Whole-population vision screening in children aged 4–5 years to detect amblyopia

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Amblyopia is a neurodevelopmental disorder that affects at least 2% of most populations and can lead to permanently reduced vision if not detected and treated within a specific period in childhood. Whole-population screening of children younger than 5 years is applied in many countries. The substantial diversity in existing programmes reflects their heterogeneous implementation in the absence of the complete evidence base that is now a pre-requisite for instituting screening. The functional importance of amblyopia at an individual level is unclear as data are scarce, but in view of the high prevalence the population-level effect might be notable. Screening of all children aged 4–5 years (eg, at school entry) confers most benefit and addresses inequity in access to timely treatment. Screening at younger ages is associated with increased risk of false-positive results, and at older ages with poor outcomes for children with moderate to severe amblyopia. We suggest that the real-life adverse effects of amblyopia should be characterised and screening and diagnosis should be standardised.

Published **Online** December 10, 2014 http://dx.doi.org/10.1016/S0140-6736(14)60522-5

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See **Online** for appendix

Introduction

Developmental neuroplasticity starting at birth drives structural and functional changes in the eye and brain during maturation of the visual system. Amblyopia is a neurodevelopmental disorder that arises secondary to disruption of normal processes during this sensitive period. It most commonly arises because of visual blur from defocus (refractive amblyopia), failure to maintain alignment of the eyes (strabismic amblyopia), structural disorders of the eye, such as cataract, that obscure incoming images (form-deprivation amblyopia), or a combination of these features. Both eyes might be affected, but the disorder is predominantly unilateral, and is generally associated with impaired or absent stereoacuity (depth perception).[1,2] Any childhood ocular disorder carries a risk of amblyopia and, therefore, it is the most prevalent disorder managed in paediatric ophthalmology. Standard clinical practice is to implement treatment within the critical period, which is thought to span from infancy to around age 7–9 years, to improve vision and enable development along as normal a vision trajectory as possible.[3]

Visual acuity is the key visual function. WHO and other organisations use acuity in the better eye to classify individuals as non-impaired, visually impaired, severely visually impaired, or blind.[4] Thus, individuals with reduced acuity in one eye, irrespective of severity, are not classified as visually impaired. In the UK, in more than 97% of children with severely reduced vision in both eyes the diagnosis is made early in childhood.[5] Diagnosis frequently arises owing to the concerns of carers and caregivers or in the context of the routine universal Newborn and Infant Physical Examination programme (figure 1) or other disorder-specific screening programmes. As amblyopia is a developmental disorder, affected children may grow up without a comparative visual experience and are likely to be unaware of the poorer vision in the amblyopic eye. Thus, screening at age 4–5 years is primarily aimed at identifying unilateral impaired vision with the aim of beginning intervention early.

In 1995, Snowdon and Stewart-Brown[6] reported a systematic review of childhood vision screening to detect amblyopia that was commissioned by the UK Health Technology Assessment body, which is responsible for independent assessment of effectiveness, costs, and effects of health-care interventions. They showed an absence of good quality research into efficacy of treatments for and disability associated with amblyopia. The conclusion was a recommendation that the UK National Screening Committee, the body responsible for the continuation, modification, or withdrawal of existing population screening programmes, consider whether to discontinue screening.[6] The findings were opposed by the international ophthalmic community, but did lead to a rationalisation of the existing practices in the UK. The findings also led to substantial primary research throughout the world that began to provide information on whole-population childhood vision screening programmes, which exist in most industrialised countries.

We undertook a systematic review of the evidence on childhood vision screening to detect amblyopia (figure 2, appendix pp 1–3). Here we summarise our findings, focusing on the fundamental public health issues—the

Search strategy and selection criteria

We searched Medline, Embase, PsychINFO, and the Cochrane library for papers published between January, 1995, and December, 2013 (appendix pp 1–2). We used the search terms "randomised control trial", "cohort", "case-control or longitudinal', "child or preschool", "amblyopia", "strabismus", "squint", "hypermetropia or myopia or anisometropia", "screening", and "prevalence or surveillance". Systematic reviews, randomised, controlled trials, and population-based observational studies were prioritised. Studies that were identified from the reference lists of selected papers but that had not been identified by the search were included. We excluded narrative reviews, conference abstracts, and non-English publications.

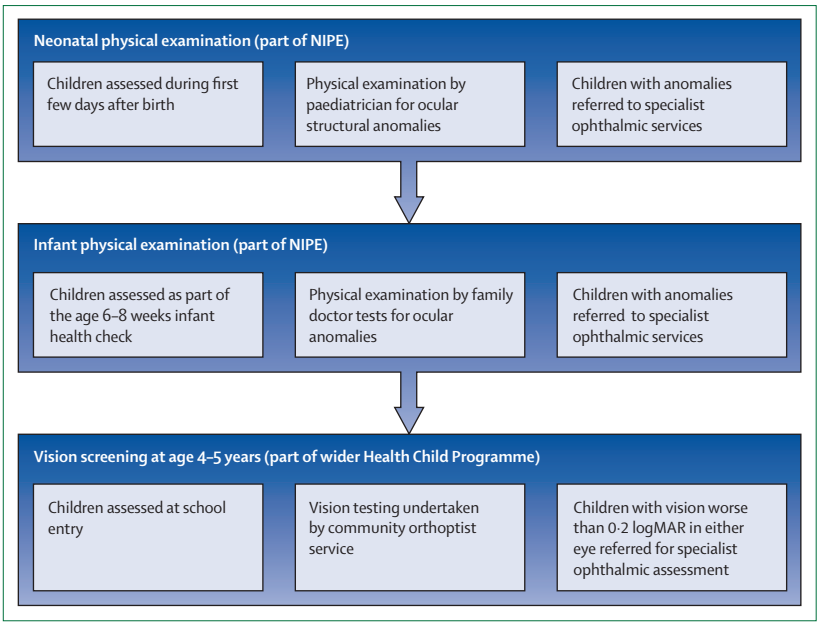


***Figure 1*: Framework of UK childhood whole-population eye and vision screening programmes**
NIPE=Newborn and Infant Physical Examination Programme.

