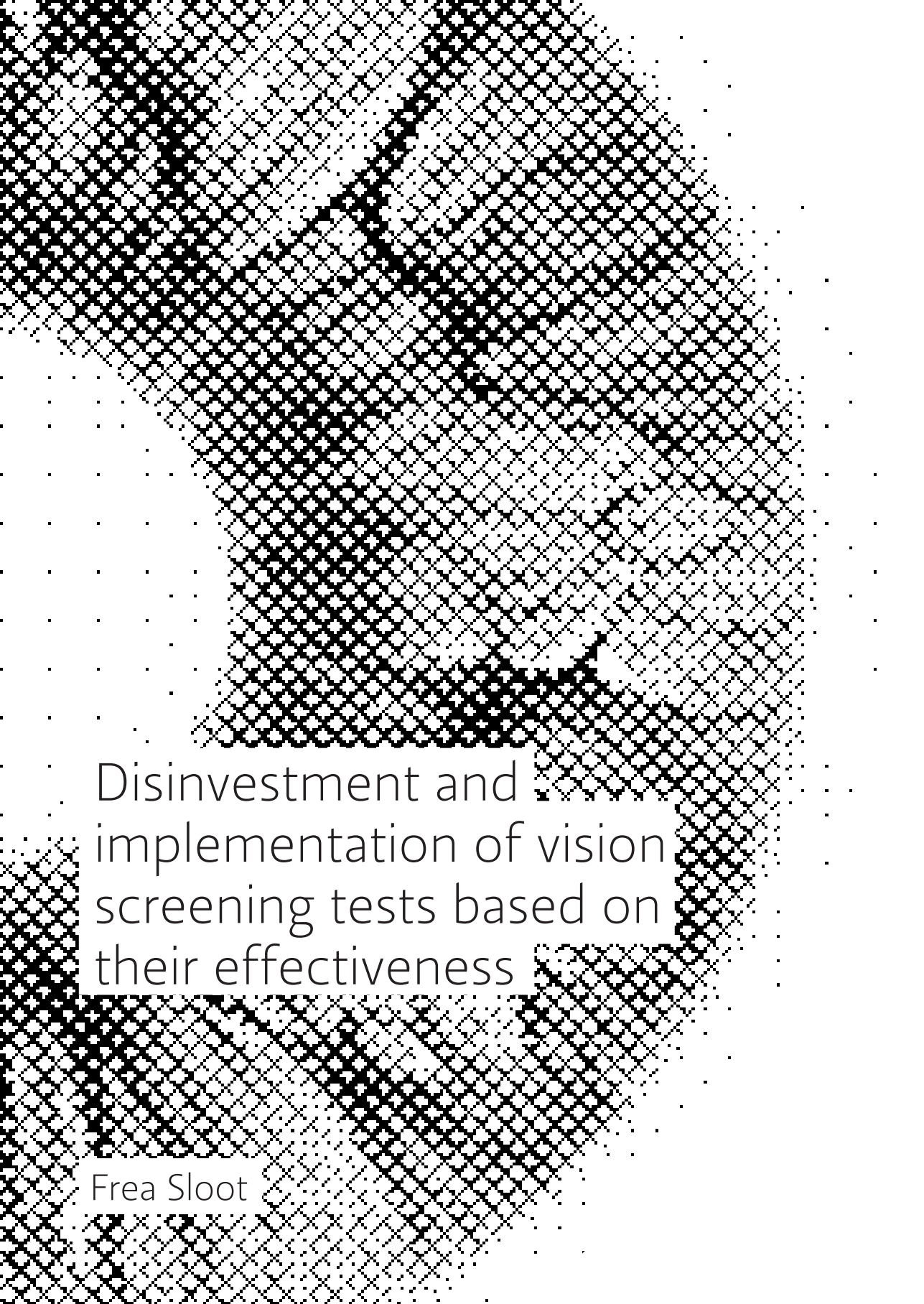
Disinvestment and implementation of vision screening tests based on their effectiveness

Frea Sloot



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DISINVESTMENT AND IMPLEMENTATION OF VISION SCREENING TESTS BASED ON THEIR EFFECTIVENESS

DESINVESTERING EN IMPLEMENTATIE VAN OOGSCREENINGSTESTS GEBASEERD OP HUN EFFECTIVITEIT

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General introduction

AMBLYOPIA

History

The term amblyopia was already used by Hippocrates to describe diminished acuity. The Greek word amblyopia means dimness or dullness of vision. Strabismus was known as a disorder of eye position and eye movement and was regarded as a symptom rather than a disease. In the Byzantine Empire strabismus was believed to be caused by a spastic state of the eye muscles. During the time of the crusades the first eye hospital, to treat patients with low vision, was opened in France by Saint Louis IX. Strabismus was believed to be caused by an unequal strength of the muscles or lack of concordance. George-Louis Leclerc, Comte de Buffon was the first to believe that strabismus was caused by disruption of binocular vision due to poor vision in one of the eyes. He also described that the weak eye could regain its strength by occluding the good eye.[1]

The basic mysteries regarding the aetiology of amblyopia were not to be resolved until the beginning of 1960 through the neurophysiological research performed by Hubel and Wiesel. They explored the receptive field properties of neurons in the visual cortex[2,3] and demonstrated the existence of ocular dominance columns.[4-6] They showed that there is an upper age limit for the development of amblyopia in animals. Subsequently they performed experiments on cats, where deprivation was induced by suturing the eyelids closed for various amounts of time and at different ages.[2] Keech and Kutschke studied the upper age limit for development of amblyopia in humans and found that no subject developed amblyopia after age 6 years.[7] Few cases of amblyopia will develop after screening, if vision screening is taken place in the late preschool period. If vision screening is performed early, a second screening session might be necessary in order to detect cases developing after the first vision screening.

Definitions and risk factors

Amblyopia has conventionally been described as reduced visual acuity despite optimal optical correction and without any signs of an organic cause. Clinically, amblyopia is often defined as a two-line difference or more in best-corrected visual acuity (VA) in LogMAR or Snellen lines between eyes in the presence of amblyopia risk factors, such as strabismus, anisometropia and/or visual axis obstruction. Currently amblyopia is defined as a form of cortical visual impairment which results from abnormal visual stimulation in the first few years of life. Most amblyopia arises as a result of ocular misalignment (strabismus), a difference in refractive errors between the two eyes (anisometropia), or a combination of both.[8] Another cause of amblyopia is deprivation

due to, for example, congenital cataract or retinoblastoma. The reduction in VA is commonly unilateral, but it can be bilateral. Amblyopia can only form during the sensitive period of visual development, which stretches over the first decade of life.

The causes for normally aligned eyes and isometropia are obscure and so also the causes for abnormalities in alignment and refraction remain obscure. In normal visual development, emmetropisation, the process of neutralization of the refractive status of the eye during childhood, takes places. Failure to emmetropise has been shown to be highly associated with development of amblyopia.[9,10] It has been shown that in unilateral amblyopia, the fixating eye becomes more myopic, while the amblyopic eye remains hyperopic. Increasing astigmatism is also highly associated with an increased risk to develop amblyopia.[11] Increasing hypermetropia has been shown to be a risk factor for esotropia (strabismus) and amblyopia.[12] The relationship between anisometropia and amblyopia is still unclear. Barrett et al suggest three different hypotheses. The first (classic) hypothesis states that anisometropia (due to failure of emmetropisation) leads to amblyopia due to the chronic, unilateral blur during early visual development. The second hypothesis suggests that an amblyogenic factor leads to amblyopia and the amblyopia consecutively leads to anisometropia. The third hypothesis proposes a third factor that causes both the amblyopia and the anisometropia. In their extensive review they cannot find enough evidence to reject any of these hypotheses.[13] Increasing anisometropia is associated with higher change of deterioration of VA after cessation of occlusion therapy.[14]

Natural history of untreated amblyopia and prevalence

There are no longitudinal studies aiming to study the natural history of untreated amblyopia. It would be unethical to withhold treatment from a child with detected amblyopia. Studies on the natural history of amblyopia due to non-compliance have shown that the VA of the amblyopic eye deteriorates during childhood[15] as well as during adolescence.[16] Studies on prevalence of amblyopia in countries without vision screening, and studies on prevalence in non-screened older age-cohorts in countries with vision screening, have shown higher prevalence than in vision screened populations.

Vision screening seems to lower the prevalence of amblyopia with VA ≤ 0.5 to between one third and half the prevalence of that in an unscreened population. The prevalence of residual amblyopia may be due to cases not attending screening, cases missed at screening, the condition having developed later, unsuccessful treatment (including

non-compliance) or incorrect diagnosis. Research on amblyopia and strabismus prevalence in multi-ethnic populations in respectively Baltimore (BPEDS study)[17] and Los Angeles & Riverside (MEPEDS study)[18] showed a prevalence of manifest strabismus (age 6-71 months) of around 3.3% for whites, 2.1% for African American and 3.55% for Asian children. Amblyopia prevalence (age 30-71 months) varied from 1.8% for whites and Asian children to 0.8% for African American. The Sydney Paediatric Eye Disease Study[19] found an amblyopia prevalence of 1.9% and no significant associations with low birth weight, preterm birth, maternal smoking, age, gender, ethnicity or measurements of socioeconomic status. Higher amblyopia prevalence rates of 3.1% were found in a rural town in Poland[20] to even up to 5.6% in an unscreened population in Germany[21]. Differences in prevalence can (partially) be explained by differences in criteria used to define amblyopia.

SCREENING

Definition of screening

The World Health Organization defines screening based on the Commission on Chronic Illness United States as "the presumptive identification of unrecognized disease in an apparently healthy, asymptomatic population by means of tests, examinations or other procedures that can be applied rapidly and easily to the target population".[22] Persons who probably have a (early-stage) disease are sorted out from persons who probably do not have a disease. Persons who were found by screening to probably have a disease must be referred for diagnosis and necessary treatment. A screening test is therefore not intended to be diagnostic and screening does not find all persons who have a disease.

For screening to be effective, in other words to give treatment to those with previously undetected disease and to avoid harm to persons who do not require treatment, Wilson and Jungner[23] described the following principles:

- The condition screened for should be an important health problem
- There should be an accepted treatment
- Facilities for diagnosis and treatment should be available
- There should be a recognizable latent or early symptomatic stage
- There should be a suitable test
- The test should be acceptable to the population

- The natural history of the condition, including development from latent to declared disease, should be adequately understood
- should be an agreed policy on whom to treat
- The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced
- Case-finding should be a continuing process

The potential negative effects of screening include the risk of imposing anxiety on positively screened individuals, an erroneous conception of health for false negative cases, unnecessary examinations for false positive cases. Also limited economic resources and growing medical expenses have to be taken into account.

Sensitivity, specificity and positive predictive value

The sensitivity of a test is the ability to detect persons who truly have the disease. The specificity of a test is the ability to detect persons free of the disease. A test with low sensitivity fails to detect a substantial part of affected individuals ("underreferrals"). A test with low specificity wrongly suspects disease in a large number of healthy subjects ("overreferrals"). The positive predictive value is the proportion of subjects found positive upon testing who truly are affected with the target condition (Table). A low positive predictive value means that few of those found positive at screening actually are affected by the disease. This might lower the confidence of the screening result among the public and can lead to low compliance with referral for more specialized care.

Table 1. Sensitivity, specificity, positive and negative predictive value.

	Truly diseased	Truly healthy	Total
Positive screening test	a	b	a + b
Negative screening test	c	d	c + d
Total	a + c	b+ d	

a = the number of subjects who have the disease and for whom the screening test is positive (true positive)
b = the number of subjects who are healthy, but for whom the screening test is positive (false positive)
c = the number of subjects who have the disease, but for whom the screening test is negative (false negative)
d = the number of subjects who are healthy and for whom the screening test is negative (true negative)

Sensitivity: a/ a+c
Specificity: d / b+d
Positive predictive value: a / a+b
Negative predictive value: d / c+d

History of eye screening

The first Child Health Care (CHC) Centre was founded in Paris, France, in 1892 by Pierre Budin. According to Budin's vision attention should be given to stimulate lactation and to check children's growth. Infants were examined and weighed every week and instruction was given to their mothers about hygiene and care. Free sterile milk was provided when breastfeeding was not possible. The rest of France, as well as other countries like Belgium, Italy, Hungary, Canada and Spain followed.[24]

Ten years later, in 1901 a Dutch paediatrician, Plantenga, inspired by the French initiative opened the first CHCC in the Netherlands, which also gave out free milk. This first private initiative was followed by other organizations and eventually became nationwide implemented in the Netherlands.[25] Vision screening was implemented in this already existing health screening programme for mother and child in 1960. Around that time population-wide vision screening was also implemented in Denmark, Finland and Sweden. Norway followed in 1970 and Austria, Belgium, France and the UK around 1980. The vision screening programme in the Netherlands was extended with preverbal vision screening tests in the 1980's.[25,26]

Aims of vision screening

The purpose of vision screening is to prevent bilateral visual impairment later in life, by reducing amblyopia. Even though the primary aim for preschool vision screening is to reduce amblyopia, it is important to recognize other beneficial effects. These include detection of visual disorders other than amblyopia, such as organic disorders, and conditions that may impede schoolwork, such as high hyperopia.

Screening tests

Red reflex examination

The red reflex test is a rapid, non-invasive, simple test usually performed at the age of 0-6 months to detect congenital disorders. A direct ophthalmoscope is used in a darkened room and the eyes are assessed individually at 30 to 45 cm. A normal red reflex requires clarity of the cornea, aqueous humour, lens and vitreous body. Leukocoria (white pupillary reflex) can, among others, indicate retinoblastoma or congenital cataract. Any asymmetry is a reason for referral for full eye examination.

Early detection of visual disorders tests (in Dutch: Vroegtijdige Opsporing Visuele stoornissen (VOV))

Corneal light reflex test

The corneal light reflex test is performed to assess ocular alignment. The test is performed by shining a light into the child eyes from a distance (40cm),with the child fixation on the light, and observing the reflections on the cornea with respect to the pupil. The location of the light reflexes should be symmetric. The test is easy to perform and can, if the test is symmetrical, proof pseudostrabismus.

Cover-uncover and alternating cover test

The monocular cover-uncover test is used to detect manifest strabismus and to distinguish latent from manifest strabismus (heterophoria versus heterotropia). Monocular cover-uncover testing is performed by having the child fixate on a small near object and occluding one eye of the child. The examiner looks for any movement in the non-covered eye. If a movement is present this indicates a manifest strabismus (heterotropia). When there is no movement of the non-covered eye the cover is removed after a short moment. If the covered eye makes a movement in one direct by application of the occlude and in the opposite direction after removal of the occlude this indicates a latent strabismus (heterophoria).

The alternating cover test is also used to detect strabismus. With the child fixating on an object the examiner moves the occlusion from one eye to the other eye, observing the direction of movement of the eye that is uncovered. This test disrupts binocular fusion and does not make a distinction between latent and manifest strabismus. Testing can be done at both near and distance fixation. Foveal fixation, patient attention and cooperation are needed to perform cover testing.

Monocular pursuit

Monocular pursuit is performed by occluding one eye and making a small movement with a pen light or fixation object. When the occlusion of one eye gives a defensive reaction this can be an indication of poor vision in the other, not occluded, eye. Smooth pursuit is in indication of normal vision. The test is used as indirect measurement of VA in young children.

Motility

Eye motility (binocular following) is tested by observing whether a child follows an object smoothly with both eyes simultaneously in 8 directions of gaze. Smooth pursuit

eye movements are used to stabilize a moving stimulus on the retina. This test indicates whether there is coordination between both eyes, tests the cerebral development and tests the function of the eye muscles.

Visual acuity

Visual acuity is the ability of the eye to distinguish detail and can be assessed with optotype acuity charts. Visual acuity measurements can be performed from the age of three years with picture optotypes. These picture optotypes however measure not only VA but also recognition and cognitive skills. From the age of 4-5 years VA can be reliably tested with normal optotypes (logarithmic or Snellen) charts. Crowded VA charts have been shown to be more sensitive in detecting amblyopia. Each eye should be tested separately with the other eye covered.

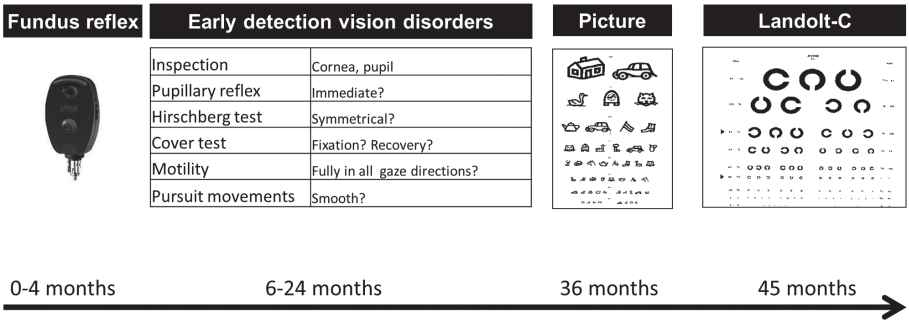
Visual acuity testing has been shown to have very high sensitivity and specificity for detection of amblyopia.[28,29] It is also sensitive to refractive errors, especially myopia, but myopia is uncommon in preschool children, and usually does not lead to amblyopia.

Visual acuity testing is relatively easy to perform and it can be carried out by non-ophthalmologic personnel. Visual acuity screening, with re-screening of inconclusive cases, has moreover been shown to be favourable from a cost-benefit point of view. It is however time-consuming and sensitive to simple refractive errors.

Conditions not affecting VA might naturally elude observation in a setting with VA based screening, e.g. strabismus with normal VA, minor ptosis or small partial cataracts. On the other hand, without impact on VA these disorders do not require treatment in preschool children. Strabismus may represent a cosmetic problem, though, but that is beyond the aim for vision screening. Large-angled strabismus will be detected without screening and strabismus that is not cosmetically obvious is not easy to detect without expert testing. Most cases of microstrabismus will not require surgery.

In the Netherlands the Amsterdam Picture Chart (APK) and Landolt C charts are most often just at the CHC centres.

Figure 1. Population-wide eye screening in the Netherlands.



