Vision screening for children 1 to 5 years of age: US Preventive Services Task Force Recommendation statement. Pediatrics 2011;127(2):340-6.

(75) Awan M, Proudlock FA, Gottlob I. A randomized controlled trial of unilateral strabismic and mixed amblyopia using occlusion dose monitors to record compliance. Invest Ophthalmol Vis Sci 2005;46:1435-9.

(76) Wallace DK, Pediatric Eye Disease Investigator G, Edwards AR, Cotter SA, Beck RW, Arnold RW et al. A randomized trial to evaluate 2 hours of daily patching for strabismic and anisometropic amblyopia in children. Ophthalmology 2006;113:904-12.

(77) Repka MX, Beck RW, Holmes JM, Birch EE, Chandler DL, Cotter SA et al. A randomized trial of patching regimens for treatment of moderate amblyopia in children. Arch Ophthalmol 2003;121:603-11.

(78) Holmes JM, Kraker RT, Beck RW, Birch EE, Cotter SA, Everett DF et al. A randomized trial of prescribed patching regimens for treatment of severe amblyopia in children. Ophthalmology 2003;110:2075-87.

(79) Agervi P, Kugelberg U, Kugelberg M, Simonsson G, Fornander M, Zetterstrom C. Randomized evaluation of spectacles plus alternate-day occlusion to treat amblyopia. Ophthalmology 2010;117:381-7.

(80) Pediatric Eye Disease Investigator G. A comparison of atropine and patching treatments for moderate amblyopia by patient age, cause of amblyopia, depth of amblyopia, and other factors. Ophthalmology 2003;110:1632-7.

(81) Scheiman MM, Hertle RW, Kraker RT, Beck RW, Birch EE, Felius J et al. Patching vs atropine to treat amblyopia in children aged 7 to 12 years: a randomized trial. Arch Ophthalmol 2008;126:1634-42.

(82) Repka MX, Kraker RT, Beck RW, Birch E, Cotter SA, Holmes JM et al. Treatment of severe amblyopia with weekend atropine: results from 2 randomized clinical trials. J Aapos 2009;13:258-63.

(83) Pediatric Eye Disease Investigator Group Writing C, Wallace DK, Kraker RT, Beck RW, Cotter SA, Davis PL et al. Randomized trial to evaluate combined patching and atropine for residual amblyopia. Arch Ophthalmol 2011;129:960-2.

(84) Medghalchi A, Dalili S. A randomized Trial of Atropine versus patching for treatment of moderate amblyopia. 2011;13 (8):7-9.

(85) Repka MX, Cotter SA, Beck RW, Kraker RT, Birch EE, Everett DF et al. A randomized trial of atropine regimens for treatment of moderate amblyopia in children. Ophthalmology 2004;111:2076-85.

(86) Pediatric Eye Disease Investigator G. A randomized trial of near versus distance activities while patching for amblyopia in children aged 3 to less than 7 years. Ophthalmology 2008;115:2071-8.

(87) Agervi P, Kugelberg U, Kugelberg M, Simonsson G, Fornander M, Zetterstrom C. Treatment of anisometropic amblyopia with spectacles or in combination with translucent Bangerter filters. Ophthalmology 2009;116:1475-80.

(88) Pediatric Eye Disease Investigator Group Writing C, Rutstein RP, Quinn GE, Lazar EL, Beck RW, Bonsall DJ et al. A randomized trial comparing Bangerter filters and patching for the treatment of moderate amblyopia in children. Ophthalmology 2010;117:998-1004.

(89) Tejedor J, Ogallar C. Comparative efficacy of penalization methods in moderate to mild amblyopia. Am J Ophthalmol 2008;145:562-9.

(90) Pediatric Eye Disease Investigator G. Pharmacological plus optical penalization treatment for amblyopia: results of a randomized trial. Arch Ophthalmol 2009;127:22-30.

(91) Clarke MP, Wright CM, Hrisos S, Anderson JD, Henderson J, Richardson SR. Randomised controlled trial of treatment of unilateral visual impairment detected at preschool vision screening. Bmj 2003;327:1251.

(92) Holmes JM, Lazar EL, Melia BM, Astle WF, Dagi LR, Donahue SP et al. Effect of age on response to amblyopia treatment in children. Arch Ophthalmol 2011;129:1451-7.

(93) Holmes JM, Melia M, Bradfield YS, Cruz OA, Forbes B. Factors Associated with Recurrence of Amblyopia on Cessation of Patching. Ophthalmology 2007;114(8):August-1432.

(94) Holmes JM, Beck RW, Kraker RT, Astle WF, Birch EE, Cole SR et al. Risk of amblyopia recurrence after cessation of treatment. J Aapos 2004;8:420-8.

(95) Schmucker C, Grosselfinger R, Riemsma R, Antes G, Lange S, Lagreze W et al. Effectiveness of screening preschool children for amblyopia: a systematic review. BMC ophthalmol 2009;9:3.