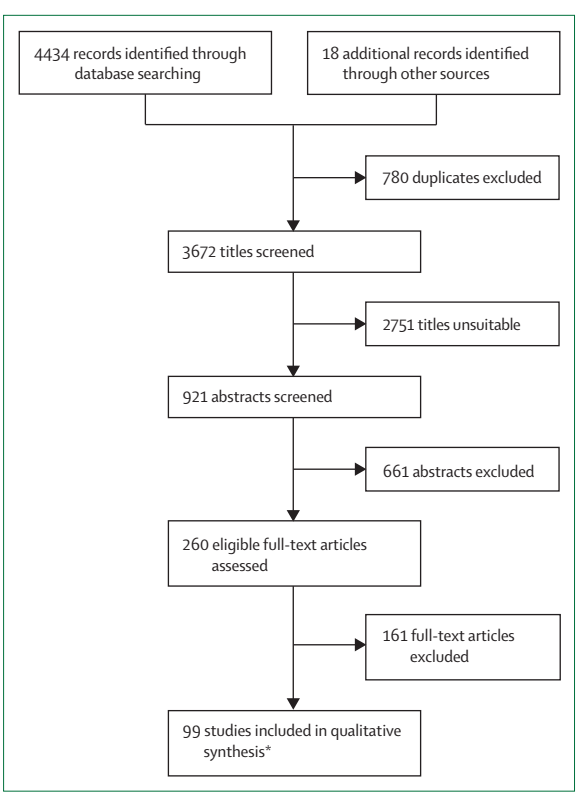


***Figure 2*: Literature search**
*Based on Centre of Evidence Based Medicine criteria.

appropriateness and effectiveness of universal childhood vision screening and the effectiveness of treatments for amblyopia.[7] For brevity we do not report on factors such as screening for risk factors or other conditions that might predispose to amblyopia or on screening thresholds. Similarly, we do not discuss other screening programmes, such as neonatal and infant programmes to detect major eye anomalies or screening of preterm children for retinopathy of prematurity, or best practice clinical surveillance of children at increased risk of ophthalmic disorders, such as those with hearing impairment or neurodevelopmental disorders.

Definitions and prevalence of amblyopia

Vision matures owing to structural and functional development of the eyes and visual pathways in early childhood. By definition, vision of 0·0 logMAR (6/6 Snellen) is taken to be normal adult acuity. Neonates have an average acuity worse than 1·0 logMAR (6/60), which improves to near adult levels by age 5–6 years.[8] As there is no internationally agreed definition or vision threshold for amblyopia, reported prevalence varies (tables 1, 2). This variation is compounded by substantial heterogeneity in study methods and characteristics of study populations, especially with respect to age and ethnic origin of participants (figure 3), with the latter in particular resulting in small subgroup sample sizes,[13–16,18] and the existence or absence of a screening programme. Among white children the prevalence of amblyopia at age 4–5 years was estimated in two studies to be 2·5%,[16,18] with an overall age-standardised estimate for children younger than 6 years of 1·9%.[14,15] These rates fall below the 4·0% population prevalence threshold for screening advocated by WHO, although, overall international prevalence estimates range from 1·0% to 5·0% (tables 1, 2). These differences make formal comparison difficult and preclude meaningful meta-analysis.

Data for the UK from the Avon Longitudinal Study of Parents and Carers (ALSPAC)[34] indicate a prevalence of 3·6% (95% CI 3·3–4·1) among children aged 7 years when the definition of amblyopia as vision worse than 0·2 logMAR (6/9·5 Snellen), an interocular difference of at least 0·2 logMAR (equivalent to 2·0 lines on a logMAR chart), or normal vision at age 7 years with a history of treatment for amblyopia is used. This estimate is higher than those derived from most studies based on national census records and using the same definition of amblyopia, which report an average prevalence of roughly 2·0%.[13,14,16,35]

Effects of amblyopia

Impaired vision in both eyes is recognised as having substantial effects on development, health, and quality of life, but the Health Technology Assessment body report by Snowdon and Stewart-Brown[6] found no robust evidence of disability in individuals with unilateral amblyopia. Research has since been directed at understanding the effects of reduced vision in one eye. Inconsistent associations have been made between unilaterally reduced vision in adulthood and impairment of mental health, general health, social functioning, and general quality of life in large