RAMSES

The Rotterdam AMblyopia Screening Effectiveness Study started in 1996 with the follow-up of a birth cohort of 4624 children in actual screening practice in the city of Rotterdam to determine the sensitivity, specificity, and effectiveness of the Dutch child vision screening program up to age of seven years. This study showed that preverbal screening contributed little to the detection of refractive amblyopia, while strabismic amblyopia was self-referred in approximately half of cases.[30]

AIM AND SCOPE/ OUTLINE OF THIS THESIS

The general aim of this thesis was to study the effectiveness of preverbal, orthoptic vision screening tests to detect strabismus, refractive and combined mechanism amblyopia and to confirm whether the omission of routine vision screening between age 6-24 months would not have a significant negative impact on the severity and total cases of amblyopia detected.

In **chapter 2** an inventory was made of current EU paediatric vision and hearing screening programmes.

In **chapter 3** the effect of omitting an early population-based vision screen in the Netherlands is evaluated by the use of a micro-simulation model.

In **chapter 4** semi structured observations are described of the population-based vision screening tests performed at Child Health Care Centres in The Netherlands.

In **chapter 5** the effect of omission of population-based vision screening only at age 6-9 months was analysed.

In **chapter 6** the effectiveness of routine population wide preschool vision screening tests at age 6-24 months in the Netherlands was evaluated.

In **chapter 7** the high rate of failed visual acuity measurements with the Amsterdam Picture Chart at the age of 36 months was described.

In **chapter 8** the first year of implementing vision screening in urban and rural Cluj County in Romania was described.

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1

2

Inventory of current EU paediatric vision and hearing screening programmes

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ABSTRACT

OBJECTIVE To examine the diversity in paediatric vision and hearing screening programmes in Europe.

METHODS Themes for comparison of screening programmes derived from literature were used to compile three questionnaires on vision, hearing and public health screening. Tests used, professions involved, age, and frequency of testing seem to influence sensitivity, specificity, and costs most. Questionnaires were sent to ophthalmologists, orthoptists, otolaryngologists and audiologists involved in paediatric screening in all EU full-member, candidate, and associate states. Answers were cross-checked.

RESULTS Thirty-nine countries participated; 35 have a vision screening programme, 33 a nation-wide neonatal hearing screening programme. Visual acuity is measured in 35 countries, in 71% of these more than once. First measurement of visual acuity varies from three to seven years of age, but is usually before the age of five. At age three and four, picture charts, including Lea Hyvarinen, are used most; in children over four, Tumbling-E and Snellen. As first hearing screening test, otoacoustic emission is used most in healthy neonates, and auditory brainstem response in premature newborns. The majority of hearing testing programmes are staged; children are referred after 1-4 abnormal tests. Vision screening is performed mostly by paediatricians, ophthalmologists or nurses. Funding is mostly by health insurance or state. Coverage was reported as >95% in half of countries, but reporting was often not first-hand.

CONCLUSIONS Largest differences were found in visual acuity charts used (12), professions involved in vision screening (10), number of hearing screening tests before referral (1-4), and funding sources (8).

INTRODUCTION

Childhood sensory functions play a key role in intellectual and social development. Vision or hearing impairment affects both personal and societal health of children. Earlier detection of visual or hearing deficits improve outcome.[1-4] Vision and hearing screening programmes are based on the same general principles, but vary both within and across European Union (EU) countries, regarding tests used, age of testing, frequency of testing, professions involved in screening, referral procedure, funding and coverage. Such differences can result in health inequities. No screening, or screening with little population coverage, can result in delayed provision of the correct treatment and increased disease burden. Excessive screening can result in inappropriate interventions and increased costs for health care systems.
Vision screening and subsequent treatment has reduced the occurrence of insufficiently detected and treated amblyopia.[5] In the Netherlands, amblyopia is now detected more than two years earlier than in the 1970s.[6] Early screening and detection of hearing disorders, and timely intervention (eg. cochlear implantation or hearing aid) largely prevents delayed language development,[1,2,7] and also improves general developmental outcome at age 3-5.[3]

Despite increased consciousness that vision and hearing screening is effective, differences exist in implementation between countries. A 2002 survey of vision screening programmes in 190 countries found that screening was often state funded, visual acuity (VA) was always tested, and that in the EU screening was predominantly voluntary.[8] In a 2012 survey of the International Orthoptic Association, 98% of responders indicated that vision screening programmes existed in their country, 44% were national programmes. Screening was performed by a wide range of professionals.[9]

An overview of universal newborn hearing screening (UNHS) in 24 European countries from 2004-2006 showed that in several countries UNHS programmes reached more than 95% of all neonates, but in many other countries programmes were recently introduced or were only partially functioning.[10] Other reports on national neonatal hearing screening programmes raise issues on implementation, test procedures, type of tests, coverage, detected cases of hearing loss, and costs.[11-19]

A Health Technology Assessment review in 2008[20] re-examining the cost-effectiveness of vision screening up to the age of 4-5 (following previous report in 1997[21]) found that, based on the accepted value of a Quality-adjusted life year, the cost-effectiveness of

screening for amblyopia depends on the long-term utility effects of unilateral vision loss and that there was currently no sustainable evidence of utility loss that would render any form of screening likely to be cost-effective.[20] Keren et al. concluded that UNHS in general has the potential for long-term cost savings compared with selective hearing screening and no screening.[22] Burke et al found that the cost-effectiveness of hearing screening depended mainly on the cost of the screening intervention per patient and on the prevalence of hearing loss in the population.[23]

We aimed to compile an inventory of population-based vision and hearing screening programmes for children in Europe, and to quantify and examine the differences. This study should assist those countries without a screening programme and new EU member states in selecting which screening protocol to adopt. If large differences between programmes in EU countries are found, further study on the relative costs and effectiveness of the different approaches to screening will be necessary.

METHODS

Drawing particularly from five major cost-effectiveness analyses,[20, 21,23-25] we selected the following items to formulate vision (Q1) and hearing (Q2) screening questionnaires:

- Type of tests, eg. visual acuity chart or hearing screening device used (otoacoustic emission (OAE), automated auditory brainstem response (aABR))
- Professions involved in screening, eg. nurses, orthoptists, doctors
- Funding, eg. State, health insurance
- Coverage, percentage of screened children

Questions formulated in a focus group were structured as multiple-choice with room for comments and multiple answers (See Appendix Q1, Q2). All forms of screening for vision or hearing problems were included (eg. inspection of the eyes was also counted as form of vision screening). To obtain a broader perspective of screening systems, a short public health questionnaire (Appendix Q3) to provide background information on screening and screening systems in all countries was developed through extrapolation of the vision and hearing questionnaires.

In each of the 28 EU full member states, five candidate states, potential candidate state Albania and associated states Israel, Moldova, Norway, and Switzerland, a paediatric ophthalmologist, orthoptist, otolaryngologist, audiologist and screening professional

were selected, based on their involvement in paediatric vision and hearing screening, and asked to complete the questionnaires for their own country. Public health representatives were identified through the Ministries of health or recommendation from the vision and hearing representatives.

The questionnaire included questions about screening tests, age, and frequency of screening. Different tests can be used to screen for one disorder, but screening programmes can also focus on more than one disorder. Two-stage or multiple-stage testing improves the screening specificity but increases screening costs, although higher specificity can reduce diagnostic follow up costs.[23,26]

Questions about the range of professions involved in screening were included because this influences the quality and costs of screening. Screening tests with higher sensitivity and specificity might require higher educated personnel and higher salary costs, which will increase the costs of screening. This increase in costs should be balanced with the increase in sensitivity and specificity.

The questionnaire also covered funding sources, including state, regional, municipal, Health insurance, parental and/or charity. The choice of funding agencies will influence the equity of screening, competitiveness, costs, coverage and cost-effectiveness.
Questions about coverage were included because the participation frequency of a screening programme is crucial for its effectiveness, and to make screening worthwhile from a population perspective. Low coverage can lead to delayed provision of the correct treatment and increased disease burden. If screening is free or compulsory, coverage will be higher. Acceptable participation frequencies may be reached by incorporating screening into an existing system with a high participation rate, eg. vaccination programmes or school start.
Questionnaires were emailed from December 2013 until April 2014. Clinicians involved in population-based screening were identified and their answers were cross-checked with those given by general screening professionals. If answers were ambiguous the questionnaires were returned to both the clinician and the screening professional and they were asked to contact each other to agree corrections. Overviews of the questionnaire answers were circulated three times to all representatives. All representatives were asked to review and correct any errors in the overviews for their own country and neighbouring countries. The overviews were also checked by external experts, involved first-hand in vision and hearing screening.

RESULTS

In all 39 countries (including two separate regions, Flanders and Wallonia, in Belgium), representatives were found. Vision representatives were found in 36 countries, hearing representatives in 38, and public-health representatives in 23 (Table 1).

Vision

Information on vision screening programmes was obtained from 36 countries including two regions in Belgian regions. No information could be obtained from Albania, Macedonia, and Moldova. Thirty-five countries have a vision screening programme in place. In Belgium, Bulgaria, Estonia, France, Romania, Spain, and Switzerland this is a regional programme. In several countries with a national vision screening programme in place, regional differences in screening protocols exist.

Infant and preverbal screening tests

Infant screening (age 0-4 months) included inspection, fixation, red reflex testing, Hirschberg test, Bruckner test, Cover test, pupillary reflexes, and motility. Most countries perform a combination of two or more of these tests. In Bulgaria, Greece, and Poland no infant screening is performed. In Germany only eye inspection is performed. In Ireland, Montenegro, and Spain, eye inspection is combined with red reflex testing. In Cyprus, Italy, Lithuania, and Malta only red reflex testing is done. In Latvia this is combined with motility testing. Preverbal screening (age 6-30 months) includes the same tests. Preverbal screening is not performed in eight countries, but most countries combine two or more tests.

Visual acuity (VA) measurements

In all countries VA is tested, but the age of the first measurement varies from 3-7 years of age. In a third of countries VA is tested once, one third twice, and in one third more than twice. In most countries, VA measurements are repeated at an older age. In children aged four years and younger VA charts are most commonly picture charts and the Lea Hyvarinen chart, above age four, Tumbling E and Snellen are most often used.

Table 1. Eligible countries.

Country	EU status	Vision	Hearing	Public
Albania	P.C.	-	+	+
Austria	M.	+	+	-
Belgium Flanders	M.	+	+	+
Belgium Wallonia	M.	+	+	-
Bulgaria	M.	+	+	+
Croatia	M.	+	+	+
Cyprus	M.	+	+	-
Czech Republic	M.	+	+	+
Denmark	M.	+	+	-
Estonia	M.	+	+	-
Finland	M.	+	+	+
France	M.	+	+	+
Germany	M.	+	+	+
Greece	M.	+	+	+
Hungary	M.	+	+	+
Iceland	C.	+	+	+
Ireland	M.	+	+	-
Israel	A.	+	+	+
Italy	M.	+	+	-
Latvia	M.	+	+	-
Lithuania	M.	+	+	-
Luxembourg	M.	+	+	-
Macedonia	C.	-	-	+
Malta	M.	+	+	+
Moldova	A.	-	+	-
Montenegro	C.	+	+	+
Netherlands	M.	+	+	+
Norway	A.	+	+	-
Poland	M.	+	+	-
Portugal	M.	+	+	+
Romania	M.	+	+	-
Serbia	C.	+	+	+
Slovakia	M.	+	+	-
Slovenia	M.	+	+	+
Spain	M.	+	+	+
Sweden	M.	+	+	+
Switzerland	A.	+	+	-
Turkey	C.	+	+	+
United Kingdom	M.	+	+	+

(EU status: A = associated state, C = Candidate, M = full member, P.C. = potential candidate).

Personnel and referral

Screening is mostly performed by paediatricians, ophthalmologist and/or nurses. In most countries children are referred to ophthalmologists for further examination; in Latvia they are referred to the General Practitioner (GP), in the UK they may also be referred to joint orthoptic and optometry clinics or optometrists, in Malta to either the orthoptist or optometrist, and in the Netherlands they are mostly referred via the GP to an orthoptist or ophthalmologist, but sometimes directly to an orthoptist, ophthalmologist, optometrist, or optician.

Funding

In most countries vision screening is free, except for the Czech Republic, Malta, Switzerland, and Turkey. Funding is 33% (partially) provided by Health Insurance and 53% (partially) by the State. Parents and charity pay (part of the) screening in the Czech Republic, Latvia, Romania, Slovakia, Spain, and Turkey.

Coverage

Coverage varied from just starting (Estonia, Portugal, Turkey) to more than 95% in Austria, Czech Republic, Denmark, Finland, Flanders, Germany, Hungary, Iceland, Luxembourg, the Netherlands, Norway, Serbia, Slovenia, Sweden, and parts of the UK. Coverage of different testing time points varied, as did number of children screened, dependent on the age at which testing was performed. The highest coverage percentage was regarded as coverage for each particular country. Further detailed data is presented in table 2 and Appendix Map 1.

Hearing

Information on neonatal hearing screening programmes was obtained from 38 countries (including two Belgian regions). No information could be obtained from Macedonia.

Nationwide UNHS programmes exist in 33 of 38 countries. Malta has nationwide selective screening only for infants from neonatal and paediatric IC units. In Bulgaria, Moldova, and Serbia local selective screening programmes for high risk groups (premature newborns) exist. In Albania a pilot nationwide UNHS programme was discontinued due to lack of funds.

Table 2. Vision screening programmes in 36 European countries.

Country	Scope	Personnel	0-4mo	6-30mo	Pres.	Chart and age	Auto.	Also	Funding	Cov. (%)
Austria	nat	Ophth, ped, school	+	+	+	Lea 3; 4; 5; 6	-	stereo	insur, state	>95
Belgium (Fl)		YHC, nurse	+	+	+	Pict 3½, HOTV 4½	+	both	region	>95
Belgium (W)	nat	Orth, ped, other	+	+	+	Snel 3½; 6	+	-	region	>40
Bulgaria	loc	GP	-	+	-	Pict, E 7	-	colour	insur	
Croatia	nat	Ophth, ped, school	+	+	+	Pict, Lea 4, E 6; 6½	-	-	insur, state	>90
Cyprus	nat	School	+	-	-	Snel 6½; 7	-	-	state	>80
Czech rep	nat	Ophth, orth, ped, YHC, optom, other	+	+	+	Pict; Lea 3, E 5, Snel 7; 9; 11; 13; 15	Loc.	colour	insur, par region	>95
Denmark	nat	Nurse, school, GP	+	+	+	Pict 3; 4; 5; 6	-	-	region	>95
Estonia	loc	Ophth, ped	+	+	+	Lea 3, Lea; Snellen 6	-	-	insur	start
Finland	nat	Nurse, school, GP	+	+	+	Lea 3; 4; 5½	-	-	state, munic	>95

France	loc	Orth, ped, nurse, school	+	+	+	Pict 4	-	-	insur, region	>80
Germany	nat	Ped	+	+	+	Lea; HOTV 3	-	-	insur	>95
Greece	nat	Ophth	-	-	+	Snel 5½	-	both	state	>60
Hungary	nat	Ped, nurse, school	+	+	+	Pict 6	Loc.	both	insur, state	>95
Iceland	nat	Ped, nurse	+	+	+	Lea; HOTV 4, HOTV; Snel 6	-	stereo	state	>95
Ireland	nat	School	+	+	-	Snel 5½	-	-	state	>80
Israel	nat	Ped, nurse	+	+	+	Pict 3; 6	-	-	state	>80
Italy	nat	Ped	+	-	+	Snel (3); 6	-	-	region	>80
Latvia	nat	Ophth, ped	+	+	+	Cardiff 1, Pict; E 3, E; numbers 6½	-	stereo	state, par	>60
Lithuania	nat	Ophth, ped	+	+	+	Pict; E; Snel 6; 6½; 7	+	-	state	
Luxembourg	nat	Orth, ped, nurse	+	+	+	Pict; E 3½, 4½, 5½, 6½	+	both	insur, state	>95
Malta	nat	Orth, nurse, optom, school	+	+	-	Snel 3, Sher 5½	-	stereo	state	>80
Montenegro	nat	Ped, nurse	+	+	+	Snel 5½	-	-	state	
Netherlands	nat	YHC, nurse	+	+	+	Pict 3, Lea; C 4	-	-	munic	>95

Norway	nat	Nurse, GP, school	+	+	+	Lea 4, Sher 6	-	-	munic	>95
Poland	nat	Ped, GP	-	+	+	Pict 4, Snel 6	-	-	state	>80
Portugal	nat	GP	+	-	+	Sher 4, E 5; E; C 5½; 6	-	-	state	start
Romania	loc	Ophth	+	-	+	Pict 3, Snel 4; 5	Loc.	-	state, charity	>80
Serbia	nat	Ophth, ped	+	+	+	Snel 6½	-	both	state	>95
Slovakia	nat	Ophth, orth, ped	+	+	+	Pict 3, Lea; E; C; Snel, 5; 6	-	both	par, insur	>90
Slovenia	nat	Ped, school	+	+	+	Pict 3; 5 Snel 6; 7	-	-	insur	>95
Spain	loc	Ped, ophth, optom	+	-	+	Pict 4, Snel 4½; 5	-	stereo	par, state	
Sweden	nat	Nurse	+	-	-	HOTV 4, KM 6	-	-	region	>95
Switzerland	loc	Ophth, orth, ped, nurse, optic, school, GP	+	+	+	Pict 4, Lea; E 4½; 5, 5½	-	stereo	insur	>80
Turkey	start	Ophth	+	+	-	E 5	-	-	par	start
UK	nat	Orth, nurse, assist	+	-	-	Sonksen; Keeler 4; 5	-	-	region	>95

***Scope** = scope of vision screening programme (nat = nation-wide, loc = local), **Personnel:** (ophth = ophthalmologist, ped = paediatrician, school = school physician, YHC = youth health care physician, orth = orthoptist, optom = optometrist, GP = general practitioner, optic = optician, assist = practice assistant), **Pres.** = preschool screening(screening before school age, school age varies across countries), **Chart and age** = visual acuity chart and age of testing (Pict = Picture chart, Lea = Lea Hyvarinen Chart (picture) C = Landolt C, E = Tumbling E, KM = Konstantin Moutakis, Sher = Sheridan Gardiner, Snel = Snellen), **Auto.** = autorefraction/ photorefraction, **Also** = testing of stereopsis and/or colour vision, **Funding =** (Insur = health insurance, Munic = Municipalities, Par = parents), **Cov.** = Coverage.*

Tests

The most widely used audiometric test is OAE. Flanders has used aABR in all neonates, but in 2013 introduced additional auditory steady state responses (ASSR). Some regions in Denmark, Estonia, France, Germany, Spain, and Sweden use aABR, OAE, or both in the same infant as first test in healthy babies. In nearly all programmes both ears are tested, except in Finland and Switzerland, where one or two ears are tested, depending on the institution or the presence of risk factors. Testing is not staged in five countries, two-staged in 13 countries, three-staged in 19 countries, and 4-staged in one country. aABR is used as final stage in the majority of countries. In high risk groups, eg. premature newborns, most programmes use aABR or a combination of OAE and aABR, but in eight countries OAE only is used. In Wallonia (Belgium) all premature infants undergo full ABR.