(96) Carlton J, Karnon J, Czoski-Murray C, Smith KJ, Marr J. The clinical effectiveness and cost-effectiveness of screening programmes for amblyopia and strabismus in children up to the age of 4-5 years: a systematic review and economic evaluation. Health Technol Assess 2008;12:iii.

(97) Powell C, Porooshani H, Bohorquez MC, Richardson S. Screening for amblyopia in childhood. Cochrane Database Syst Rev 2005;CD005020.

(98) Powell C, Hatt SR. Vision screening for amblyopia in childhood. Cochrane Database Syst Rev 2009;CD005020.

(99) Eibschitz-Tsimhoni M, Friedman T, Naor J, Eibschitz N, Friedman Z. Early screening for amblyogenic risk factors lowers the prevalence and severity of amblyopia. J AAPOS 2000 August;4(4):194-9.

(100) Kvarnstrom G, Jakobsson P, Lennerstrand G. Visual screening of Swedish children: an ophthalmological evaluation. Acta Ophthalmol Scand 2001;79:240-4.

(101) Williams C, Northstone K, Harrad RA, Sparrow JM, Harvey I, Team AS. Amblyopia treatment outcomes after screening before or at age 3 years: follow up from randomised trial. Bmj 2002;324:1549.

(102) Williams C, Northstone K, Harrad RA, Sparrow JM, Harvey I, Team AS. Amblyopia treatment outcomes after preschool screening v school entry screening: observational data from a prospective cohort study. Br J Ophthalmol 2003;87:988-93.

(103) Majeed M, Williams C, Northstone K, Ben-Shlomo Y. Are there inequities in the utilisation of childhood eye-care services in relation to socio-economic status? Evidence from the ALSPAC cohort. Br J Ophthalmol 2008;92:965-9.

(104) Horwood J, Waylen A, Herrick D, Williams C, Wolke D. Common visual defects and peer victimization in children. Invest Ophthalmol Vis Sci 2005;46:1177-81.

(105) Williams C, Horwood J, Northstone K, Herrick D, Waylen A, Wolke D. The timing of patching treatment and a child's wellbeing. Br J Ophthalmol 2006 June;90(6):670-1.

(106) Holmes JM, Beck RW, Kraker RT, Cole SR, Repka MX, Birch EE et al. Impact of patching and atropine treatment on the child and family in the amblyopia treatment study. Arch Ophthalmol 2003;121:1625-32.

(107) Webber AL, Wood JM, Gole GA, Brown B. Effect of Amblyopia on Self-Esteem in Children. [Article]. Optometry & Vision Science November 2008;85(11):1074-1081(11):1074-81.

(108) Loudon SE, Passchier J, Chaker L, de Vos S, Fronius M, Harrad RA et al. Psychological causes of non-compliance with electronically monitored occlusion therapy for amblyopia. Br J Ophthalmol 2009;93:1499-503.

(109) Hrisos S, Clarke MP, Wright CM. The emotional impact of amblyopia treatment in preschool children: randomized controlled trial. Ophthalmology 2004;111:1550-6.

(110) Koklanis K, Abel LA, Aroni R. Psychosocial impact of amblyopia and its treatment: a multidisciplinary study. Clin Experiment Ophthalmol 2006 November;34(8):743-50.

(111) Choong YF, Lukman H, Martin S, Laws DE. Childhood amblyopia treatment: psychosocial implications for patients and primary carers. Eye (Lond) 2004 April;18(4):369-75.

(112) Konig H-H, Barry J-C, Leidl R, Zrenner E. Economic evaluation of orthoptic screening: Results of a field study in 121 German kindergartens. Investigative Ophthalmology and Visual Science 2002;43(10):October-3215.

(113) Konig HH, Barry JC. Cost-utility analysis of orthoptic screening in kindergarten: a Markov model based on data from Germany. Pediatrics 2004;113(2):Feb-108.

(114) Konig H-H, Barry JC, Leidl R, Zrenner E. Cost-effectiveness of orthoptic screening in kindergarten: A decision-analytic model. Strabismus 2000;8(2):2000-90.

(115) Joish VN, Malone DC, Miller JM. A cost-benefit analysis of vision screening methods for preschoolers and school-age children. J AAPOS 2003 August;7(4):283-90.

(116) Newsham D. The effect of recent amblyopia research on current practice in the UK. Br J Ophthalmol 2010;94:1352-7.

(117) Newsham D, Reinecke RD. Randomized controlled trial written information: Effect on parental nonconcordance with occlusion therapy. Evidence-Based Eye Care 2003;4(1):January-55.

(118) Tjiam AM, Groenewoud JH, Passchier J, Loudon SE, De GM, Hoogeveen WC et al. Determinants and outcome of unsuccessful referral after positive screening in a large birth-cohort study of population-based vision screening. Journal of Aapos: American Association for Pediatric Ophthalmology & Strabismus 2011 June;15(3):256-62.