	Age at testing (years)	Study population	Participation rate (%)	Amblyopia definition	Number of participants	Prevalence (%)	Population screening programme
Acuity in worse eye ≥0·3 logMAR							
Fan et al, 2011[9]	3·0–6·0	Randomly selected preschool children in Hong Kong in 1996 and 2006	1996, 96·5%; 2006, 99·3%	≥0·3 logMAR	1996: 601; 2006: 823	1996, 3·8%; 2006, 2·7%	No
Polling et al, 2012[10]	3·0–12·0	Primary-health-care register in Poland	71%	≥0·3 logMAR or interocular difference 0·2 logMAR plus amblyogenic factors	402	3·1%	No
Robaei et al, 2006[11]	5·0–8·0	Stratified sampling from national census data in Australia	79%	≥0·3 logMAR or interocular difference ≥0·2 logMAR	1739	1·8%	No
Ganekal et al, 2013[12]	5·0–15·0	Random cluster sampling of schools in India	Not reported	>0·3 logMAR or interocular difference ≥2·0 lines	4020	1·1%	No
Acuity in worse eye ≥0·2 logMAR							
Friedman et al, 2009[13]	2·5–6·0	Stratified sampling from national census data in USA	97%	≥0·2 logMAR and interocular difference 0·2 logMAR	2546	1·8%	No
Multi-ethnic Pediatric Eye Disease Study Group, 2008[14]	2·5–6·0	Stratified sampling of African American and Hispanic children from national census data in USA	77%	≥0·2 logMAR and interocular difference 0·2 logMAR	3350	2·1%	No
McKean-Cowdin et al, 2013[15]	2·5–6·0	Stratified sampling from national census data in USA	80%	≥0·2 and interocular difference 0·2	9172	1·8%	No
Pai et al, 2012[16]	2·5–6·0	Stratified sampling of Asian and non-Hispanic white children from national census data in Australia	74%	≥0·2 logMAR or interocular difference 0·2 logMAR plus amblyogenic factors	1422	1·9%	No
Fu et al, 2014[17]	6·0–9·0	Stratified cluster sampling of all primary school children in China	93%	>0·2 logMAR or interocular difference ≥0·2 logMAR plus amblyogenic factors	2860	1·0%	No
Acuity in worse eye ≥0·18 logMAR							
Chia et al, 2010[18]	0·5–6·0	Residents of public housing in Singapore	72%	>0·18 logMAR or interocular difference 0·2 logMAR plus amblyogenic factors	1682	1·2%	Yes (ages 5–6 years)
Khandekar et al, 2009[19]	3·0–6·0	National screening programme in Iran	66%	>0·18 logMAR	1·4 million	1·3%	Yes

Table 1: **Prevalence of amblyopia in children younger than 6 years**

population-based studies in industrialised countries.[36,37] All the studies, however, investigated the effects of loss of previously normal vision due to disease or injury rather than abnormal vision development. In this section we discuss the evidence for effects of unilateral impaired vision due to amblyopia on the risk of visual impairment or blindness due to loss of vision in the better-seeing eye, on quality of life, general and mental health outcomes, and on education, employment, and other social outcomes.

General visual function

In individuals with unilateral amblyopia, loss of vision in the non-amblyopic eye can lead to permanent bilateral visual impairment or blindness. These outcomes have been investigated in three population-based studies, the Blue Mountain Eye study of Australians older than 49 years,[38] a longitudinal study of 7983 adults in Rotterdam, Netherlands,[32] and a national study in the UK, done through the British Ophthalmic Surveillance active surveillance network of clinicians, which identified 370 adults and children over a 1-year period who had loss of vision in the non-amblyopic eye.[33] The Australian and UK investigators defined visual impairment as being socially relevant if vision in the better eye was worse than 0·3 logMAR, which precludes driving in most industrialised countries, whereas the Rotterdam study used the WHO definition of acuity worse than 0·5 LogMAR (6/18 Snellen) in the better eye. The risk of bilateral visual impairment was increased by 2·7 times (95% CI 1·6–4·6) in the Australian study[38] and 2·6 times (95% CI 1·4–4·5) in the Rotterdam study.[39] In the UK study the lifetime risk of bilateral visual impairment was 1·2–3·3%.[40]

Unilateral amblyopia might result in failure to develop stereoacuity. Whether impaired stereoacuity can be reversed or avoided by amblyopia treatment is not yet established. Some negative effects on basic motor tasks (eg, threading beads) have been reported in experimental settings,[41,42] but in real life the degree of effect is unclear, especially as individuals with unilaterally impaired vision from any cause can use alternative visual cues, such as shade and relative size, to judge depth or distance.[43]

Quality of life

Evidence on the effects of amblyopia itself, rather than its associated outcomes or treatment, on quality of life during childhood or adulthood is limited.[44,45] This shortage of data

	Age at testing (years)	Study population	Participation rate (%)	Amblyopia definition	Number of patients	Prevalence (%)	Population screening programme
Acuity in worse eye ≥0·3 logMAR							
Lithander et al, 1998[20]	6–7	Random sampling of schools from national census data in Oman	92%	>0·3 logMAR	6292	0·9%	No
Donnelly et al, 2005[21]	8–9	All state school children included in national screening programme in UK	Not reported	≥0·3 logMAR	1582	1·1	Yes
Ohlsson et al, 2003[22]	12–13	Non-random sampling of state school children in Mexico	78%	≥0·3 logMAR and interocular difference ≥0·2 logMAR	1035	2·5%	No
Gunnlaugsdottir et al, 2008[23]	>50	Cluster sampling from national census data in Iceland	63·9%	≥0·3 logMAR	1045	1·9%	No
Acuity in worse eye ≥0·2 logMAR							
Groenewoud et al, 2010[24]	7	Population-based longitudinal cohort study in the Netherlands	76%	>0·2 logMAR or interocular difference ≥0·2 logMAR	2964	3·4%	Yes (ages 3–5 years)*
Salomão et al, 2008[25]	11–14	Cluster sampling of state school children in Brazil	86%	≥0·2 logMAR	2441	1·0%	No
Ohlsson et al, 2001[26]	12–13	Non-random sampling from screening programme in Sweden	67%	≥0·2 logMAR	1046	1·1%	Yes
Wang et al, 2011[27]	>30	Cluster sampling of rural population in China	90%	≥0·2 logMAR	6799	2·8%	
Attebo et al, 1998[28]	>49	Stratified sampling from national census data in Australia	82%	≥0·2 logMAR and interocular difference ≥0·2 logMAR	3654	2·6%	No
Acuity in worse eye ≥0·18 logMAR							
Jamali et al, 2009[29]	6	School health check attendees in Iran	92%	>0·18 logMAR or interocular difference ≥2·0 lines	815	1·7%	No
Faghihi et al, 2011[30]	6–21	Cluster sampling from national census data in Iran[30]	86%	>0·18 logMAR or interocular difference ≥2·0 lines	2150	1·9%	No
Multi-ethnic Pediatric Eye Disease Study Group, 2008[14]	7	Population-based longitudinal cohort study in the UK	56%	>0·18 logMAR or interocular difference 0·2 logMAR	2037	3·6%	Yes
Donnelly et al, 2005[21]	8–9	All state school children included in national screening programme in Northern Ireland	Not reported	≥0·18 logMAR	1582	2·2%	Yes
Brown et al, 2000[31]	>40	Cluster sampling from national census data in Australia	86%	>0·18 and interocular difference ≥0·1	4744	3·1%	No
Attebo et al, 1998[28]	>49	Stratified sampling from national census data in Australia	82%	≥0·18	3654	3·2%	No
Tananuvat et al, 2000[32]	6–7	School year group in Thailand[32]	Not reported	Interocular acuity difference of ≥0·1	6898	1·1%	No
Acuity in worse eye ≥0·1 logMAR							
He et al, 2004[33]	6–15	Cluster sampling from national census data in China	Not reported	>0·1	3469	1·9%	No