In less than half of the countries, a hearing test in pre-school or early school age children is a regular part of health screening programmes.

Referral

Neonates who do not pass the test are referred to a combined audiology / ear, nose, throat (ENT) institution in most countries, in some countries to an audiologist, and in a few countries to an ENT specialist.

Funding

In most countries the government or health insurance finances the neonatal hearing screening programme. Other reported funding includes hospital, parents, and private funds.

Coverage

UNHS programmes cover an estimated 10-50% in Romania, 50-95% in nine countries, and more than 95% in 23 other countries. Malta has a nationwide selective screening programme with good coverage, whereas Bulgaria, Moldova, and Serbia have local selective screening programmes, with low coverage. Albania's discontinued pilot nationwide UNHS programme had a low coverage. Further detail is available in table 3 and Appendix Map 2.

Public-health

Extra information on public health screening programmes was obtained from 23 countries including one Belgian region (Flanders). All have a public health screening programme, but in Albania, Belgium, and Spain this is a regional programme.

Table 3. Overview of neonatal hearing screening programmes in 38 European countries.

Country	Scope	Strat	Test	St	Last test	Ears	Test risk group	Refer	Funding	Cov (%)	Child
Albania	past	all	OAE	3	full ABR	2	OAE	ENT	private	<10	-
Austria	nat	all	OAE	3	aABR	2	OAE	audio	state	>95	-
Belgium (Fl)	nat	all	aABR+ ASSR	2	aABR	2	aABR + ASSR	audio	state	>95	
Belgium (W)	nat	all	OAE	2	full ABR	2	full ABR	both	par, state	90	-
Bulgaria	loc	select	OAE	2	aABR	2	aABR	both	private, hosp	25	
Croatia	nat	all	OAE	3	aABR	2	aABR	both	insur	>95	-
Cyprus	nat	all	OAE	3	aABR	2	aABR	audio	NGO	>95	+
Czech rep	nat	all	OAE	1		2	OAE	ENT	insur	>50	
Denmark	nat	all	OAE or aABR	2	aABR	2	OAE+aABR	audio	state	>95	+
Estonia	nat	all	OAE or aABR	3	aABR	2	OAE	both	insur	>95	+
Finland	nat	all	OAE	2	OAE	1/2	aABR	both	state	>95	+
France	nat	all	OAE or aABR	3	aABR or full ABR	2	aABR	both	state	>50	+
Germany	nat	all	OAE or aABR	2	aABR	2	aABR	both	insur	>95	+
Greece	nat	all	OAE	1		2	aABR	both	par	>50	+
Hungary	nat	all	OAE	2	OAE	2	aABR	both	insur, state	>50	+
Iceland	nat	all	OAE	3	aABR	2	OAE	both	state	>50	-
Ireland	nat	all	OAE	2	aABR	2	OAE+aABR	audio	state	>95	-
Israel	nat	all	OAE	3	aABR	2	OAE+aABR	audio	state	>95	+
Italy	nat	all	OAE	3	aABR	2	OAE+aABR	both	hosp	70	
Latvia	nat	all	OAE	3	ABR	2	aABR and/or other	both	state	>95	+

Lithuania	nat	all	OAE	3	aABR	2	OAE+aABR	both	insur	50-90	-
Luxembourg	nat	all	OAE	2	OAE	2	aABR	ENT	state	>95	+
Malta	nat	select	OAE	1		2	aABR	both	state	>95	
Moldova	loc	select	OAE	2	aABR	2	OAE	both	int. project	>50	-
Montenegro	nat	all	OAE	4	aABR	2	aABR	both	state	>95	-
Netherlands	nat	all	OAE	3	aABR	2	aABR	audio	state	>95	+
Norway	nat	all	OAE	3	aABR or full ABR	2	aABR	both	state	>95	
Poland	nat	all	OAE	2	OAE	2	OAE	both	insur	>95	-
Portugal	nat	all	OAE	3	aABR	2	aABR	both	hosp	>95	-
Romania	nat	all	OAE	2	aABR	2	OAE+aABR	both	state	>10	-
Serbia	loc	select	OAE	1		2	OAE	both	hosp	25	+
Slovenia	nat	all	OAE	3	aABR	2	aABR	both	insur	>95	-
Slovakia	nat	all	OAE	2	OAE	2	aABR	both	insur, state	>95	
Spain	nat	all	OAE or OAE+aABR	3	aABR	2	aABR or OAE+aABR	audio	state	>95	-
Sweden	nat	all	OAE or aABR	3	aABR or full ABR	2	OAE+aABR or aABR	both	state	>95	+
Switzerland	nat	all	OAE	1		1/2	OAE or aABR	both	hosp	>95	+
Turkey	nat	all	OAE	3	aABR	2	aABR	both	state	90	
UK	nat	all	OAE	3	aABR	2	aABR	audio	state	>95	+

***Scope** = scope of hearing screening programme (nat = nation-wide, loc = local, past = pilot from 2004-2008), **Strat =** screening strategy (all = all neonates, select = only neonates at risk e.g. prematures), **Test =** test used for well babies in the programme (first test when staged)(test a or test b = both tests are used in the programme, test a + test b = both tests are used in one neonate), **St =** stages (number of tests before referral), **last test** = test before referral if staged, **ears =** ears tested (both or only the first ear with a pass), **test risk group** = test used in neonates at risk (first test when staged), **refer =** referred to ENT, audiological institution or a combination (both), **funding =** (insur = health insurance, hosp = hospital, par = parents, NGO = non-government organization, int. project = international project), **Cov = coverage** (infants screened / infants meant to be screened x 100), **child**: standard hearing test in screening programme at child age.*

In the Netherlands and Sweden a combination of national and regional programmes exists. Almost all countries have a programme for all children, except Albania, where screening is selective. Screening is not free in Albania, Bulgaria, and Czech Republic, and is compulsory in Bulgaria, Flanders, Greece, Hungary, and Turkey.

Tests

Weight, height and head circumference are measured in all countries, cardiac function in all but Albania, lung function in all but Albania and Flanders, vision in all but Albania and Turkey, hearing in all but Albania and Malta, motor skills in all but Czech Republic and the UK, speech and language development in all but Albania, Bulgaria, Czech Republic, and the UK, cognitive development in all but Albania, Czech Republic, Flanders, and the UK. Psychosocial development is assessed in all countries but Albania, Bulgaria, Czech Republic, Flanders, Germany, Israel, Sweden, and the UK.

Referral, funding and coverage

Referral is most often to a specialist. Funding is provided mostly by the government or health insurance. Coverage is above 80% in all countries, except Albania. Further data is presented in table 4 and Appendix Map 3.

Questionnaire answer check

Changes were made based on the first round of questionnaire answers. In hearing screening data: for Belgium (Flanders) the ASSR was added as test for neonates at risk; for Finland "testing one ear" was changed to "testing one ear or both ears"; for France "testing one ear and testing both ears" was changed to "always testing both ears"; for Italy coverage of "> 95%" was changed to "70%"; Malta selective screening, not population-wide screening, was confirmed; for Poland "non-staged screening" was changed to "staged screening"; for Israel, Italy, Lithuania, and Switzerland "only aABR testing" for neonates at risk was corrected to "OAE and/or aABR".

Vision screening data was revised: for Austria funding was changed from "health insurance" to "health insurance and state"; for Belgium (Flanders) personnel was changed from "nurse" to "nurse and youth health care physician", testing of stereopsis and colour vision was added and VA chart was changed from "Landolt C" to "Pictures and HOTV"; for Croatia VA chart was changed from "only Tumbling E" to "Pictures, Lea and Tubling E"; for Czech Republic Pictures and Lea chart were added; for Denmark the "Snellen chart" was changed to "Pictures" and coverage was changed from ">80%" to ">95%"; for Iceland Snellen chart was added; for Israel coverage

was changed from ”>95%” to ”>80%”; for Italy funding was changed from ”state” to ”regions”; for Latvia ”Picture chart and Tumbling E” was corrected to ”Cardiff, Pictures, Tumbling E and numbers”; for Norway the Sheridan Gardiner chart was added; for Slovenia autorefraction was corrected as in Slovenia autorefraction is only performed in ophthalmology clinics for referred children and not for screening; for Sweden the Konstantin Moutakis chart was added; for the UK funding was corrected from ”state” to ”regions”, and personnel were changed from ”orthoptist, optician and optometrist” to ”orthoptist, nurse and practice assistant”.

Table 4. Public health screening programmes in 23 European countries.

Country	Scope	All	Vision	Hearing	WHH	Heart	Lung	Motor	Speech	Cog	Psycho	Funding	Cov (%)
Albania	loc	-	-	-	+	-	-	+	-	-	-	state, par	>10
Belgium (Fl)	nat	+	+	+	+	+	-	+	+	-	-	state	>95
Bulgaria	nat	+	+	+	+	+	+	+	-	+	-	state, insur	>95
Croatia	nat	+	+	+	+	+	+	+	+	+	+	insur	>95
Czech rep	nat	+	+	+	+	+	+	-	-	-	-	insur	>80
Finland	nat	+	+	+	+	+	+	+	+	+	+	state, munic	>95
France	nat	+	+	+	+	+	+	+	+	+	+	state	>95
Germany	nat	+	+	+	+	+	+	+	+	+	-	insur	>80
Greece	nat	+	+	+	+	+	+	+	+	+	+	state, par	
Hungary	nat	+	+	+	+	+	+	+	+	+		state	>95
Iceland	nat	+	+	+	+	+	+	+	+	+	+	state	>95
Israel	nat	+	+	+	+	+	+	+	+	+	-	state	>95
Macedonia	nat	+	+	+	+	+	+	+	+	+	+	state, insur	>95
Malta	nat	+	+	-	+	+	+	+	+	+	+	state	>95
Montenegro	nat	+	+	+	+	+	+	+	+	+	+	insur	>95
Netherlands	nat	+	+	+	+	+	+	+	+	+	+	state, munic	>95
Portugal	nat	+	+	+	+	+	+	+	+	+	+	state	>95
Serbia	nat	+	+	+	+	+	+	+	+	+	+	insur	>80
Slovenia	nat	+	+	+	+	+	+	+	+	+	+	insur	>95
Spain	loc	+	+	+	+	+	+	+	+	+	+	state	>95
Sweden	nat	+	+	+	+	+	+	+	+	+	-		>95
Turkey	nat	+	-	+	+	+	+	+	+	+	+	state	>95
UK	nat	+	+	+	+	+	+	-	-	-	-	state	

Scope *= public-health screening programme (nat = nation-wide, loc = local),* ***All*** *= screening programme for all children,* ***WHH*** *= weight, height and head circumference,* ***Cog*** *= cognitive development,* ***Psycho*** *= psychosocial aspects,* ***Funding*** *(insur = Health Insurance, par = parents, munic = Municipalities)* ***Cov*** *= Coverage).*

DISCUSSION

This study showed that large differences exist in tests used, age, and frequency of testing in paediatric population-based vision and hearing screening programmes throughout the EU. First measurement of VA varies from ages 3-7, but in most countries it is measured before age five. In children aged 3-4, picture charts, including Lea Hyvarinen, are used most; in children over four Tumbling E and Snellen. Vision screening is performed mostly by paediatricians, ophthalmologists, or nurses. As a first hearing screening test, OAE is used most in healthy neonates, and ABR in premature newborns. The majority of hearing testing programmes are staged. Children are referred after one, two, three, or four abnormal tests. Funding is by health insurance, state, regions, municipalities, charity, hospital, parents or private funding. A high coverage is reached in most countries for both vision and hearing screening.
Our study was limited by the difficulty in obtaining referenced or first-hand data sources from respondents. Where possible we tried to maintain the quality of our data by involving clinicians involved in population based screening, and cross-checking their answers with those from general screening professionals. Obtaining accurate information on funding and coverage was the most difficult. Information on tests, personnel, and age was easier to acquire. Coverage may have been overestimated by the country representatives

Screening for vision and hearing deficits has similarities, but also differences. An essential difference is that objective tests are available for hearing screening at a very early age, enabling screening directly after birth. This is probably the reason for the more uniform approach and higher coverage reported for hearing screening compared to vision screening. We assumed that the personnel operating the screening apparatus at the hospital or during home visits would be a technician, so we did not ask the profession explicitly. The only two tests for hearing screening are OAE and aABR, so the major difference in hearing screening is the number of screening stages before referral. Multiple stage screening is more expensive, but yields higher specificity, which reduces the number of false referrals to specialized and expensive audiological care centres.[23,26] There are most frequently two or three stages of screening before referral, generally with OAE as the first test and aABR as last test. It has been suggested that three stages may be more cost-effective,[26] but this is not based on combined use of OAE and aABR. Pre-school or early school-age hearing tests may potentially discover hearing loss acquired during the years after birth, but this occurs rarely and these tests have been abolished in many European countries.

The wide differences between European screening programmes may have occurred because these programmes arose piecemeal, before robust evidence on effectiveness and cost-effectiveness was available to guide protocol design or implementation. In addition, most preventive health care programmes are government funded and, therefore, competition is lower than in curative health-care. Further assessment is needed on the influence of funding source (eg. state, health insurance, or municipalities) on the efficiency of screening.

Further study should also be undertaken into the relative costs and effectiveness of different approaches to screening, as in Europe, 12 different VA charts are used, 10 professions are involved in vision screening, one to four hearing screening tests take place before referral, and eight funding sources are involved. The large number of screening tests used in vision screening should be compared. Efficiency of screening (ie. sensitivity and specificity per euro) should be calculated for screening performed by different screening professions.

We now plan to include data sources in a much larger and more detailed questionnaire. The EUS€REEN study group, an EU-wide consortium (see list at end of paper), is currently preparing a Europe-wide study to compare and optimize the cost-effectiveness of vision and hearing screening, and give country-specific advice in all candidate, associate, and full EU-member states.

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APPENDIX A

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APPENDIX B

Glossary:

aABR: automated Auditory Brainstem Response; detects responses in the brainstem after offering clicks of 35 or 40 dB via headphones.

Amblyopia (lazy eye): reduced vision, usually in one eye caused by abnormal visual experience in early childhood e.g. strabismus and refractive error.

Bruckner test: A direct ophthalmoscope is used in a darkened room and the red reflex in both eyes is assessed simultaneously at 0.6 to 0.9 metres. The colour and brightness of the red reflexes are compared. The colour is often more orange than red. The test is easy and quick to perform and can reliably detect media opacities. Strabismus and refractive error can also be detected, but with a lower sensitivity. Refractive error can give a yellow-white edge to a red reflex.

Hirschberg test: corneal light reflex test. The corneal light reflex test is performed to assess ocular alignment. The test is performed by shining a light into the child eyes from a distance and observing the reflections on the cornea with respect to the pupil. The location of the light reflexes should be symmetric.

OAE: Otoacoustic emissions; sounds produced by inner ear hair cells if the hearing threshold is better than 35 dB and picked up by a microphone in the ear canal.

Q1

In your country is there a:										
Public-health screening programme?	None	Regional	National	Employer-based	Other					
Eye screening programme?	None	Regional	National	Employer-based	Other					
Who pays for eye screening?	Parents	Health Insurance	Councils	Provinces-Regions	State	Parents employer	Companies		Charity	Other
Who does the eye screening?	Ophthal-mologist	Orthoptist	Paedia-trician	Youth health care physician	Nurse	Ophth practice assistant	Opto-metrist	Optician	School physician	Other:
Coverage among eligible children?	>95%	>90%	>80%	>60%	>40%	>20%	>10%	<10%	Just starting	Other:
Parents' secondary benefits:	Eye exam is free	Eye exam is cheap	Financial reward	During working hours	Condition for school entry	Free glasses	Obligatory			Other:
Infant eye-screening tests?	Inspection	Fixation	Red fundus reflex	Hirschberg	Brückner	Cover test	Pupillary reflexes	Motility		Other:
At approx	1 week	2 weeks	3 weeks	1 month	6 weeks	2 months	10 weeks	3 months	4 months	Other:
Preverbal eye-screening tests?	Inspection	Fixation	Red fundus reflex	Brückner	Pupillary reflexes	Motility	Hirschberg	Cover test		Other:
at approx	6 months	9 months	1 year	15 months	18 months	21 months	2 years	27 months	30 months	Other:
Autorefraction-photoscreening at:	6 months	9 months	1 year	15 months	18 months	21 months	2 years	27 months	30 months	Other:
Preschool eye screening?	Inspection	Fixation	Red fundus reflex	Brückner	Pupillary reflexes	Motility	Hirschberg	Cover test		Other:
visual acuity measured with:	Picture chart	Lea Hyvarinen	HOTV	Tumbling E	Landolt C	Snellen	Also:	Stereopsis	Color vision	Other:
at approx	3 years	3,5 years	4 years	4,5 years	5 years	5,5 years	6 years	6,5 years	7 years	Other:
Positively screened children referred to:	General practitioner	Ophthal-mologist	Orthoptist	Optician	Opto-metrist					Other:

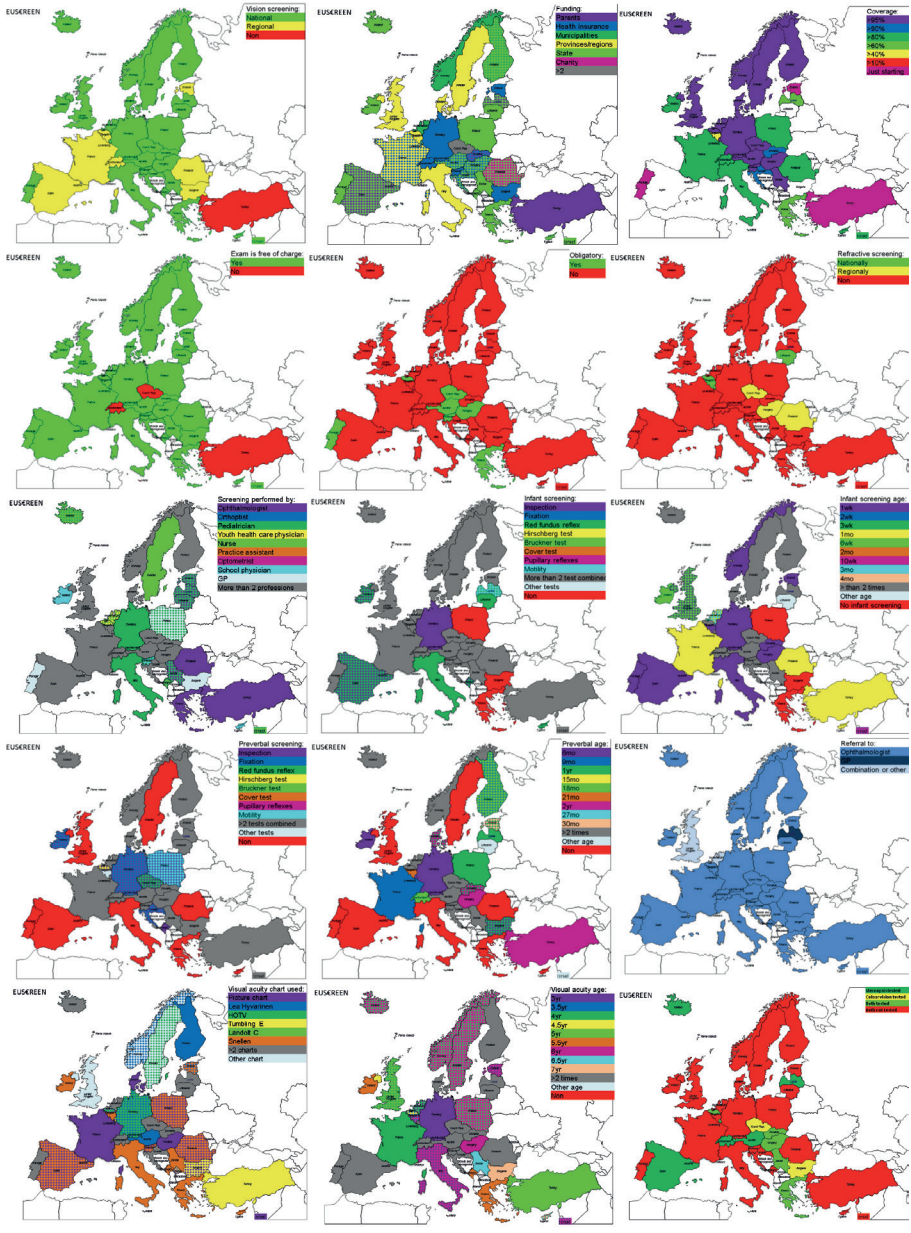
Q2

In your country is there a:				
Public-health screening programme for children?	no	regional	national	other
Neonatal hearing screening programme (NHS)	no	regional	national	other
In what year approximately did the programme start?				
How is the NHS programme financed?	parents	hospital	government	health insurance
What % of neonates are actually screened?	>95%	>50%	>10%	<10%
Which test is used for NHS?	OAE	aABR	other	
Different test for neonates at risk, f.e. prematures?	no	aABR	other	
Are both ears tested?	one ear	both ears		
Is NHS staged?	no	OAE-aABR	OAE-OAE-aABR	other
Is NHS in your country	universal?	selective?		
What is the follow up if a neonate tests positive on NHS?	audiologic examination	ENT	combination	other

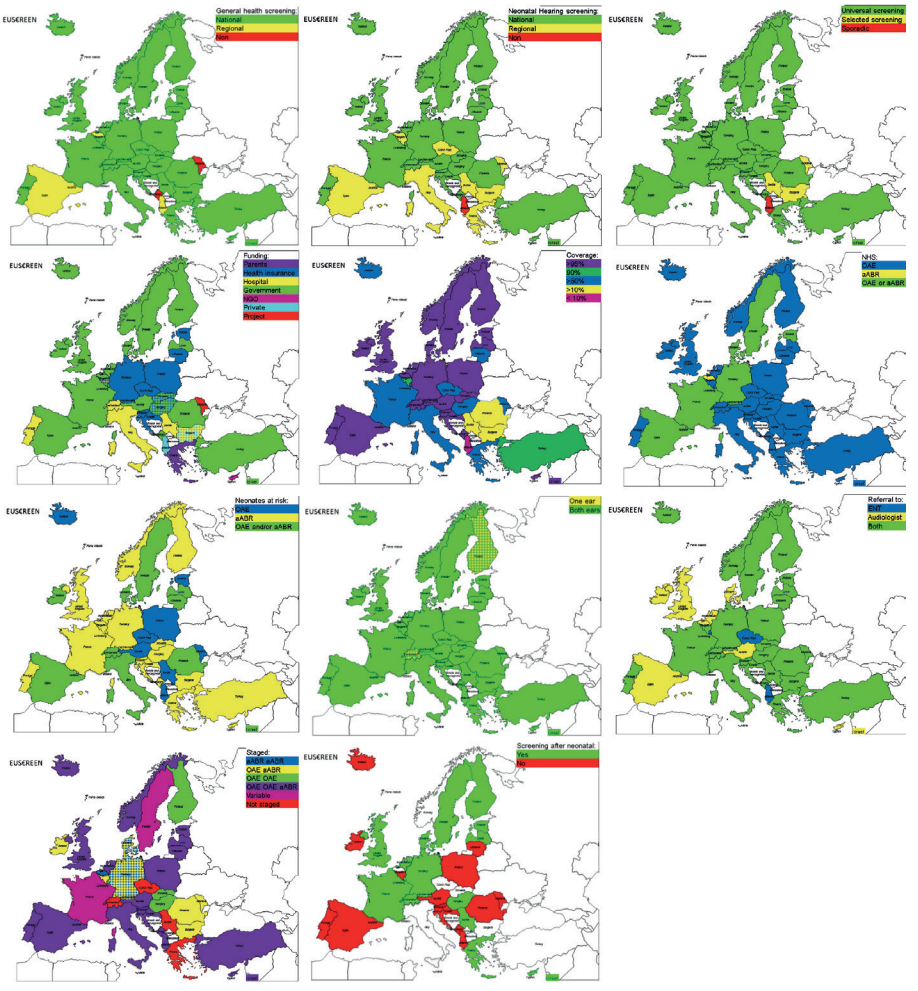
Q3

In your country is there a:										
Public-health screening programme for children?	no	national	regional							other
In what year did the programme start?										
General or selective screening	no screening	general	selective		risk groups					
Who pays for the screening programme?	parents	charity	hospital	government	health insurance					other
Parents' secondary benefits:	exam is free of charge	exam is cheap	financial reward	during working hours	obligatory					other
Coverage among eligible children?	>95%	>80%	>50%	>10%	<10%					
At what age is screening performed?										
Are the following tests performed	weight, height, head circum-ference	heart	lung	vision	hearing	motor skills	speech and language	cognitive development	Psycho social aspects	other
Who performs the screening?	doctors	para-medic	nurses	screening physician	school physician					other
Positively screened children are referred to:	GP	hospital	specialist	private clinics						other

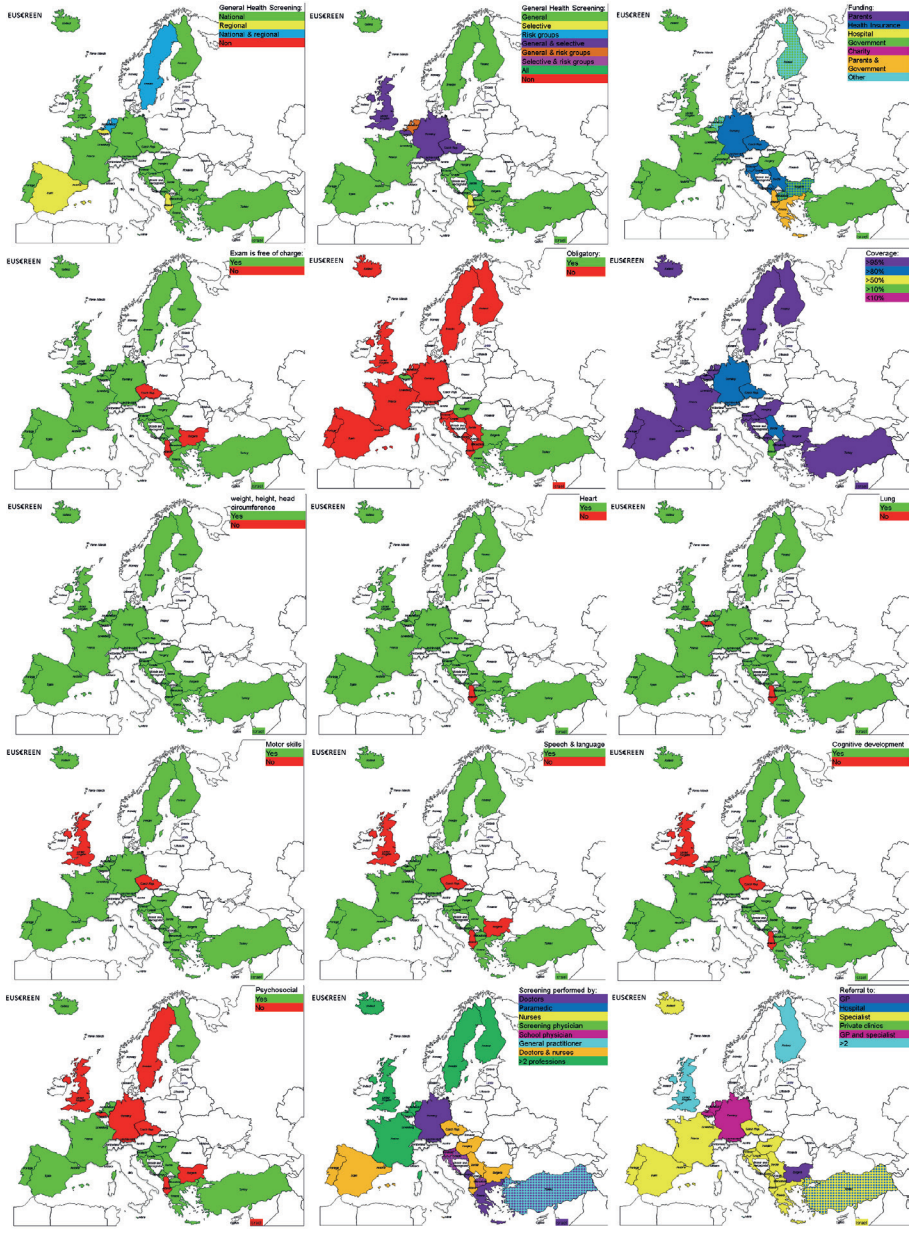
Map 1: Vision screening.



Map 2: Neonatal hearing screening.



Map 3: General health screening.



3

The effect of omitting an early population-based vision screen in the Netherlands: A micro-simulation model approach

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ABSTRACT

OBJECTIVE To estimate the effect of omitting an individual screen from a child vision screening programme on the detection of amblyopia in the Netherlands. A previous study (Rotterdam Amblyopia Screening Effectiveness Study) suggested that the three screens carried out between 6 and 24 months contributed little.

METHODS We developed a micro-simulation model that approximated the birth-cohort data from the previous study, in which 2964 children had completed follow-up at age 7, and 100 amblyopia cases were detected. Detailed data on screens, referrals, and orthoptic follow-up, including the cause of amblyopia, were available. The model predicted the number of amblyopia cases detected for each screen and for the entire screening programme, and the effect of omitting screens. Incidence curves for all types of amblyopia caused by strabismus, refractive anomalies or by both were estimated by approximation of the observational data, in conjunction with experts' estimations and the literature.

RESULTS We calculated mean actual sensitivity per screen per type of amblyopia, and the effect per screen. Screening at 24 months was found to be least effective. The impact on the screening programme, estimated by summing the effectiveness per screen, omitting the 24-month screen, was a reduction of 3.4% (57 vs. 59 cases) in the number of detected cases of amblyopia at age 5.

CONCLUSIONS The effectiveness of the Dutch vision screening programme would hardly be affected by omission of the 24-month screening examination. A disinvestement study is warranted.

INTRODUCTION

In most vision screening programmes, visual acuity (VA) is measured at age 3–6 years. In the Netherlands, VA measurement is preceded by primarily orthoptic examination to detect visual disorders on four occasions between age 0 and 24 months. At 0–4 months, screening consists of inspection of the eye, pupillary reflexes, and examination of the red fundus reflex, to assess media opacities. At the three screening examinations between 6 and 24 months, tests also include corneal reflexes of a light held by the examiner (Hirschberg test), cover test, alternating cover test, eye motility, and quality of ocular pursuit movement (appendix table).[1–3] VA is measured at 36 months with the Amsterdam Picture Chart, and at 45 months with the Landolt-C chart.[3]

The four main types of amblyopia are refractive amblyopia due to anisometropia (unequal strength of glasses), strabismic amblyopia due to misalignment of the eyes, combined-mechanism amblyopia (a combination of misalignment and unequal strength of glasses) and, rarely, deprivation amblyopia due, for example, to congenital cataract or retinoblastoma. Strabismic amblyopia can be noticed by the parents, but refractive amblyopia is not externally apparent, and is often not found until VA is measured.

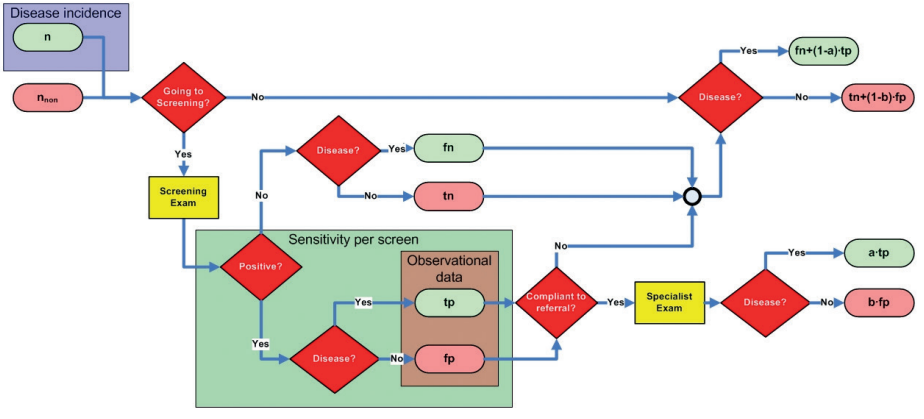
In the Rotterdam Amblyopia Screening Effectiveness Study (RAMSES)[4,5] 4624 children born in Rotterdam between September 1996 and May 1997 were followed for 7 years, through all routine vision screening examinations (0–4, 6–9, 14, 24, 36, 45, and 54–60 months) and diagnostic follow-up. Of the 3897 children still living in Rotterdam at age 7, 2964 underwent the final orthoptic study examination. Amblyopia had been diagnosed in 100 children (3.4%). Screening between 6 and 24 months of age contributed little to the detection of refractive amblyopia.[4,5]

If detailed data are available, the impact of omission or introduction of a single screen can be calculated, but this is difficult if that screen is part of a programme consisting of consecutive screens. To calculate the impact of omission of parts of the early vision screening, we formulated a model, inputting these data.

METHODS

We developed a micro-simulation model, programmed in MATLAB R2008b (MathWorks), to assess modification of the Dutch eye screening programme. Monte Carlo simulations with various incidence and sensitivity combinations were used to approximate the observational data. The model simulates the path followed by a subject during consecutive screens within the Dutch amblyopia screening programme, which consists of seven exams between age 0 and 60 months. VA is measured from 36 months onwards. A child can attend or not attend a screen test. If the child attends screening, the result can be positive or negative. Positive cases can comply with the referral for diagnostic follow-up. Screen positive cases who have the disease are the true positives (tp). The number of tp and the number of children with the disease not screen-detected at that time (i.e. false negatives (fn)), determine the sensitivity (tp/(tp + fn) of the test (Figure 1). For the approximation of the RAMSES data, input parameters were varied until the model predicted the detection of the cases of amblyopia actually detected by screening (i.e. not by the parents or others) at the corresponding screen for each of the four types of amblyopia. Thereafter a programme with one of the screens omitted was simulated to determine the relative effect on the detection of amblyopia.

Figure 1. Schematic representation of the path that an individual undergoing screening follows.



Indicated are the data obtained from observational studies, the disease incidence and the sensitivity per screen within the path, which are used in the model. Here, n is the number of diseased population and nnon is the number of the healthy population. The fn, fp, tn and tp are the false negatives, false positives, true negatives and true positives, respectively. Here, a and b are the fractions of true positives and false positives, respectively, that comply with the referral.

A major problem in developing this model is that the true incidence curves of the disease are unknown. It is known that amblyopia does not exist at birth, but may develop after age 3 months in cases where one eye is used less for vision. Generally, amblyopia does not develop after age 6. Refractive amblyopia may develop at an older age than strabismic amblyopia and can be treated at an older age.[6–8] The incidence curves for refractive, strabismic, combined-mechanism, and deprivation amblyopia were derived by approximation of the observational data in conjunction with experts' estimations. Data collected during the RAMSES study, in which the prevalence of amblyopia between ages 0 and 7 years was 3.4%, were used.[4]

In the RAMSES study, 100 amblyopia cases were found, 73 with a positive screening and 27 with no positive screening. Of the 73 cases with a positive screening, 60 had been detected by screening, and 12 were detected by the parents but were positively screened later on. In one case, it was unclear whether the child visited the ophthalmology department after the positive test. Four children had been unsuccessfully referred. All 100 amblyopia cases had been differentiated by amblyopia type, and a further differentiation in age of detection for each of the four types was made. We used the combined data about the cause of amblyopia with the screen at which each case of amblyopia was detected (Table 1).

Table 1. Number of tests and detected amblyopia cases in the RAMSES study differentiated to the four main causes of amblyopia and the screen at which each case was detected.