*Study cohort also underwent preverbal screening at age 9–24 months.

Table 2: **Prevalence of amblyopia in children older than 6 years and adults**

is due partly to the challenge of assessing self-reported quality of life in children and a shortage of robust instruments,[45] although some are being developed.[46,47] In a North American study, use of an parent-proxy instrument that measures generic health-related quality of life showed no significant difference between children aged 2–6 years with (n=71) and without (n=3247) amblyopia, although the limitations of proxy reporting versus self-reporting were acknowledged.[48]

General and mental health outcomes

Evidence from the prospective 1958 British Birth Cohort Study[49] suggested that amblyopia was not associated with adverse effects on general or mental health outcomes in later life, apart from moderate to severe amblyopia (acuity worse than 0·5 logMAR), which was associated with an increased risk of road traffic accidents in young adults. Self-esteem in teenage life seemed to remain intact, as assessed with the Rosenberg Self-Esteem Scale in the

Dunedin Multidisciplinary Health and Development Study, a birth cohort in New Zealand.[42] Many study participants, however, had the highest scores on the scale, which led to a ceiling effect and limited the generalisability of the findings. An attempt to directly measure impairment of overall health status in Dutch patients with established amblyopia was made in a retrospective study.[50] Health status was slightly reduced in amblyopic individuals, who expressed that they would be prepared, on average, to sacrifice 1 year of life for perfect vision. Although small, this decrease in overall health needs to be taken into account in assessments of population-level effects because of the high prevalence of amblyopia.

Socioeconomic outcomes

Statutory minimum vision requirements in many countries limit the occupation choices of some individuals with amblyopia, despite little evidence supporting the need for such recommendations. Studies in the UK and New Zealand found no associations between childhood amblyopia and subsequent educational level, ability to achieve employment, occupation type (including prohibited occupations), social mobility, or social behaviour or interactions.[42,49]

Treatment

Effectiveness

The natural history of untreated amblyopia in human beings is not well documented, which is unsurprising as screening and treatment have long been established. The existing data, however, support the notion of a sensitive period for diagnosis and treatment.

Conventional treatment comprises correction of the amblyogenic defect, most commonly by refractive correction combined with so-called penalisation of the non-amblyopic eye through physical (occlusion with patches) or pharmacological (cycloplegic eye drops that impair focus) means. 19 randomised controlled trials comparing conventional treatments have been reported since 1995 (table 3).

Three Cochrane systematic reviews have reported on the effectiveness of conventional treatment for strabismic,[69] refractive,[70] and stimulus-deprivation amblyopia,[71] respectively. Some benefit was found with occlusion therapy for the treatment of strabismic amblyopia[69] and with refractive correction for purely refractive ambylopia,[70] but major differences in outcome measures and methods meant that meta-analysis was inappropriate. No randomised, controlled trials were available on the treatment of stimulus-deprivation amblyopia, perhaps because it is more severe than other ambylopia types and generally arises due to a specific ocular disorder that requires separate complex treatment and, therefore, physicians consider it differently.[72] Nevertheless, we suggest that taken together these trials indicate that occlusion treatment, on average, is associated with a gain in acuity of at least one line on a logMAR chart in amblyopic children aged 3–5 years. Equally, there is no clear evidence for one occlusion regimen being better than another for mild or moderate amblyopia, but in older children with severe amblyopia increased hours of occlusion are likely to have a benefit (table 3). Chemical penalisation of the non-amblyopic eye with atropine used twice weekly achieves similar outcomes to occlusion in children with moderate amblyopia, but is associated with ocular and systemic side effects, including mild amblyopia in the previously non-amblyopic eye (table 3). No direct investigation of whether these effects are perceived as better or worse than the personal and social effects of occlusion therapy has so far been done.

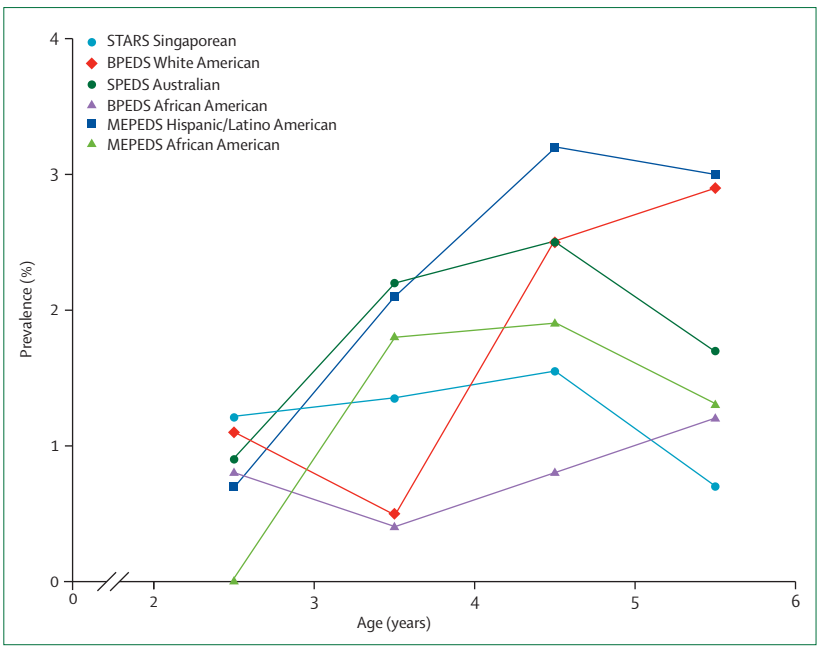


Figure 3: **Prevalence of amblyopia by age, ethnic origin, and study**
Amblyopia is defined as acuity of 0·2 logMAR in the worst eye. STARS=Strabismus, Amblyopia and Refractive Error in Singapore study.[18] BPEDS=Baltimore Pediatric Eye Disease study.[13] SPEDS=Sydney Pediatric Eye Disease study.[16] MEPEDS=Multi-Ethnic Pediatric Eye Disease study.[14,15]

Little and non-robust evidence is available on the efficacy and risk profiles of non-conventional treatments for amblyopia, such as the use of levodopa to target neuroplasticity as an adjunctive therapy in children and adults.[73,74] Although findings suggest levodopa is as effective as occlusion therapy and well tolerated in the short term, the duration of effects is unclear because long-term use is precluded by the risk of systemic side-effects. Acupuncture has also been investigated but without any clear mode of action and has only been assessed in unmasked and uncontrolled trials.[75]

Only two trials, both done in the UK, have included no treatment or delayed treatment arms. Both showed positive effects with occlusion by eye patch in children younger than 6 years. Clarke and colleagues[76] recruited children aged 3–5 years with unilateral amblyopia who were identified through UK screening programmes.

	Age (years) and number of patients	Study population	Treatment groups	Loss to follow-up	Findings	Adverse events
Occlusion therapy						
Stewart et al, 2007[51]	3–8, n=80	Mild to severe vision <0·1 logMAR and interocular difference >0·1 logMAR	6 h *vs* 12 h patching daily plus refractive adaptation for 18 weeks for children with refractive errors	0	No significant difference between treatment groups but assessment by length of occlusion showed better visual outcome achieved with longer occlusion	Not reported
Repka et al, 2003[52]	3–7, n=189	Moderate amblyopia 0·3–0·6 logMAR	2 h *vs* 6 h patching daily plus 1 h near work daily	4% (n=3 *vs* n=5)	No significant difference: at 5 weeks, 1·8 *vs* 1·9 lines improvement; at 4 months, >2·0 lines improvement in 75% *vs* 76%	Social stigma questionnaire score worse in 6 h group
Holmes et al, 2003[53]	3–7, n=175	Severe amblyopia 0·7–1·3 logMAR	6 h *vs* 24 h patching daily plus 1 h near work daily	10% (n=6 *vs* n=12)	No significant difference: at 4 months, mean 4·8 *vs* 4·7 lines improvement	No difference in tolerance or social stigma score
Agervi et al, 2010[54]	4–5, n=40	Moderate to severe amblyopia 0·5–1·3 logMAR	Patching ≥8 h for 6 days per week *vs* 8 h on alternate days	5% (one in each group)	No significant difference in visual improvement or time to improvement; mean change 0·6 *vs* 0·8 logMAR (2·0 line difference)	Not reported
Stanković and Milenković, 2007[55]	5–26, n=53	Moderate to severe amblyopia ≥0·4 logMAR	Full-time occlusion *vs* alternating patching of sound eye for 1 h per year of age daily	Not reported	No significant difference at end of follow up (mean 16 months); 52% of children aged >9 years gained 2·0 lines of acuity	Not reported
Occlusion therapy and chemical penalisation with atropine						
Pediatric Eye Disease Investigator Group, 2003[56]	3–7, n=419	Moderate amblyopia 0·3–0·7 logMAR	Daily atropine *vs* at least 6 h patching daily (reviewed at 4 months)	4% (n=7 *vs* n=10)	No significant difference: 2·8 *vs* 3·2 lines improvement, 74% *vs* 79%; patients prescribed >10 h patching daily gained the most vision	Not reported
Scheiman et al, 2008[57]	7–12,n=193	Moderate to severe amblyopia 0·3–1·3 logMAR	Weekend atropine *vs* 2 h patching daily	5% (n=8 *vs* n=2)	No significant difference: at 17 weeks, 1·5 *vs* 1·7 lines mean improvement	Ocular side-effects 16%, systemic side-effects 3% (atropine group), skin irritation 5% (patching group)
Repka et al, 2009[58]	7–12, n=40	Severe amblyopia 0·7–1·3 logMAR*	Weekend atropine *vs* 2 h patching daily	18% (n=2 *vs* n=5)	No significant difference: at 17 weeks, 1·4 *vs* 1·8 lines mean improvement	Reverse amblyopia 5%, light sensitivity 15%, systemic side-effects 15% (atropine group)
Scheiman et al, 2005[59]	7–17, n=507	Moderate to severe amblyopia 0·3–1·3 logMAR	Daily atropine for 7–12 plus 2–6 h patching per day *vs* optical correction alone	8% (n=10 *vs* n=19)	At 24 weeks, >2·0 lines improvement in acuity in amblyopic eye in 53% *vs* 25% (p<0·001); improvement in 47% *vs* 20% in children aged 13–17 years with no previous treatment	Atropine discontinued in 4% children <12 years due to difficulty with near work
Wallace et al, 2011[60]	3–10, n=55	Residual amblyopia 0·2–0·5 logMAR	Intense treatment with 6 h patching and atropine daily *vs* weaning treatment with 4 weeks of 2 h patching and atropine weekly followed by spectacles alone	0	No significant difference: 11% *vs* 22% >2·0 lines improvement	Not reported
Medghalchi and Dalili, 2011[61]	4–10, n=120	Moderate amblyopia 0·3–0·7 logMAR	Atropine twice weekly *vs* 2 h patching daily	0	No significant difference: 74% *vs* 76% >2·0 lines improvement; at 2 years, vision better than 20/25 in 50%	Not reported
Menon et al, 2008[62]	8–20, n=63	Anisometropic amblyopia only, Moderate to severe amblyopia 0·5–1	Atropine daily *vs* full-time patching plus patching of sound eye 1 day per week	9% (three in each group)	At 6 months no difference in vision improvement (mean improvement 2·4 lines) but faster and greater improvement in near acuity in patching group	Eye redness (one patient discontinued atropine)
Chemical penalisation						
Repka et al, 2004[63]	3–7, n=168	Moderate amblyopia 0·3–0·6 logMAR	Atropine daily *vs* atropine at weekends	5% (n=6 *vs* n=2)	No significant difference: at 5 weeks 1·6 *vs* 1·7 lines improvement; at 4 months, 2·6 lines improvement in each group	Reverse amblyopia 6% (n=6 *vs* n=4)
Other						
Pediatric Eye Disease Investigator Group, 2008[64]	3–7, n=425	Moderate to severe amblyopia 0·3–1·3 logMAR	2 h patching plus near work daily *vs* 2 h patching plus distance work (1·8 m) daily	7% (n=14 *vs* n=16)	No significant difference: at 6 weeks, 2·6 *vs* 2·5 lines improvement; at 17 weeks, 3·6 lines improvement in each group	Not reported