Age of positive screening	Tests	Strabismus	Refractive	Combined-mechanism	Deprivation	Unknown type	Total amblyopia
6–9 Months	3272	3	1	4	0	0	8
14 Months	3297	1	0	2	2	0	5
24 Months	2982	1	0	7	1	0	9
36 Months	2659	5	4	4	0	1	14
45–54 Months	2457	3	15	5	1	1	25
60 Months	2824	0	8	3	1	0	12
No positive screen		6	14	5	2	0	27
Sum		19	42	30	7	2	100

Note: The screening exams before 6 months of age were not included in the RAMSES study.
No positive screen means that the child was detected outside of screening, for example because parents had noticed abnormalities and had gone to their General Practitioner or to the hospital

Several orthoptists and strabismologists were asked as experts (i) to report the youngest age at which patients were diagnosed with strabismic, refractive, combined mechanism, and deprivation amblyopia, and (ii) to estimate the highest age at which each of the four types of amblyopia could develop. For instance they were asked whether they had ever seen a patient with refractive amblyopia diagnosed at age 5 who had good VA at age 3. By approximation of the observational RAMSES data, in conjunction with experts' estimations and literature,[6–8] incidence curves for the four types of amblyopia were estimated, with upper and lower estimated boundaries. From the literature and expert opinion we assumed that the sensitive period for amblyopia to develop starts at 3 months (t_{start}) and that there is no additional amblyopia development after the age of 5 years (t_{end}).[6–8] The upper limit follows a negative polynomial function (equation (1)). For the lower estimate, the progression is more conservative and stagnates in time, described by a parabolic function (equation (2)).

$$I(t) = \alpha + \frac{1}{\beta \cdot t} \quad (1)$$

$$I(t) = a \cdot t^2 + b \cdot t + c \quad (2)$$

Where I(t) is the incidence at time t and a, b, c, α and β are variables indicated in the input function:

$$a = \frac{p}{-(t_{end})^2 + \left(-(t_{start})^2 + 2 \cdot t_{start} \cdot t_{end}\right)}$$

$$b = -2 \cdot t_{end} \cdot a$$

$$c = a\left(-(t_{start})^2 + 2 \cdot t_{start} \cdot t_{end}\right)$$

$$\alpha = \frac{p}{1 - t_{start} / t_{end}}$$

$$\beta = -\frac{1}{t_{start} \cdot \alpha}$$

where t_{start} is the age for which the first diseased cases start to develop, t_{end} is the age for which the incidence rate reaches zero or is equal to zero, and p is the prevalence at the end of amblyopia development, that is when incidence rate is zero.

We simulated eight incidence curves with lower and upper estimates. A best-fit approximation for the incidence curve was performed during the fitting of the sensitivity, using the discrete quasi maximum likelihood method, comparing the observed values in the study with the predicted values (appendix figure). In this way, the most likely incidence curve was estimated.

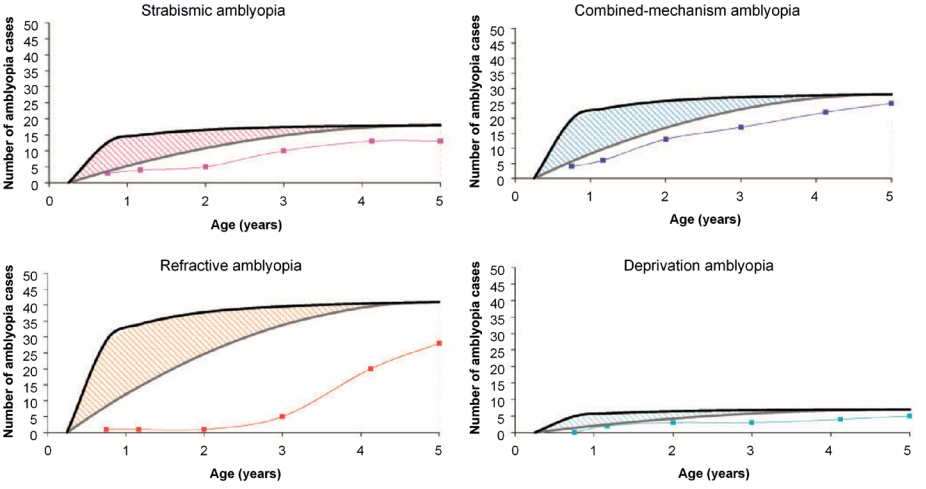
To calculate the mean sensitivity, we assumed that all screens using the same combination of tests (appendix table) had the same sensitivity. The model was run with 20 different values of sensitivity between 0% and 100%. We first estimated the mean sensitivity of the 6–24 months orthoptic screens. For each incidence curve, screening was simulated using the 20 values of sensitivity for the preverbal screens. The available subjects for that specific screen examination were obtained from the incidence curve. For each screen the screening test was simulated per subject, subsequently using one sensitivity out of the range. This resulted in a number of positively screened subjects per screen. For each incidence-sensitivity combination this was repeated 4000 times. Each time the simulated number of detected subjects for the preverbal screens was equal to the number of detected subjects in the observational study, the sensitivity used was implemented in an array. After the simulation, a mean sensitivity for that incidence curve was calculated, based on the sensitivity values in the array. The mean sensitivity for screens using the VA test was obtained in a similar way.
Overall sensitivity of the Dutch vision screening programme had been calculated as 73% in the RAMSES study (73 of the 100 detected amblyopia cases had been positively screened).[5] For this calculation, sensitivity had been defined as the proportion of children with amblyopia who had a positive vision screening result at any point in time. Because 12 of the 73 amblyopia cases with a positive screening had been detected by the parents, but were positively screened later on, and in one case it was unclear whether this child visited the ophthalmology department after the positive test, in the current evaluation only the 60 screen-detected cases with amblyopia were used.

Using the incidence curves and the mean sensitivity per screen, we simulated the entire screening programme. With the estimated effect per detected case, we estimated the effect per screen. The effectiveness of the programme was calculated by summing the effect per screen. Starting with the scenario of the current vision screening programme, we subsequently calculated what the effectiveness of the screening programme would be after omission of the screen that was found to be least effective in the original simulation.

RESULTS

The estimation of the incidence curves per amblyopia type resulted in four graphs each with an upper and lower estimate, based on approximation of the observational data in conjunction with the experts' estimations and literature.[6–8] For upper and lower estimates of incidence curves, we consulted several orthoptists, who are involved in the treatment of children with amblyopia, and strabismologists. All agreed that amblyopia does not develop before the age of 3 months, or after the age of 5 years. Elston and Timms have previously shown that the lower age limit before the start of the sensitive period for development of amblyopia is at least 4–6 weeks after birth.[6] Basic neurophysiologic research on amblyopia performed by Hubel and Wiesel showed that there is an upper age limit for the development of amblyopia in animals.[7] Keech and Kutschke found that no human subject developed amblyopia after age 6 years.[8] The model simulated 10 incidence curves per amblyopia type which, together with the cumulative number of cases found per screen, produced the plots shown in Figure 2. The incidences of combined-mechanism amblyopia and refractive amblyopia were highest (between 30 and 40 cases per 2964 children), the incidence of pure strabismic amblyopia was lower (less than 20 cases per 2964 children) and the incidence of deprivation amblyopia was lowest (less than 20 cases per 2964 children).

Figure 2. The estimated cumulative incidence per amblyopia type for a cohort of 2964 children.



Dots represent the detected amblyopia cases in the RAMSES study by screening only (cumulative). The upper black lines represent the upper estimate and the lower grey line represents the lower estimate of the incidence curves.

The sensitivity of the total programme is different from the sensitivity per screen. If all the separate screens are combined into one programme, this will give a higher overall sensitivity. The sensitivity curves presented here are estimated per screen per amblyopia type (Figure 3).

For each amblyopia type, the mean actual sensitivity per screen was calculated. The sensitivity of the preverbal screens was less than 15% per screen. The sensitivity of the VA screens was 17–26% per screen. Using the incidence curves and the mean sensitivity per screen, we estimated the effect per screen.

The Monte Carlo simulation that best approached the observational data was used to estimate the effect of each screen. Using the estimates for mean incidence and mean sensitivity, we determined the cumulative detection over the subsequent screens per amblyopia type. From 2964 children, 59 amblyopia cases were detected by screening by the age of 5 years (Figure 4). For a screening programme with omission of the 24-month screen, more children were detected at the screens at age 3 years and later. The number of detected cases of amblyopia at age 5 would be reduced by 3.4% (57 vs. 59 cases) (Figure 4).

Figure 3. The estimated test sensitivity per screen per amblyopia type for the six screening examinations.

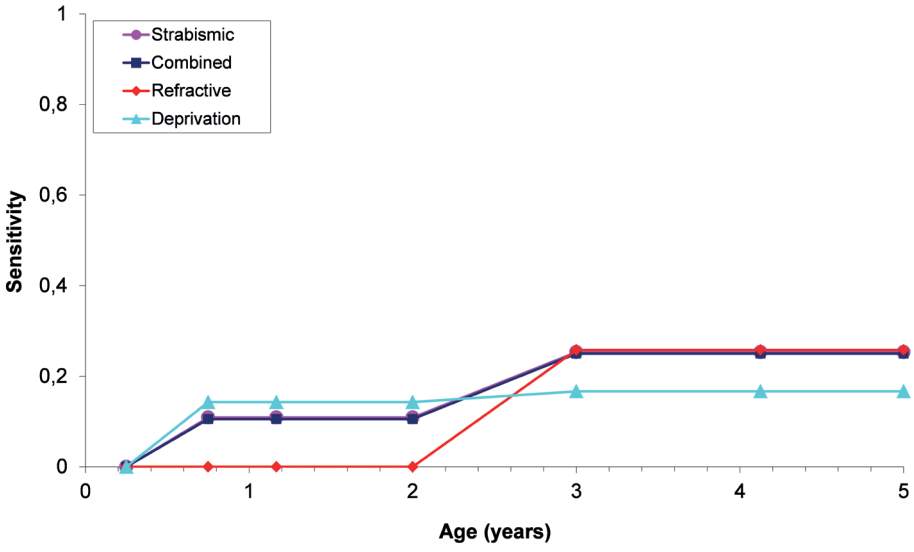
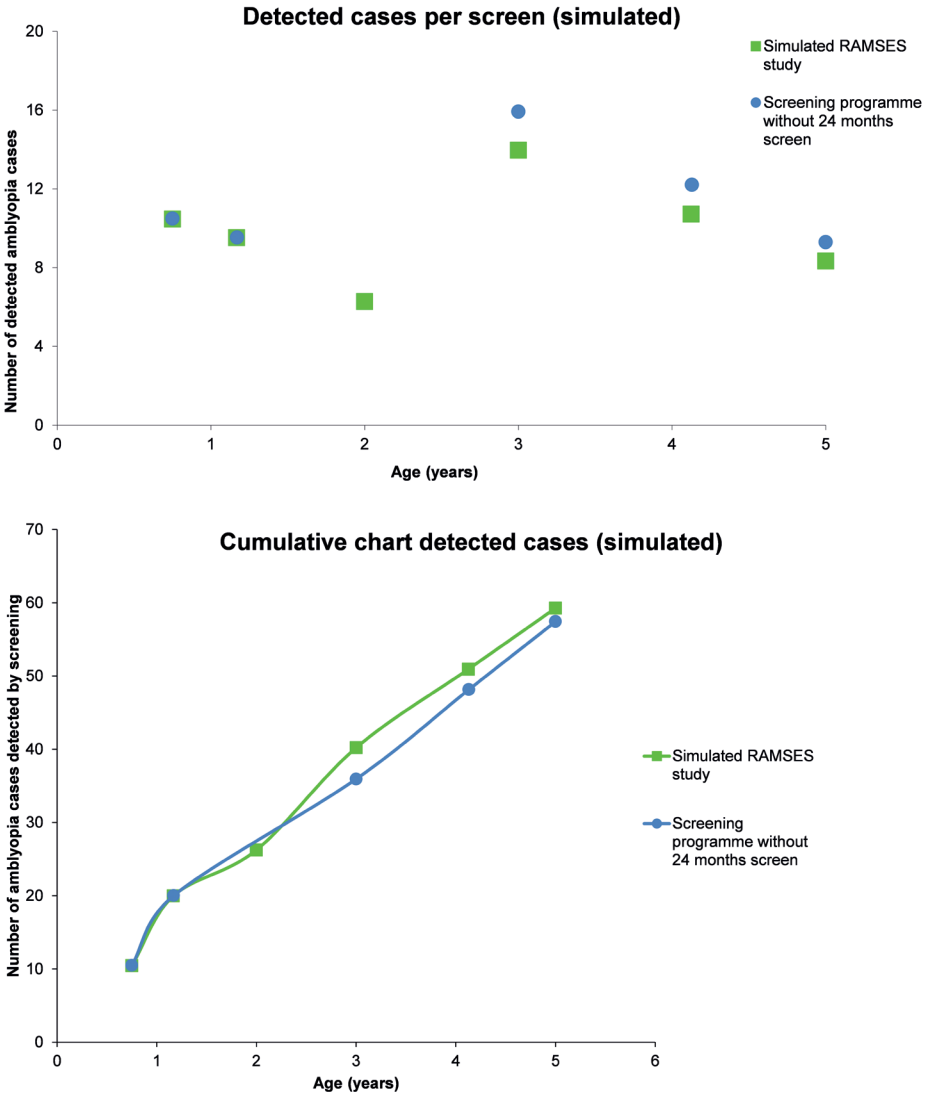


Figure 4. (a) The predicted number of children detected per screen for amblyopia in the simulated RAMSES study.
(b) The cumulative predicted number of children detected with amblyopia per screen for amblyopia in the simulated RAMSES study.



The squares represent the simulated present screening programme and the dots represent the effectiveness of the simulation of a reduced programme in which the screen at the age of 24 months is omitted. The lines represent the present screening programme in the Netherlands (squares) and a reduced programme in which the screen at the age of 24 months is omitted (dots).

DISCUSSION

This study shows that the effect of omission of components of a screening programme can be calculated with the micro-simulation model, provided that sufficient and detailed data are available. It confirms the suggestion, from a large prospective birth-cohort observation study, that part of the screening programme seemed to add little to the detection of amblyopia. Analysis of the data had shown that screening at 6–24 months, an age when VA cannot be measured yet, contributed little to the detection of refractive amblyopia, whereas strabismic amblyopia was detected outside of screening in half of cases.[4] With the micro-simulation model, the screening examination at 24 months was found to be least effective. Omitting this screen reduced the total number of detected cases of amblyopia at age 5 years from 59 to 57 (3.4%).

Our model has limitations. It is not incontrovertible to adapt some of the less well determined input parameters, like the incidence curves, to fit the detailed data from the RAMSES study, but our pragmatic approach served as a good starting point of the simulation of omission of part of the programme. For micro-simulations, accurate data on the prevalence and incidence of the disease at the time of screening and on the sensitivity of the screening methods are essential, but these data are difficult to obtain from observational studies. The age-specific incidence also varies per amblyopia type. But the curves for the four types are essential for the simulation of the effectiveness of each screening examination. We had to make assumptions to estimate these incidence curves, and for the sensitivity of the tests. To calibrate the upper and lower limits of the amblyopia incidence curves, we therefore had to use indirect derivatives such as the RAMSES data, literature, and expert opinion. If the age specific incidence of amblyopia were in fact lower than estimated, the incidence curves would be closer to the curves of detected cases in the RAMSES study, and the sensitivity of the screen would be higher. If the incidence curves were higher than estimated, the sensitivity would be lower than estimated. If children were to be tested at a later age, when they would probably be easier to test, the sensitivity of the tests would increase, leading to a higher amblyopia case detection.

It is difficult to compare our incidence curves with data in current literature. Atkinson et al. identified manifest strabismus and strabismogenic and amblyogenic refractive errors in children aged 7–9 months and found a hyperopia (≥3.5D) prevalence of 5–6% and an anisometropia and manifest strabismus prevalence of<1% each. Untreated hyperopes developed strabismus in 21%.[9] The children were not classified as amblyopic or not,

but our incidence curves also showed an increase in strabismic amblyopia after age 6 months and a higher incidence of refractive amblyopia in comparison with strabismic amblyopia. Williams et al. reported a prevalence of 0.7–3.4%, depending on whether the children had undergone preschool screening and the definition of amblyopia.[10]
We assumed equal sensitivities for all preverbal exams at 6–9, 14, and 24 months, as these screening examinations comprise the same tests. In the RAMSES study, however, as in real practice, these multi-component screening examinations were considered as one screen. It is possible that testing at an older age would have had a higher sensitivity, because of better cooperation and understanding of the tests. Also, if all separate screens are combined into one programme, this will give a higher sensitivity.

The low number of refractive amblyopia cases detected might be explained by the fact that strabismus causing amblyopia is often noticed by the parents, but a refractive error is not.
Complete and detailed observational data are useful to analyse the effectiveness of population-based screening programmes, but, because observational data is not dynamic, it is difficult to predict the effect of changes in a screening programme. Analysis is complex as the net effect of omission of one link in the chain is difficult to predict. Evaluation of alternative different screening strategies is difficult, as such studies are often expensive and time consuming. A micro-simulation model is dynamic, and can be used to evaluate different screening scenarios and compare their effectiveness. As our model was able to compute the mean number of detected true cases for each consecutive screen, it is well suited to evaluate a screening programme consisting of repeated screens. Further work is needed to validate and extend the model, so that it can be used to simulate screening programmes using different tests for each screen. With more input data, the model might be used as a general tool for evaluating the effectiveness of screening programmes with multiple screenings. As the input can easily be altered per disease specification, it could simulate screening for different disease types.

Further work is needed before the model is able to provide evidence for modifications of screening programmes, but it can be used as a tool to compare the effectiveness of different screening programmes, for instance in different countries in Europe, provided that detailed input data such as sensitivity of the tests used and background prevalence, are available.[11] Since the completion of this microsimulation model study, we have started a disinvestment study, comparing two sequential birth cohorts of approximately 6000 children in a care region in the Netherlands. In the second birth

cohort, specific eye examination during general screening between the age of 6 and 24 months was omitted. The first results of this disinvestment study confirm the predictions of the microsimulation model for the screens at age 6–9 months: the screened and unscreened groups differed little in the proportion of children referred and found to have amblyopia. On further examination, all cases of amblyopia detected were caused by strabismus, not by refractive errors, and most cases of strabismic amblyopia were found because the parents had noticed the strabismus.[12] At age 14–24 months, referral was still mostly based on conspicuous strabismus or other visually apparent disorders noted by parents or screening physicians, but, although still a minority, specific eye screening led to more referrals than at 6-9 months.[13]

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Semistructured observation of population-based eye screening in The Netherlands

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ABSTRACT

BACKGROUND In the Netherlands, child healthcare physicians screen children seven times for vision disorders between the ages of 1 and 60 months. Examination consists of inspection of the external structures of the eye, fundus red reflex, Hirschberg test, pupillary reflexes, cover-uncover test, alternating-cover test, eye motility, monocular pursuit, and, from 36 months onwards, visual acuity. We observed how well these tests are done.