(Table 3 continues on next page)

	Age (years) and number of patients	Study population	Treatment groups	Loss to follow up	Findings	Adverse events
(Continued from previous page)						
Agervi et al, 2009[65]	4–5·5, n=76	Anisometropic amblyopia only, moderate to severe 0·18–1·18 logMAR	Refractive correction *vs* refractive correction plus Bangerter occlusion filter over sound eye	13% (ten in each group)	At 1 year no difference (4·0 lines improvement in each group)	Not reported
Rutstein et al, 2010[66]	3–10, n=186	Moderate amblyopia 0·3–0·6 logMAR	Occlusion with Bangerter filter *vs* occlusion with patching	9% (n=8 *vs* n=9)	No significant difference, but 0·4 line logMAR improvement favouring patching at 24 weeks	Vision worse in sound eye in 1% *vs* 6%
Tejedor and Ogallar, 2008[67]	2–10, n=70	Mild to moderate amblyopia, vision better than 0·5 logMAR	Atropine twice weekly *vs* defocusing lens in sound eye	10% (n=4 *vs* n=3)	Significantly more patients improved in patching group: 26% *vs* 81%; at 6 months 2·0 lines improvement	Reverse amblyopia (n=1 in atropine group)
Pediatric Eye Disease Investigator Group, 2009[68]	3–7, n=180	Moderate amblyopia 0·3–0·7 logMAR	Atropine at weekends *vs* atropine at weekends plus defocusing with plano lens	5% (n=6 *vs* n=2)	No significant difference: at 18 weeks, 2·4 *vs* 2·8 lines improvement	Facial flushing 4%, ocular symptoms 7%
Repka et al, 2009[58]	3–6, n=60	Severe amblyopia 0·7–1·3 logMAR	Atropine at weekends *vs* atropine at weekends plus defocusing of sound eye with plano lens	8% (n=2 *vs* n=3)	No significant difference: at 18 weeks, 4·5 *vs* 5·1 lines improvement (0·5 line difference)	Reverse amblyopia (4% *vs* 19%), ocular side-effects 11%, facial flushing (n=1)

*Nested within study in reference 56.

***Table 3*: Randomised, controlled trials comparing treatments for amblyopia**

Children were randomised to delayed treatment (n=59), refractive correction only (n=59), or refractive correction plus occlusion therapy (n=59). After 52 weeks, children who received refractive correction plus occlusion therapy had a slight to moderate improvement in acuity (mean gain of 0·1 logMAR, or one line on a logMAR chart, 95% CI 0·05–0·17; p<0·001) compared with the delayed treatment group, with more substantial improvements being seen in those with worse acuity at recruitment. Awan and colleagues[77] studied 60 amblyopic children aged 3–5 years and reported a strong association between visual outcome and duration of daily occlusion with eye patches. Children who achieved 3–6 h of occlusion daily had significantly good visual results at 12 weeks, with acuity increasing by an average of 8% for each hour of patching per day, compared with children who received no occlusion treatment. Of note, in these two trials an average increase in acuity of 0·1–0·2 logMAR was seen with no or delayed treatment. This finding might be due to physiological age-related maturation of vision, ability to cooperate with testing resulting in apparently improved acuity, or both. Natural resolution of amblyopia in this age group, however, cannot be excluded as natural history data are insufficient to be able to reliably distinguish between these scenarios. Importantly, the long-term stability of outcomes for treated children is unclear and some decline in acuity or recurrence of amblyopia is seen in up to 25% of children within 1 year of stopping occlusion treatment.[78] One study of 18 children aged 4–5 years who were diagnosed as having amblyopia but did not receive treatment showed that all but one child had worse vision 1 year after diagnosis.[79]

No robust evidence is available from randomised, controlled trials on whether stereoacuity improves with amblyopia treatment versus no treatment. A non-randomised comparative study based on pooled data from 248 children enrolled to six different US Pediatric Eye Disease Investigation Group (PEDIG) randomised, controlled trials suggested that 28% of children displayed improved stereoacuity after amblyopia therapy.[2] However, one randomised trial of 177 children reported only a non-signficant improvement in stereoacuity with 1 year of refractive correction or occlusion treatment.[1] This finding is consistent with a non-comparative study, based on pooled data from six different randomised, controlled trials involving 966 children done by the PEDIG.[2]

Timing of treatment

In the study by Clarke and colleagues[76] overall visual outcomes did not differ significantly between children who received no, delayed, or full refractive and occlusion treatment. When assessed by age group, however, the authors concluded that a 1-year delay in treatment for amblyopia did not negatively affect children younger than 5 years at diagnosis, but in children older than 5 years, early treatment was associated with better outcomes. Extensive findings have been reported from PEDIG on the various treatment methods for amblyopia, including that children younger than 7 years were more responsive to treatment than older children, with the effect of age increasing with increasing severity of amblyopia.[80]

Interest has been increasing in residual neuro-developmental plasticity outside the classic sensitivity period of the first 7–9 years of life. Rahi and co-workers[40] found that within 1 year of losing vision in their better

eye, 31% of adults with amblyopia diagnosed in childhood showed improved acuity in their amblyopic eye. The likelihood of improvement was higher in those who had a definite history of amblyopia treatment during childhood than in those with unclear treatment histories. Chua and Mitchell[38] reported that one in ten adults with amblyopia had visual improvement of more than 0·2 logMAR (more than two lines on a logMAR chart) in the amblyopic eye 5 years after onset of sight loss in the non-amblyopic eye. These findings support adult neuroplasticity[81] and potentially open up new pathways for intervention. Nevertheless, the focus of amblyopia treatment should remain on intervention within the sensitive period of childhood to keep to a minimum the risk of permanent visual deficit in the amblyopic eye. To this end, screening for reduced vision in children aged 4–5 years potentially enables detection of those with established amblyopia at a sufficiently early stage for treatment to be effective.

Amblyopia screening

Effectiveness

A European population-based cohort study showed a low rate of residual amblyopia (0·8%) at age 7 years in children who underwent intensive screening (seven assessments by age 6 years) compared with published rates for unscreened populations.[82] This finding supports a positive effect with screening. No randomised controlled trials, however, have shown that vision screening in children aged 4–5 years efficaciously lessens morbidity and other health effects. Thus, several systematic reviews have concluded that no high-level evidence is available on childhood vision screening.[83–86]

A randomised trial embedded within ALSPAC showed that intensive vision screening between the ages of 6 months and 3 years (n=1914), compared with one-off screening at age 3 years (n=826), was associated with a small but significant difference in mean visual acuity in children with amblyopia at age 7·5 years (0·14 *vs* 0·20 logMAR [difference 0·5 lines on a logMAR chart], p=0·002). Nearly half (45%) of recruited children, however, were lost to follow-up, but no difference was found between the two groups when they were analysed by intention to screen.[87,88] Families with low socioeconomic status, classified by parental occupation, were more likely to have children with an eye disorder (mainly hypermetropia and amblyopia) than those in higher status groups, but were significantly less likely to consult an eye care specialist (odds ratio 0·65, 95% CI 0·43–0·98).[89] This finding underlines the potential usefulness of universal screening of captive populations (eg, at school entry) to address inequity in access to health services.

Benefits and potential harms

Little research has been done on the possible negative effects of unnecessary diagnostic interventions and clinic attendance on children whose screening results are found to be false positive. In contrast, substantial evidence is available on the negative effects of treatment (refractive and occlusion therapy) on children's self-reported and parent-proxy-reported quality of life, specifically on a child's perception of self and on relationships with carers and peers.[90–97] Compared with age-matched controls, reduced self-esteem was reported by children aged 10–12 year who had previously undergone amblyopia treatment.[93] Within the ALSPAC cohort, episodes of verbal and physical bullying by peers were 35% more frequent among children who were undergoing occlusive therapy or refractive correction for amblyopia than among children who had not undergone any treatment for amblyopia.[90] A multidisciplinary qualitative study of the psychosocial impact of amblyopia, based on interviews with children aged 3–18 years and their families, showed that for some children starting amblyopia treatment led to feelings of stigma and withdrawal from peers.[96] Conversely, in a prospective study based on parent-proxy reports of children aged 4–6 years, although negative perceptions towards children after the start of treatment were reported, no association between occlusion therapy and carers' perceptions of their own stress or of the children's wellbeing was evident.[97]

The adverse effects of amblyopia treatment include skin irritation from eye patches, which, although rarely reported, affected 5% of children in one randomised controlled trial.[57] Adverse systemic and topical events associated with atropine use have also been described in several of the PEDIG trials (table 3).

In summary, from studies that directly measure children's experiences and perceptions, amblyopia therapy is associated with negative effects in some children. Research into the adverse effects of false-positive screening results and undergoing unnecessary further testing is warranted. The absence of data from robust population-based longitudinal studies of quality of life, socioeconomic outcomes, and other health effects perceived by patients makes quantification of benefits and harms of amblyopic treatment difficult.