METHODS Screening test performance was assessed with semi-structured observations. Two orthoptic students developed a semi-structured observation form. In addition to extensive instructions form an orthoptist and child healthcare physicians instructor, they attended two one-day courses for child healthcare physicians. Tests were assessed using criteria based on the Dutch Child Vision Screening Guideline version 2010 and the Dutch Manual for Orthoptic Examination. Type of chart, testing distance, and starting eye were recorded for the visual acuity measurements. The observations in the first week were done simultaneously by the two observers and checked for concordance.

RESULTS Concordance between the two observers was good. Twenty-five child healthcare physicians were observed during 100 days in total. Two physicians were excluded because they examined few children. The remaining 23 physicians examined 329 children, of whom 82 were 1-4 months, 157 aged 6-24 months, and 90 aged 36-45 months. Fundus red reflex was performed in 89% of children, Hirschberg test in 88%, pupillary reflexes in 14%, cover-uncover test in 65%, alternating-cover test in 62%, eye motility in 68% monocular pursuit in 23%, and visual acuity at 36-45 months in 94%. Forty-eight percent of cover-uncover tests, 36% of alternating-cover tests and 7% of eye motility tests were performed correctly. Visual acuity testing was measured at three meters in 2%, others at five meters in accordance with the guideline. A picture chart was used instead of the Landolt-C at the age of 45 months in 23%. Visual acuity measurements were performed correctly in 89%, fundus red reflex in 89% and Hirschberg test in 87%.

CONCLUSIONS Hirschberg test, fundus red reflex and visual acuity were adequately tested in most cases. Cover-uncover test, alternating-cover test and eye motility were often performed inadequately. Pupillary reflexes were skipped often as room lights could not be dimmed.

INTRODUCTION

The first child healthcare (CHC) centre in the Netherlands was opened in 1901 to improve the general health of children.[1,2] In 1960, measurement of visual acuity (VA) became part of the screening programme. It was suggested that the CHC centres could play an important role in the detection of amblyopia.[3-4] Eye screening is now carried out by CHC nurses and CHC physicians, who are medical doctors trained to perform eye screening. They follow a one-day eye-screening course given by a screening instructor, an orthoptist, which is repeated once every five years. The eye screening programme in the Netherlands was extended in the 1980s to include examinations at the ages between 1 and 24 months, as the general belief was that the earlier amblyopia was discovered and treated, the better.[5-6]
The current eye screening programme consists of seven eye exams (at 1, 2, 3, 6–9, 14–24, 36 and 45 months) as part of the population-based, comprehensive health, no-cost, voluntary screening and vaccination programmeme.[5-6] At 1-4 months, eye screening includes inspection of the external structures of the eye, fundus red reflex, Hirschberg test, and pupillary reflex. At 6-24 months eye screening comprises inspection of the external structures of the eye, Hirschberg test, pupillary reflex, cover-uncover test, alternating-cover test, eye motility and monocular pursuit. Fundus red reflex is only done in children younger than four months of age. At 36 months VA is measured with the Amsterdam Picture Chart (APK) and at 45 months with the Landolt-C chart (Appendix 1).

The Rotterdam Amblyopia Screening Effectiveness Study (RAMSES), a prospective observational birth cohort study, showed that the vision screening programme was effective in detecting amblyopia.[7-8] The RAMSES study showed that amblyopia caused only by refractive errors is not detected before the age that VA is measured and before that age most cases of amblyopia are detected by parents noticing strabismus.[7] This has since been confirmed in the Optimization of Amblyopia Screening (OVAS) study, which compares two sequential birth cohorts, with and without eye screening tests, between 6 and 24 months of age.[9-10] In its first report, concerning the omission of the screening at 6-9 months, there was little difference in referral rate and detection of amblyopia with or without eye screening at that age.[9]

These results raise the question why the detection rate of amblyopia with the current screening tests is low. One of the causes could be the use of orthoptic tests performed by non-orthoptists. In the current study we observed whether and how well these tests

are done. We assessed the quality of screening tests by semi-structured observations of CHC physicians screening children aged 1-45 months.

METHODS

This semi-structured observation study is part of the OVAS study.[9-10]
The Medical Ethical Committee of the Erasmus Medical Center declared that the Medical Research Involving Human Subjects Act did not apply to the OVAS study as it concerned population-based prevention and that the 'Besluit Publieke Gezondheid' (Public Health Decision, Ministry of Health 2008) applied, where only permission is required from the health inspector to deviate from the national screening guidelines (reference number MEC-2012-003) and this permission was granted by the health inspector. The research adhered to the tenets of the Declaration of Helsinki.
For this observational study, a form for semi-structured observations was specifically developed to provide a systematic framework to the evaluator's observation of the screenings tests and to minimize evaluator's bias. To evaluate the performance of the eye screening tests, observations were performed by two orthoptic students in their fourth and final year of their orthoptic study. During this study, they were coached by a tutor at Utrecht University of Applied Sciences. The two orthoptic students had extensive instructions before the start of the observations from one of the screening instructors, an orthoptist, who trains CHC physicians for eye screening throughout the Netherlands. They attended two one-day eye screening courses of CHC physicians before the start of the observations. The observations took place at the CHC centres of Icare (Public Health Service) in a rural part of the Netherlands in the provinces Drenthe, Gelderland, and Flevoland from February 25th to April 19th, 2013, four days a week. At the start of each consultation permission to attend the consultation was asked of the parents of the participating child. During the consultation, the orthoptic students took notes on the semi-structured observation forms of the performances of all eye screening tests carried out by the CHC physicians, without any involvement in the screening procedure. The children were divided, for analysis, into age categories according to the screening tests (Appendix 1).

The observation form development was based on the Dutch Vision Screening Guideline version 2010,[11] the Dutch manual of orthoptic examination techniques,[12] studies on quality of examination[7-8,13-15] and expert opinion. The observation form contained a general-record section to document the age of the child, his or her health development

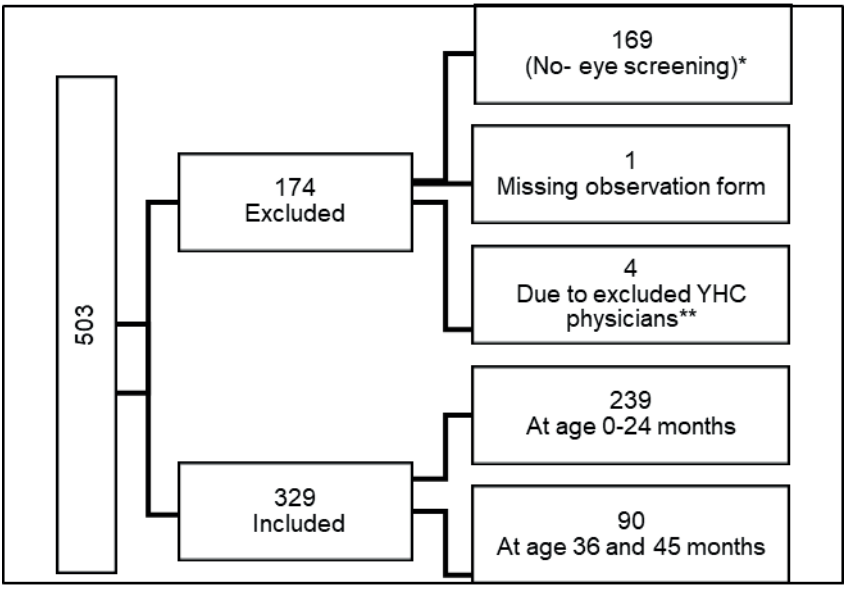
and other relevant diagnoses, visual history of the child and his or her family, the child's parents' language skill, and the working experience of the CHC physician. In addition, all the examinations of the eye were listed on scoring checklists on the observation form to rate the performance quality of the tests, including the inspection of the external structures of the eye, fundus red reflex, and pupillary reflexes, and whether these tests were performed in light or dark conditions.
The cover-uncover and alternating-cover test were scored as "not possible to perform", "not performed according to the guidelines": incomplete covering of the eye and/or too quick switching from the covered to the uncovered eye; or "well performed": complete covering of the eye and/or switching adequately from the covered to the uncovered eye. Eye motility was scored as "not performed", "partially performed": not all the eight gaze directions; or "well performed": maximum in all directions of gaze. The test of monocular pursuit movement, used as indirect measurement of VA, was scored as "not performed", "not performed according to the guideline: performed using a fixation object without a pen light; or "well performed": with pen light and fixation object. VA measurement was scored in detail, with scores for the type of optotype chart used, distance between chart and the child, and whether the exam was started with the right or left eye. Finally, to contact the parents after referral, permission was asked for follow-up of the child in case the child was referred to an orthoptist or ophthalmologist (Appendix 2).

In the first week, the observations were done simultaneously by the two orthoptic students, and after a week results of the observations were compared and checked for concordance. After the observation period, all observation forms were collected and analysed. Afterwards all CHC physicians were asked to participate in feedback sessions, where the general outcomes and findings of the observations were presented and discussed.
Excluded were children who took part in the study cohort of the OVAS study (children born between January 1st and June 30th 2012), because no eye screenings tests were performed in this cohort between 6 and 24 months of age. Children were also excluded when parental consent to attend the consultation and do the observation was not obtained. Children with missing observation forms were also excluded.
SPSS version 20 (for Windows IBM Corp., Armonk, NY, USA) was used to analyse the collected data.

RESULTS

In total, 25 CHC physicians were observed for a period of eight weeks, four days weekly, while examining 503 children aged 1-45 months. Of these 503 children, 169 were excluded because they were included in the study group of the OVAS study. Two CHC physicians were excluded due to a very low number of children examined and one child was excluded because the observation form was missing (Figure 1). In the age group 1-24 months 239 children (73%) were included, 82 (34%) of which were 1-4 months of age and 157 (67%) were 6-24 months of age. The other 90 (27%) children were 36-45 months of age. The observations in the first week had been done simultaneously by the two orthoptic students, and after the first week of observation these were compared and found to be in good concordance. The findings of both observers were matched.

Figure 1. Flowchart.



** Children born between January1st and June 30th 2012 without specific eye screening. They participate in the OVAS study about the effect of omission of eye screening at age 6-24 months on the detection of amblyopia comparing two consecutive birth cohort with and without specific eye screening.*
** * YHC physicians who examined less than 5 children during the observation period were excluded.*

Age category between 1 and 24 months of age

Fundus red reflex testing was performed in 73 out of 82 children (89%). CHC physicians performed the Hirschberg test in 210 out of 239 children (88%), two of the 210 (1%) performed Hirschberg tests could not be assessed due to lack of cooperation of the child. In the remaining 29 out of 239 children (12%), Hirschberg test was not performed for unknown reasons. Pupillary reflexes were tested in 33 out of 239 children (14%), 19 (58%) of these tests were performed in a lit room; in most cases the light could not be switched off. Twenty-four out of 33 (73%) pupillary reflexes were performed on children younger than four months. Of the 239 children, 157 were between 6 and 24 months of age. Cover-uncover test was not performed in 55 out of 157 children (35%) and alternating-cover test was not performed in 59 children (38%). Fifteen of the 102 (15%) performed cover-uncover tests and 14 of the 98 (14%) performed alternating-cover tests could not be assessed due to lack of cooperation of the child. Incomplete covering of the eye and/or too quick switching from the covered to the uncovered eye was noted in 38 of performed cover-uncover tests (37%) and 49 of performed alternating-cover tests (50%) (Table 1).

Eye motility was tested in 106 out of 157 children (68%). Not all the eight gaze directions (horizontal, vertical and diagonal) were tested in 99 of the 106 performed eye motility tests (93%) (Table 1). Monocular pursuit was tested in 57 out of 157 children (36%); 52 of the 57 (91%) were well performed, but in five children (9%) a fixation object was used without a pen light.

Age category between 36 and 45 months of age

Ninety children were included in this group. Of these, 28 children (31%) were 36 months old and 62 children (69%) were 45 months old. VA measurement was performed in 85 out of 90 children (94%). From the remaining five children, four children (5%) were under treatment of an orthoptist and therefore not screened and in one child (1%) it was unknown why VA measurements had not been performed. Three out of the 85 (3%) performed VA measurements failed due to developmental problems.

VA charts were used at 5-meter distance in 80 children (94%). In two cases, APK chart distance was three meters due to a small room size. According to the guidelines, CHC physicians have to start with measurements of the right eye to avoid wrong notations. In 14 children (16%) VA measurements were started with the left eye. In 4 of these 14 children (29%), this was done due to an uncertain examination result of the left eye at the last screening examination or because the parents had noticed something conspicuous with the left eye. In some children, the CHC physician did not measure

beyond 0.5 decimal VA line. VA was measured up to the highest level on the optotype chart in 75 children (89%). Here the problem is that, according to the Guideline, the child passes when both eyes reach 0.5 VA with the Landolt-C but when a difference of 2 lines is found, for instance 0.5 and 0.8, the child should be referred. The Landolt-C chart was not used in 15 of the 62 children of 45 months of age and the APK was used alternatively.

In total 13 out of 329 children (4%) were referred. Ten children (77%) were referred due to insufficient VA at age of 36 or 45 months. These referrals were based on correctly performed VA measurement by the CHC physicians with an insufficient result. The other three children (23%) were referred between the ages of 0-24 months. One child was referred because of abnormal, but correctly performed fundus red reflex. One child was referred because the parents had noticed strabismus, positive family history of strabismus, and a correctly performed cover-uncover test and eye motility test. The final child was referred because the parents had noticed strabismus, positive family history of strabismus, but not correctly performed cover-uncover test.

After referral, children were followed up by calling the parents to enquire the results of the referral. In five children, no results could be obtained because parental permission was not given or the parents could not be reached. Data were obtained for eight children, all between 36 and 45 months of age and referred due to low VA. Two of them were diagnosed with amblyopia, one child had an exotropia with good vision, one child had a moderate bilateral hypermetropia, two children had normal findings (false positives), and the parents of one child did not comply with the referral.

General results of this study were presented to all participating CHC physicians during three meetings. During these meetings the majority of the CHC physicians stated that they indeed had difficulty with the performance and interpretation of the cover-uncover test, alternate-cover test, and monocular pursuit. In addition, some of them would like to have an additional training to improve their execution of eye screening tests. They also reported that they often skipped pupillary reflexes because the room lights cannot be switched off. Further, it appeared that about half of the CHC physicians thought that testing monocular pursuit gave an indication of eye motility and had not understood that monocular pursuit movement is an indirect measurement of VA.

Table 1. Performance of all eye screening tests and by which professional performed the exam.

	Fundus red reflex	Hirschberg test	Pupillary reflex	Cover test	Alternating cover test	Motility	Monocular pursuit	Visual acuity
Professional performed the test	YHC physician	YHC physician	YHC physician	YHC physician	YHC physician	YHC physician	YHC physician	YHC physician and nurses
Age range	1-4m	1-24 m	1-24m	6-24m	6-24m	6-24m	6-24m	36-45m
Total = N	82	239	239	157	157	157	157	90
Not examined	9(11%)	29(12%)	206(86%)	55(35%)	59(38%)	51(32%)	100(67%)	5(6%)
Examined	73(89%)	210 (88%)	33(14%)	102(65%)	98(62%)	106(68%)	57 (23%)	85 (94%)
Insufficient cooperation*		2 (1%)		15(15%)	14(14%)			3 (3%)
Performed correctly		208 (99%)	14(42%)	49(48%)	35(36%)	7(7%)	52 (91%)	75(89%)
Performed incorrectly**			19(58%)	38(37%)	49(50%)	99(93%)	5 (9%)	7(8%)

* Insufficient cooperation =due to lack of cooperation of the child, child was crying, unwilling to look.

**Performed incorrectly = not performed according to the guidelines: Pupillary reflex: tested in a lit room. Cover-uncover test and alternating-cover test: incomplete covering of the eye and/or too quick switching from the covered to the uncovered eye Motility: not tested in all eight gazes directions. Monocular pursuit movement: a fixation object was used without pen light. VA: YHC physician did not measure beyond the 0.5 decimal line.

DISCUSSION

We found that the Hirschberg test and the fundus red reflex in children aged 1-24 months and VA measurements in children aged 36-45 months were performed in accordance with the guidelines in most cases. All examinations at the Icare CHC Centres were performed by CHC physicians, except the VA measurements, which were performed by CHC nurses and CHC physicians. The orthoptic examinations: cover-uncover test, alternating-cover test and eye motility were often not performed correctly. Either the eye was not covered completely or switching from the covered to the uncovered eye happened too quickly for the child to pick up fixation. In most cases, eye motility was not maximally tested in all eight directions of gaze; some even had made the children make a circular movement around the primary position, which had been taught by an instructor long ago. Pupillary reflexes should be tested in dim illumination, but due to the fact that the room lights could not be dimmed in many cases, pupillary reflexes were often not tested.

Finally, the monocular pursuit was not tested in the majority of children. A smooth monocular pursuit movement at the age of 6-24 months provides an indirect indication of good VA of that eye. Amblyopic patients have poor fixation stability and unsmooth monocular pursuit in their ambyopic eye as compared with visually health people.[16] CHC physicians were often unaware of the true purpose of this test.

In another part of the OVAS study, anonymous questionnaires were sent to all participating CHC physicians[9]. In 56 out of 80 sent questionnaires, CHC physicians reported the orthoptic tests at 6–9 months to be difficult. Seventy-five percent of CHC physicians found the cover test difficult, 50% found monocular pursuit difficult, and 25% considered testing eye motility difficult. Only 35% of these CHC physicians wanted to have more training in eye screening.

König and Barry showed that eye screening had low effectiveness when performed by untrained general practitioners or paediatricians due to limited experience with eye examination.[17] In contrast, screening had high effectiveness when carried out by nurses who were professionally trained to do the screening examination. Most orthoptic tests require a lot of experience to do them well, which is difficult to be obtained within a one-day course, repeated once every five years.

A first limitation of this study was that the two orthoptic students used criteria based on their almost concluded four years of study to become an orthoptist. They were still

close to their own formal teaching. Their training contrasted starkly with that of the CHC physicians who follow a one-day course for eye screening once every five years. It is possible that orthoptists with years of experience would have been more lenient in some parts and more strict in other parts of the examination. In addition, the two orthoptic students were not trained observers although they followed standard procedures for semi-structural observations, like testing for concordance by comparison of a week of simultaneous observations and were coached for the semi-structural observations by their tutor at Utrecht University of Applied Sciences.

Secondly, the test performance could be biased, because the CHC physicians and nurses were presumably on their "best behaviour" while being observed, so this study might represent a maximum standard of test performance.

Thirdly, we do not know whether the children who were not referred did not have amblyopia or another eye disorder. Two of the eight referred children were false positives. In that sense we have no gold standard with which to compare the quality of the examinations. Finally, with 100 days of observation the sample size was still limited.

The question is then whether the cover test should be used at all for eye screening in the general population when not performed by orthoptists. The study by Williams and colleagues showed that the cover test has a sensitivity of 25% (range 9-41%) before the age of 25 months. [18]

The performance of cover test could be improved with extra courses, but this would increase costs. Another possibility would be to abolish this part of the screening.

CONCLUSIONS

In summary, Hirschberg test, fundus red reflex, and VA were adequately tested in most cases. Cover-uncover test, alternating-cover test, and eye motility were often performed inadequately. Pupillary reflexes were skipped often as room lights could not be dimmed.

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Appendix 1: Overview of the Dutch eye screening program (Nederlands Centrum Jeugdgezondheidszorg 2010)

Age in months	1-2	3-4	6-9	14-24	36	45
Examinations						
Inspection of the anterior segment of the eye	x	x	x	x	x	x
Pupillary reflex: *In the dark, the pupils are inspected for size and equal reaction to light.*	x	x	x	x		
Fundus red reflex: *the optic media are assessed with a co-axial light by viewing the eye at 15cm distance, through an ophthalmoscope for a white pupil caused by retinoblastoma, congenital cataract or other opacities.*	x	x				
Hirschberg test: *The observer shines a white penlight into the eyes of the child and observes whether the corneal light reflections in both eyes are approximately at the same distance of the edge of the pupil.*			x	x		
Cover test: *The child looks at a penlight and one eye is covered. If the other eye moves to fixate the penlight that eye was squinting.*			x	x		
Alternating cover test: *The child looks at a penlight and the eyes are covered alternatingly. If the eye moves to fixate when the cover is removed, that eye was squinting.*			x	x		
Eye motility: *The child follows a penlight to test free movement in up, down, right, left, bottom left, bottom right, top left and top right gaze.*			x	x		
Pursuit movements: *While one eye is covered, the child follows an object that moves from left to right or right to left. A steady, smooth pursuit movement is only possible when vision of the eye is good. This test is a strong indicator of amblyopia in young children.*			x	x		
Visual acuity with Amsterdam Picture Chart: *a non-logarithmic Dutch picture optotype chart. A VA of 5/6 or more in both eyes, with no more than one line difference between the eyes at 36months is considered sufficient. Tests should be repeated within three months in case of uncertain outcome, for instance lack of cooperation or a near-threshold VA. If a child fails the screening or has two uncertain outcomes a referral is made to a general practitioner, orthoptist or ophthalmologist.*					x	
Visual acuity with Landolt-C Chart: *A non-crowded logarithmic chart. A VA of 0.5 or more in both eyes, with no more than one line difference between the eyes at 45 months is considered as sufficient. Tests should be repeated within three months in case of uncertain outcome, for instance lack of cooperation of the child or a near-threshold VA. If a child fails the screening or has two uncertain outcomes a referral is made to a general practitioner, orthoptist or ophthalmologist.*						x

Appendix 2: Observation form

How many years have you been employed as an YHC physician?
Age of the child:

☐ 4 weeks ☐ 2 months ☐ 3 months ☐ 6 months ☐ 9 months ☐ 12 months
☐ 14 months ☐ 1.5 years ☐ 2 years ☐ 3 years ☐ 4 years ☐ 4.5 years

Language level parents:
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
1. No Dutch 2. Poor Dutch 3. Moderate Dutch 4. Good Dutch 5.Native Dutch

Other important diagnoses of the child

Health development of the child:
☐ Personality, social behaviour ☐ Language development ☐ Gross motor skills
☐ Fine motor skills ☐ Self and society
☐ Physical condition, overall health

Visual functions history of the child and his family

Performance of the VOV
Hirschberg test:
☐ Performed ☐ Not performed ☐ Pen light ☐ Fixation object

Cover test:
☐ Performed ☐ Not performed
☐ With pen light ☐ With ophthalmoscope ☐ With fixation object
☐ Child on the lap of parents ☐ Child not on the lap of parents
☐ Complete covering of the eye ☐ Incomplete covering of the eye
☐ Too quick switching ☐ Switching adequately ☐ Not possible to perform

Alternating cover test:

☐ Performed ☐ Not performed

☐ With pen light ☐ With ophthalmoscope ☐ With fixation object

☐ Child on the lap of parents ☐ Child not on the lap of parents

☐ Complete covering of the eye ☐ Incomplete covering of the eye

☐ Too quick switching ☐ Switching adequately ☐ not possible to perform

Motility:

☐ Performed ☐ Not performed

☐ With pen light ☐ With ophthalmoscope ☐ Fixation object

☐ Horizontal ☐ Vertical ☐ Diagonal

☐ Fully in all gaze directions ☐ Not fully in all gaze directions

Pursuit movements:

☐ Performed ☐ Not performed

☐ Pen light ☐ Fixation object

Fundus red reflex:

☐ Performed ☐ Not performed

☐ Light on ☐ Light off

Pupillary reflex:

☐ Performed ☐ Not performed

☐ Light on ☐ Light off

Visual acuity:

Chart:

☐ APK ☐ APK-TOV ☐ Landolt C ☐ .....

Distance:

☐ 1m ☐ 2m ☐ 3m ☐ 4m ☐ 5m

Explain test:

☐ Binocular ☐ Monocular ☐ With the chart ☐ With a copy of the chart

☐ Practiced at home ☐ Not practiced at home

With which eye is the test started:
☐ OD ☐ OS

Tried to measure up to the highest VA level:
☐ Yes ☐ No

Visual acuity value:
VOD…… VOS…….. VODS…….

Referral:
☐ Yes ☐ No ☐ Doubt
Reason for referral……

Permission to contact parents about referral
☐ Yes ☐ No
Date of Birth:……
Phone number:……
Address:……

5

Effect of omission of population-based eye screening at age 6-9 months in the Netherlands

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ABSTRACT

PURPOSE To investigate omission of population-based eye screening at age 6-9 months in the Netherlands.

METHODS Prospective population-based consecutive birth cohort study was used. In two consecutive birth cohorts, children were eye screened at 1-2 and 3-4 months, but at general-health screening at 6-9 months, the second cohort was not eye screened, unless anything conspicuous was noted or in case of positive family history. Data were collected from screening records and anonymous questionnaires. Semi-structured daylong observations were made of physicians examining children aged 0-4 years, including children from the cohorts, by two orthoptic students.

RESULTS 58 out of 6059 children (0.96%), in the screened, and 48 out of 5482 children (0.88%) in the unscreened group were referred to orthoptist or ophthalmologist, mostly for observed strabismus. Amblyopia, all combined with strabismus, was diagnosed in ten screened (0.17%) versus six unscreened children (0.11%). Most physicians found preverbal examinations and decisions to refer difficult. The observations by orthoptic students revealed that cover test, pupillary reflexes, pursuit movements and eye motility were frequently performed inadequately, contrary to the Hirschberg test, at this age.

CONCLUSIONS The screened and unscreened group differed little regarding the number of children referred and found to have amblyopia. Referral was mostly based on observed strabismus.

INTRODUCTION

Pierre Budin, an obstetrician, opened the first baby clinic in 1892 in Paris, where babies were examined, weighed and instructions and advices were given to mothers about hygiene and breastfeeding.[1,2] In 1901 a Dutch paediatrician Dr. Plantenga inspired by the French initiative opened the first Child Healthcare Centre (CHC) in the Netherlands, an office where mothers came with their newborns. This first private initiative was followed by other organizations and eventually became nationwide implemented. Aim of these organizations was to improve the overall health of infants and lower the infant mortality.[3] Since approximately 1960, eye screening became implemented in this health screening programme. Examination included inspection, ocular alignment, monocular visual acuity and stereo acuity testing in children from the age of three. It was suggested that the CHC's could play an important role in the detection of amblyopia.[4,5] As the general belief was that the earlier amblyopia was discovered and treated the better, eye screening was extended in the 1980's with the preverbal VOV ("Vroegtijdige Onderkenning Visuele stoornissen": early detection of visual disorders) test. At 0-6 months this test comprises inspection of the eyes, pupillary reflexes, red fundus reflex and eye motility. At 6-24 months, this test comprises also Hirschberg test, cover test and pursuit movements, but no red fundus reflex testing.[6,7]

Nowadays, with four preverbal eye exams (at 1-2, 3-4, 6-9, 14-24 months) and three visual acuity tests (at 36, 45 and 54-60 months) the Netherlands have one of the most extensive eye screening programmes worldwide. A high participation rate is reached, 97% coverage, because the eye screening is imbedded in a population-based, no-cost, voluntary, comprehensive health promotion, screening and vaccination programme.[8] Eye screening at the CHC's is performed by preventive child healthcare (CHC) physicians and nurses. These physicians follow a one-day eye screening course, given by an orthoptist that should be repeated once every 5 years.

To evaluate the effectiveness of the amblyopia screening in the Netherlands, the RAMSES birth-cohort study (N=4624) was performed. This study showed that preverbal screening contributed little to the detection of refractive amblyopia, while strabismic amblyopia was self-referred in approximately half of cases.[9]

Therefore, the Optimization of Amblyopia Screening (OVAS) study assesses whether the omission of preverbal eye screening leads to a decrease in the number of detected amblyopia cases at the age of 45 months.

In this paper, the effect of omission of population-based eye screening at age 6-9 months on the detection of amblyopia is reported, comparing two consecutive birth cohorts, with and without specific eye screening. Evaluation of the screening and referral process in this study will also comprise omission of eye screening at the age of 14-24 months and visual acuity testing with the Amsterdam Picture Chart at 36 months.

MATERIALS AND METHODS

Study Design

Our study was a prospective population-based consecutive birth cohort study.

Patient Population

Preverbal screening between 6 and 9 months was omitted in one of two birth cohorts (together approximately 11 000 children; 6.5% of the Dutch birth rate) born in the regions of two CHC organizations: Icare, serving the provinces of Drenthe, east Flevoland and mid Gelderland (87 CHC's) and the Municipal Health Service of Amsterdam, serving, among other parts of Amsterdam, its northern district (3 CHC's).

Screened group

Children born between July 1st and December 31st 2011 were eye screened according to national protocol with the VOV test which at 1-2 and 3-4 months comprises inspection of the eyes, pupillary reflexes, eye motility and red fundus reflex testing and at 6-9 months comprises inspection of the eyes, pupillary reflexes, eye motility, Hirschberg test, cover test and pursuit movements.

Unscreened group

Children born between January 1st and June 30th 2012 were only eye screened at 1-2 and 3-4 months. These children attended the general screening exams at 6-9 months, but specific eye screening was omitted. Preventive CHC physicians were instructed only to perform an eye exam in this group in case of observed eye problems (by either parent or physician) or positive family history.
Parents in this group were informed through an information leaflet and had the possibility to decline participation, and receive an eye examination at age 6-9 months.

The Medical Ethical Committee of the Erasmus Medical Center declared that the Medical Research Involving Human Subjects Act did not apply to this research

proposal as it concerned population-based prevention and that the "Besluit Publieke Gezondheid" (Public Health Decision, Ministry of Health 2008) applied, where only permission to deviate from the national screening guidelines is required (reference number MEC-2012-003). Permission was granted from the Dutch Health Care Inspectorate to deviate from the national screening guidelines. The research adhered to the tenets of the Declaration of Helsinki.

Data Collection

Screening

Vision screening data were collected from the electronic screening records from the CHC's. The CHC organizations provided an Excel dataset to the researchers. Treating orthoptists working in the study area provided clinical orthoptic data. Orthoptists filled out a standardized form for each first hospital visit of a child in the two birth cohorts about diagnose and treatment. The treating orthoptists were asked to indicate whether the child (possibly) had amblyopia and, if amblyopia was suspected, whether it was strabismic, refractive, combined-mechanism or deprivation amblyopia.

Anonymous questionnaires

Anonymous questionnaires were designed to evaluate preventive CHC physicians' opinion about preverbal screening and referral. Questionnaires were made by the research team in a focus group and were distributed to all participating preventive CHC physicians twice. The questionnaire included detailed questioning about preverbal and preschool eye screening, that is, questions about demographics, different tests used, execution of the different tests, difficulty of the different tests and referral procedures. Questions about the adherence to the study protocol were also incorporated.

On-site observations

On-site observations were performed by two orthoptic students (A.S. & H.K.) in a separate study population, that is, at the participating CHC's, but not necessarily children from one of the two birth cohorts. Fifteen CHC's with 25 employed preventive CHC physicians were participating. Of the entire physical examination, only eye screening was observed in a semi-structured fashion. The observation comprised demographics, parents' language skill and detailed assessment of physicians' performance of fundus reflex, pupillary reflex, Hirschberg test, cover and alternating cover test, eye motility, visual-acuity measurement, room and chart illumination, type of chart and testing distance.

Outcome measures and Statistical Analysis

The primary outcome measure was the number of referred children and the number of diagnosed amblyopia cases in both groups.

All data were entered into an Excel file and SPSS database. Statistical analysis was performed with the statistical package SPSS version 20.0 (for Windows IBM Corp., Armonk, NY, USA). Descriptive statistics were used. The questionnaires frequencies were analysed.

RESULTS

Inclusion

All children born in the area of, and registered at, the participation CHC's were included at baseline.

Screened group

The screened group comprised a total of 6188 children. No data were available for 129 children (dropouts) because they had either moved out of the area, had no screening record or were non-users of the CHC (e.g. treated for other disorders or because of religious reasons). Another 28 children did not visit the CHC at 6-9 months, but underwent screening before and after this timeframe. 524 children visited the CHC, but the physician did not specifically screen the eyes in these cases, because of, in many cases, other priorities of the child. These children were not regarded as dropouts, based on intention-to-treat principle (Table 1).

Unscreened group

The unscreened group comprised a total of 5623 children. No data were available for 141 children (dropouts). Another 27 children did not visit the CHC at 6-9 months, but underwent screening before and after this timeframe. In case of 434 children in the unscreened group, screening was performed, mostly because of predetermined study criteria: observed eye disorders or positive family history. Some were, however, screened erroneously out of routine or per accident. In 1596 children it remained inconclusive whether eye screening had indeed not been performed. In these cases, only a box was ticked in the electronic screening record without further specifications, indicating that there were no abnormalities found or that screening had not been performed. However, eighteen of 26 physicians declared, when asked by phone interview, that they had adhered to the protocol and not performed the screening when they had ticked the box (Table 1).

Positive screening and referral

Screened group

Fifty-eight of 6059 children (0.96%) were referred (Table 1). Five (8.6%) were referred for visually apparent problems (eyelid disorder, anisocoria, ptosis, dacryostenosis). Three (5.2%) were referred based on failure of the test. Observed strabismus by either parents or screening physician was the referral reason, after eye examination, in 39 children (67.2%) and the VOV test, as primary screening instrument, in eleven children (19.0%).

In the screened group three children did not comply with referral (5.2%). Referral status is unknown of three children (5.2%).

Unscreened group

Forty-eight of 5482 children (0.88%) were referred (Table 1). Nine (18.8%) were referred for visually apparent problems (eyelid disorder, anisocoria, ptosis, dacryostenosis and infection). One child (2.1%) was referred based on failure of the test. Observed strabismus was the referral reason, after eye examination, in 31 children (64.6%) and the VOV test, as primary screening instrument, in seven children (14.6%).

In the unscreened group three children (6.3%) did not comply with referral. Referral status is unknown of two children (4.2%).

Orthoptic diagnosis

Screened group

From the 52 children who complied with referral, two had a dacryostenosis, one a ptosis. Four children had a refractive problem (astigmatism and/or hyperopia) without amblyopia, six had strabismus without amblyopia. Amblyopia was diagnosed in ten children (0.17%); eight had strabismic amblyopia, two combined mechanism amblyopia. Twenty-six children had neither strabismus nor amblyopia. No refractive amblyopia without strabismus was diagnosed. Diagnosis is unknown in three children (Table 1).

Unscreened group

From the 43 children who complied with referral, four had a dacryostenosis, two a ptosis. Four had strabismus without amblyopia. Amblyopia was diagnosed in six children (0.11%); three had strabismic amblyopia, three combined-mechanism amblyopia. Twenty-six children had neither strabismus nor amblyopia. No refractive amblyopia without strabismus was diagnosed. Diagnosis is unknown in one child (Table 1).

Table 1. Results

	Screened group	Unscreened group
Inclusion	6188	5623
Drop-outs	129 (2.1%)	141 (2.5%)
Total	**6059**	**5482**
No 6-9 mo visit	28 (0.5%)	27 (0.5%)
Children not screened in the screened group	524 (8.6%)	
Children screened in the unscreened group		434 (7.9%)
Inconclusive if screened in the unscreened group		1596 (29.1%)
Referred	58 (0.96%)	48 (0.88%)
Uncompliant with referral or unknown diagnosis	9 (15.5%)	6 (12.5%)
No ophthalmologic diagnosis	26 (44.8%)	26 (54.2%)
Ophthalmologic diagnosis	23 (39.7%)	16 (33.3%)
Amblyopia	10 (0.17%)	6 (0.11%)

Anonymous questionnaires

Of the 80 distributed questionnaires, 56 questionnaires were returned and these have been evaluated. A few questionnaires were not filled out completely. 86% of preventive CHC physicians found the VOV test at 6-9 months difficult. Cover test was considered most often as difficult, by 75% of physicians. Fifty percent considered pursuit movements and 25% motility as difficult (36 questionnaires).
The decision to refer a child based on the screening test was found difficult by 87%, mainly because of a non-cooperative child or doubtful test results (38 questionnaires). 92% admitted that vision screening is sometimes left out at 6-9 months, mostly due to lack of cooperation of the child (39 questionnaires). Only 35% said that they would like to have more training in eye screening.

Questions about adherence to the study protocol showed that 84.4% of preventive CHC physicians estimated their own percentage of unscreened children in the screened group 10% or lower.