Cost-effectiveness

In an analysis commissioned by the UK Health Technology Assessment body,[84] the cost-effectiveness of screening of children aged 3–5 years led by orthoptists who specialise in the assessment of vision in childhood to identify amblyopia and amblyogenic factors, was modelled with parameter values from the literature, assuming a high prevalence of amblyopia (4·8%). The lowest estimated cost per quality-adjusted life-year (QALY) gained through screening was UK£134 963, which is substantially higher than the £20 000–30 000 cost per QALY recommended by the UK National Institute for Health and Care Excellence to be a cost-effective use of resources.[98] Because amblyopia is

	Programme
Europe	
England, Scotland, and Wales	Whole-population screening with orthoptist-led visual acuity testing in children aged 4–5 years
Northern Ireland	Whole-population screening with acuity testing done by school nurse in children aged 4–5 years
Ireland	Whole-population screening with orthoptist-led visual acuity testing in children aged 4–5 years
France	None
Germany	Whole-population screening programme with orthoptist-led visual acuity and visual alignment testing in children aged 3 years
Sweden	Whole-population screening programme with orthoptist-led serial testing of visual acuity in children aged 3–6 years
Netherlands	Whole-population screening programme with orthoptist-led serial testing of visual acuity in children aged 3–6 years
USA	None, although a policy review has been done;[99] heterogeneous community, state-based, and cross-state screening of acuity and amblyogenic features (refractive error and strabismus) exist (some established by optometry industry)
Canada	Whole-population screening led by public health nurses with at least one assessment of visual acuity with age-appropriate tools in children aged 3–5 years
Israel	Whole-population screening with nurse-led assessment of acuity in children aged 3 years and ophthalmologist-led or optometrist-led assessments in children aged 5–6 years
Singapore	School-based screening led by doctors and nurses with assessment of visual acuity and refractive state in children aged 4–5 years and serial refractive testing in children aged 5–8 years
Australia	None; heterogeneous state-based programmes exist
China	None; heterogeneous state-based programmes exist
India	None; heterogeneous state-based programmes exist

Table 4: **Examples of national programmes of childhood vision screening**

common, however, the cost-effectiveness of screening for impaired childhood vision was highly sensitive to health effects directly related to amblyopia, particularly those related to loss of vision in the non-amblyopic eye. A theoretical 2·0% reduction in utility (the value assigned by a patient to his or her general health state) due to amblyopia, which is less than the 3·7% reduction reported by a Danish group of adults with amblyopia,[50] would cut the estimated QALY cost to £17 000.[84]

Policies on childhood screening

In the UK, vision screening for reduced acuity in either eye is advocated in all children aged 4–5 years. Testing is led by orthoptists who specialise in childhood vision. Each eye should be tested separately with a crowded visual acuity chart (ie, multiple letters or shapes per line rather than a single letter or shape per line). Several logMAR-based acuity charts exist, including the Kay, ETDRS, HOTV, and Lea charts or cards, although there are no recommendations in the UK about which to use. The US Prevention Service Task Force systematic report into childhood screening found that the HOTV and Lea charts were the most appropriate for vision screening in children younger than 5 years.[99] Children with vision worse than 0·2 logMAR should be referred promptly for further specialist assessment, as this level of acuity could have functional effects in real life (eg, the vision threshold for driving is 0·3 logMAR or 6/12 Snellen). Specialist assessment is required to rule out other causes of reduced vision and to identify the underlying associated amblyogenic factors. In the UK, however, as in established programmes in other countries (table 4), there are no agreed standards for this diagnostic pathway.

Conclusions

We have found no robust evidence to support making significant changes to the overall content of the existing UK National Screening Committee's recommended programme for children aged 4–5 years, despite being more conservative than the intensive programmes of repeated testing up to age 5 years in other European countries. This finding is noteworthy in view of the European Union Horizon 2020 initiative on screening.[100] Also of note is that revisions to the US national recommendations[99] bring the USA in line with UK policy. Several areas of uncertainty, however, need to be addressed. Country-specific estimates of the prevalence and incidence of amblyopia would aid service planning and assessment of cost-effectiveness. The increased risk of vision impairment or blindness in individuals with unilateral amblyopia, due to loss of vision in the non-amblyopic eye, is notable but preventable. Nevertheless, at a population level preventive approaches are uncommon, and without formal economic analyses of health effects it is difficult to assess whether this outcome is sufficient justification for screening. The most pressing need is to clarify the real-life health and quality-of-life effects of amblyopia across the whole course of life, and the extent to which screening and treatment might permanently reduce these. To make such assessments, robust, population-based, long-term assessments of outcomes after treatment will be required and should include appraisal of quality of life, socioeconomic status, difficulties in socialisation and behavioural issues, and patients' perceptions of these factors. Such research will be challenging but without it, understanding of the value of screening will remain incomplete.

Variations in screening programmes between and within countries reflect the absence of standardised guidance on tests and diagnostic pathways. Equally, guidance on how to standardise frameworks for audit and governance of screening services is required. Despite heterogeneity, building on existing programmes and practices could lead to well designed assessments that address areas of incomplete evidence, such as stability and long-term visual outcomes in treated and untreated individuals.

Contributors

All authors were involved in the conception, writing, and revisions of the original draft of this Review and approved the version for publication.

Declaration of interests

All authors declare no competing interests.

Acknowledgments

Part of this Review was written as a commissioned external review for the UK National Screening Committee. JSR has received funding from the Department of Health. ALS and JSR are supported by the National Institute for Health Research Biomedical Research Centre. ALS and PMC are members of the Ulverscroft Vision Research Group. The views expressed in this publication are those of the authors and not necessarily those of the Department of Health, National Health Service, or National Institute for Health Research.

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