For the unscreened group, 88.9% of preventive CHC physicians estimated their own percentage of screened children for predetermined reasons at 10% or lower. For non-predetermined reasons (mainly accidently or out of routine) 88.6% of preventive CHC physicians estimated their own percentage of screened children in the unscreened group at 10% or lower.

On-site observations

Semi-structured daylong observations were made of physicians screening children aged 0-4 years, including children from the birth cohorts, by two orthoptic students. The results of all the on-site observations, comprising also the 0-6 months and visual acuity testing at age 3 and 4 years, will be published separately. General impression was that visual acuity was measured well.

In the 6-24 months age range, the two orthoptic students observed 157 children, examined by 23 preventive CHC physicians. The Hirschberg test was almost always performed adequately. The cover test was not performed in 35%; the alternating cover test not in 38%. Of the performed cover tests and alternating cover tests, incomplete covering of the eye and/or too quick switching from the covered to the uncovered eye was noted in 37% and 50%, respectively. Only five out of 23 physicians always performed the cover test correctly, according to the orthoptic students. Motility was performed in 68% of observed children, but only in 7% fully and in all gaze directions. Pursuit movements and pupillary reflexes were performed in 36% and 6% respectively.

DISCUSSION

Our study demonstrated that there is little difference in referral rate with or without preverbal eye screening at the age of 6-9 months. Most children were referred because of observed strabismus or visually apparent disorders. These disorders are detected at the CHC visit regardless of specific eye screening. All cases of amblyopia were strabismus or combined-mechanism amblyopia, and none were pure refractive amblyopia, which was to be expected as visual acuity was not measured.

This study intended to compare population-based, general-health infant screening with and without specific eye screening and there was little difference in referral rate with or without preverbal eye screening. A weakness of the comparison was, however, that the physicians may have detected more cases than physicians who were not trained to perform eye examinations would have detected: (i) the physicians were

used to specific eye screening within the general-health screening examination, (ii) they actively had to omit eye screening in the intervention group and (iii) they had to exclude conspicuous eye disorders and a positive family history for strabismus in the intervention group, all raising their level of attention for eye disorders.

Another weakness of our study is that in a third of the unscreened group (1596 out of 5623 children), it was not explicitly stated that the child indeed had not been screened, because a box had been ticked in the examination record that could denote both adherence to the protocol and no screening or no abnormalities found at screening. However, physicians were questioned about these cases and two-third of physicians declared that eye screening was not performed, in accordance with the protocol.

The sensitivity of the screening was not very much affected by limiting the eye examination to children with something conspicuous or a positive family history.

The preventive CHC physicians, however, also add to the effectiveness by limiting the number of unnecessary referrals, particularly of pseudostrabismus in the studied age group. The possibility to assess the specificity of the screening in this study was limited by the protocol dictating eye examination when anything conspicuous or positive family history was present.

The effectiveness and cost-effectiveness of eye screening has been questioned.[10-12] Snowdon and Stewart-Brown concluded that there is a lack of good-quality studies on the natural course of amblyopia, the disability associated with amblyopia and the efficacy of treatment.[10] The Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG) stated that, due to the small number of studies, the limited quality and the fact that the results were inconsistent and no studies on the potentially harmful aspects of vision screening were available, no robust conclusions could be made whether a benefit of preschool vision screening exists.[11] Jill Carlton et al. expressed doubt whether any form of screening would be likely to be cost-effective, because little evidence about the long-term utility effects of unilateral vision loss was found. Small utility effects of bullying would improve cost-effectiveness of early screening.[12]

Additional data about costs of the screening programme will be needed to assess whether, in the Netherlands, preverbal eye screening at age 6-9 months is cost-effective.

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5

6

Effectiveness of routine population-wide orthoptic preschool vision screening tests at age 6-24 months in The Netherlands

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ABSTRACT

PURPOSE the effectiveness of preverbal orthoptic tests at age 6, 9, 14 and 24 months in population-wide screening was assessed.

METHODS Two consecutive birth-cohorts at 134 centres were compared. At general health screening visits, children born July-December 2011 were vision screened four times between 6-24 months with inspection, pupillary reflexes, eye motility, Hirschberg, cover test and monocular pursuit. Children born January-June 2012 were vision screened at general screening visits only in case of visually apparent abnormalities or positive family history. After referral, cause and severity of amblyopia were determined. Visual acuity was measured in all children at 36 and 45 months.

RESULTS The control and intervention group comprised 5649 versus 5162 children. Amblyopia was diagnosed in 185 (3.3%) versus 159 children (3.1%), outside of screening in 21 (11.4%) versus 25 (15.7%). Between 6-24 months 44 (23.8%) versus 27 (17%) (RR = 0.67 [95%CI 0.42, 1.09]) were referred and after visual acuity measurement 120 (64,9%) versus 107 (67,3%). Of 109 versus 108 children with refractive or bilateral amblyopia, 94 (86,2%) versus 92 (85,2%) were detected with visual acuity measurements. Visual acuity of the amblyopic eye, after referral, was not significantly different between groups (p 0.896), nor was the time to amblyopia diagnosis (intention to screen (p 0.55); per protocol (p 0.11)).

CONCLUSIONS The effectiveness of vision screening was not influenced by omission of orthoptic tests at general health screening at 6-24 months. Refractive and bilateral amblyopia were almost exclusively found by visual acuity measurements.

INTRODUCTION

The Netherlands has one of the most extensive amblyopia screening systems worldwide.[1] Children are screened seven times from birth to five years of age.[1] In 1901, the first Child Healthcare (CHC) centre was opened in the Netherlands.[2] In 1960, measurement of visual acuity (VA) after three years of age was included. Preverbal orthoptic vision screening tests ('Vroegtijdige Onderkenning Visuele stoornissen (VOV)': early detection of visual disorders) were introduced in 1980.[3,4] Preventive youth healthcare (YHC) physicians and nurses perform eye screening at CHC centres, as part of the screening for general health disorders and vaccinations, of all children younger than four years of age according to the national protocol ('Opsporing visuele stoornissen 0-19 jaar').[5] This includes inspection of cornea and pupil, pupillary reflexes, fundus reflex and eye motility at 1-2 and 3-4 months to detect congenital disorders like retinoblastoma and cataract. Preverbal orthoptic tests are performed at 6-24 months: Hirschberg test, cover test and pursuit movements , but no fundus reflex testing (Table 1).[3-5] At 36 and 45 months VA is tested, respectively, with the Amsterdam Picture Chart (APK) and the Landolt C. Visual acuity measurements are repeated at school at 54-60 months. An overall participation rate of 97% of at least one visit in the first two years is reached, because eye screening is imbedded in a population-based general health care screening and vaccination programme.[6]

To evaluate the effectiveness of the amblyopia screening in the Netherlands the RAMSES birth-cohort study (N=4624) was performed. This study showed that preverbal screening contributed little to the detection of refractive amblyopia, while strabismus amblyopia was referred outside of screening in approximately half of cases.[7]

The Optimisation of Amblyopia Screening study (OVAS) was designed to assess whether and to what extent omission of orthoptic vision screening tests as part of general health screening between the age of 6-24 months would affect the detection of strabismus, refractive and combined-mechanism amblyopia and to confirm whether the omission of routine orthoptic vision screening tests between age 6-24 months would have no negative impact on the severity, time to and total cases of amblyopia detected. Parts of these results concerning screening at age 6-9 months have been published earlier.[8] In another previous study the performance of CHC physicians with these orthoptic tests was assessed with semi-structured observations. We now report the outcomes of the total OVAS study, after 5-year follow-up.

Table 1. Examinations at CHC centres according to the National guideline.

Age	Inspection	Pupillary reflex	Fundus red reflex	Hirschberg test	Cover test	Quality of pursuit	Motility	VA APK	VA Landolt-C
1-2 m	X	X	X						
3-4 m	X	X	X						
6-9 m	X	X		X	X	X	X		
14-24 m	X	X		X	X	X	X		
36 m	X							X	
45 m	X								X
60 m	X								X

Age in months.
APK = Amsterdam Picture Chart, VA = visual acuity

MATERIALS AND METHODS

Study Design

A birth-cohort study was conducted with sequential control and intervention groups. The large sample size aimed for precluded individual randomization from a practical point of view. Based on their date of birth, participants were allocated for orthoptic vision screening tests as part of general health screening, the current standard in the Netherlands (control group, born between 1st of July and the 31st of December 2011) or general health screening without orthoptic vision screening (intervention group, born between 1st of January and the 30th of June 2012) at age 6-24 months. Parents in the intervention group were informed through an information leaflet about the change in screening protocol and could opt out of the study and request screening according to the national protocol. The nature of the intervention precluded participant blinding. All data were prospectively acquired in the Netherlands.

The Medical Ethical Review Committee of the Erasmus Medical Centre declared that the Medical Research Involving Human Subjects Act did not apply to this research proposal as it concerned population-based prevention and that the "Besluit Publieke Gezondheid" (Public Health Decision, Ministry of Health 2008) applied (reference number MEC-2012-003). Permission was granted from the Dutch Health Care Inspectorate to deviate from the national screening guidelines. The study protocol and consent procedure adhered to the tenets of the Declaration of Helsinki.

Sample size calculation

We calculated the sample size for this comparative two sampled non-inferiority study, based on the assumption that an incidence of only 2.7% amblyopia could occur, the most disadvantageous incidence threshold in the RAMSES study. In the RAMSES study, 2964 children had undergone the complete 7 years follow-up and vison testing, yielding an amblyopia diagnosis in 100 children (3.4%, 95%CI: 2.7-4.0%).[7] Using a type 1 error rate of 0.05 (α), a power of 80% (1-β, wherein the β (type 2 error) is 0.20) and a non-inferiority margin of 0.8%, we calculated that 5076 subjects were required per study group. We added a 5% anticipated loss to follow-up and dropout rate, yielding a minimum study population size of 10660 children.

Screening examinations

All children were invited to visit the CHC centres at 6, 7.5, 9, 11, 14, 18, 24, 36 and 45 months of age for general health screening. In the first National protocol, vision screening should be performed at 6, 9, 14 and 24 months by CHC physicians. In a later version of the National protocol, vision screening was only obligatory at 6-9 and 14-24 months.

Control (standard screening) group 6-24 months

Children born between July and December 2011 were vision screened according to the national protocol at 1-2 and 3-4 months with inspection of the eyes, pupillary reflexes, eye motility and red fundus reflex testing to rule out congenital eye disorders. At 6-24 months, the orthoptic vision screening took place at least two times: at age 6-9 and 14-24 months. The examination consisted of inspection of cornea and pupil, pupillary reflexes, eye motility, Hirschberg test, cover test and pursuit movements (table 1).

Intervention (reduced screening) group 6-24 months

Children born between January and June 2012 were eye screened at 1-2 and 3-4 months. These children attended general health screening visits at 6-24 months, but were only vision screened in case an eye abnormality was noticed or suspected by the screening physician or parent or in case of a positive family history.

Visual acuity measurements at 36-45 months in both groups

Visual acuity measurements were performed in both groups at the age of 36 and 45 months at the CHC centres with the APK and Landolt C chart, respectively. According to the national protocol, the result of the VA measurement can be sufficient or insufficient or the measurement itself fails (table 2). Insufficient and failed measurements must be

repeated within 3 months according to the national protocol, or the child had to be referred to an orthoptist, general practitioner (GP) or ophthalmologist. At 36 months, the VA measurement should be repeated with a VA of 5/10 for both eyes or with a VA above 5/10 with one-line difference between the eyes. In case of VA below 5/10 or a two-line difference, the child should be referred directly. At 45 months, the VA measurement should be repeated when at the first measurement the VA was above 0.5 decimal but with a one-line difference between the eyes. In case of VA below 0.5 for either eye or a two-line difference, the child should be referred directly. If the result of the second VA measurement also proved insufficient, or failed, the child must be referred.

Table 2. Criteria for referral or repeat measurement, according to the Dutch National protocol for vision screening, for sufficient, insufficient or failed measurement at age 36 and 45 months with the Amsterdam Picture Chart* and Landolt-C (Coenen – van Vroonhoven et al. 2010, Telleman et al. 2019).

	36 months	45 months	
	Amsterdam picture chart	Amsterdam picture chart	with Landolt-C
VA measurement sufficient	Monocular VA ≥ 5/6 for both eyes	Monocular VA ≥ 5/5 for both eyes	Monocular VA ≥ 0.5 for both eyes
VA measurement insufficient	Monocular VA < 5/6 for one or both eyes	Monocular VA < 5/5 for one or both eyes	Monocular VA <0.5 for one or both eyes
	One line interocular difference*	One line interocular difference*	Two lines interocular difference
VA measurement failed	The measurement failed		
	Only binocular VA obtained		
	VA was measured of one eye only		

*(not logMAR, however: 5/5, 5/6, 5/10, 5/15, etc.)

Data Collection

Child healthcare centre

Vision screening data was collected from the electronic screening records from the CHC centres. The CHC organizations provided an Excel data set to the researchers. The follow-up visits at the CHC also provided information about children referred outside of screening.

Orthoptists

Orthoptists working in the study area were contacted and visited before the start of the study. Treating orthoptists provided clinical orthoptic data if the child was referred based on initials and date of birth. Some orthoptists also provided information about children from the selected cohorts, who were referred outside of screening by others than the CHC centres, like general practitioners or paediatricians. For each first hospital visit of a child in the two study-arms, orthoptists filled out a standardized form about orthoptic examination, VA, diagnosis and treatment (Appendix). The treating orthoptists were asked to indicate whether the child (possibly) had amblyopia and, if amblyopia was suspected, whether it was strabismus, refractive, combined-mechanism or deprivation amblyopia (type of amblyopia).
Received data of the CHC centres were matched with the orthoptic data, provided with initials and date of birth, and thereafter anonymized by the researchers.

Data analysis

If one of the VA measurements (36, 45 or 60 months) at the CHC centre was sufficient according to the national protocol,[5] the child was classified as having no amblyopia. If no or one failed or insufficient VA measurement was available, without orthoptic information, the child was classified as lost-to-follow up. If the VA measurement was insufficient twice or had failed twice, and no orthoptic information was available, children were invited for extra VA measurements by the study orthoptist or the 60 months VA measurement result was requested from the CHC centre if available. If no extra VA result could be obtained the child could not be diagnosed as amblyopic or non-amblyopic, but was classified as a separate loss-to-follow group because of a slightly higher chance of amblyopia.
When orthoptic information was available for children who had been referred at an age before VA measurement was possible, the amblyopia presence was based on the opinion of the treating orthoptist: amblyopia present: definitively, probably, probably not or not, fixation preference and the presence of an amblyogenic factor (strabismus, refractive disorder or deprivation).

When a VA measurement from the treating orthoptist was available, amblyopia diagnosis was based on the first VA measurement, before glasses adaptation. The orthoptists classified children into definitively, probably, probably not or no amblyopia. This classification was mainly based on a VA difference 2 logMAR lines difference between the eyes or a bilateral VA ≤0.5 snellen VA before glasses adaptation or strong fixation preference or amblyopic factor.

The research orthoptist (MT), researcher (FS) and ophthalmologist (HJS) determined the definitive presence, type and severity of amblyopia in both groups, taking all VA measurements, from both the CHC centres and the treating orthoptists, and the orthoptist' classification into account. If amblyopia was present, the type of amblyopia was defined based on the presence of an amblyogenic factor (strabismus, deprivation or refraction). Refractive amblyopia, for all age groups, was diagnosed when spherical equivalent between the eyes differed ≥1.00 dioptres or astigmatism with oblique axis, especially with opposite direction was present. Strabismus amblyopia was diagnosed when strabismus was determined by the orthoptist.

Statistical Analysis

All analyses were performed with the statistical package for social sciences (SPSS, IBM Corp.) software, version 25.0.0.2. Statistical significance was set at the 0.05 level and all testing was two sided. Testing of categorical variables (e.g. two by two tables) was conducted with a Chi square test. We aimed to study and compare both groups, with respect to their time to referral and time to amblyopia diagnosis. The time to amblyopia analysis follows an intention to screen method (primary end-point). Secondarily, a per protocol analysis (no screening versus at least 1 screening test) was performed. These time to event analyses, including the corresponding hazard ratio's (HR) and figures, were performed with a Cox regression model for proportional hazards. In the sensitivity analysis, a covariate was added to the model to study its influence on the results. A Mann-Whitney U-test was performed to investigate difference in depth of amblyopia between the two groups (not normally distributed data).

RESULTS

Inclusion

All children born in the area of and registered at the participating CHC centres were included at baseline. Inclusion into both study groups (n 10 811) was distributed equally across the 134 participating centres (p 0.13). The control group comprised 5649 children of whom 89 dropped out of the study (1.6%) prior to their first screening moment (moved out of the area, had no screening record or were non-users of the CHC centre). The intervention group included 5162 children with 100 dropouts, either prior to their first screening moment or because of declined participation (1.9%) (p 0.15) (Figure 1). After excluding the dropouts, the total study population consisted of 10 622 children (5479 male, 5132 female) with 37 722 patient-years of on study exposure time. Loss to follow-up – at any time point after the first screening visit – occurred equally in both groups with 491 / 5560 (8.8%) and 468 / 5062 (9.2%) cases, respectively (p 0.46) (Figure 1). Loss to follow-up was mainly due to no VA measurement or relocation of the child. An orthoptic form was received of 532 (out of 771) referrals in the control group versus 464 (out of 755) referrals in the intervention group. In addition, 84 forms in the control group and 108 forms in the intervention group were received of children referred outside of screening.

Attendance

Attendance to general health screening visits at 0-45 months was 7.95±1.42 visits in the control and 7.71±1.40 visits in the intervention group. The distribution of visits was slightly skewed with more visits in the control group. In the control group a mean of 3.12±1.07 orthoptic vision screening tests were performed at 6-24 months, as compared to 1.03±1.06 screening tests in the intervention group. Complete absence of screening in the intervention group was achieved in 1989 children (39.3%), while 1598 (31.6%) underwent a single vision screening exam and 1475 (29.1%) children two or more vision screening tests (Figure 2). Vision screening was allowed in the intervention group in case an eye abnormality was noticed or suspected by the screening physician or parent or in case of a positive family history.

Figure 1. Lost-to-follow up per screening moment of the control group (n=5649) and intervention group (n=5162), the drop-out for each study arm (89 vs. 100, p 0.15) and the loss to follow up after each CHC centre visit (in total 491 vs. 468, p 0.46).

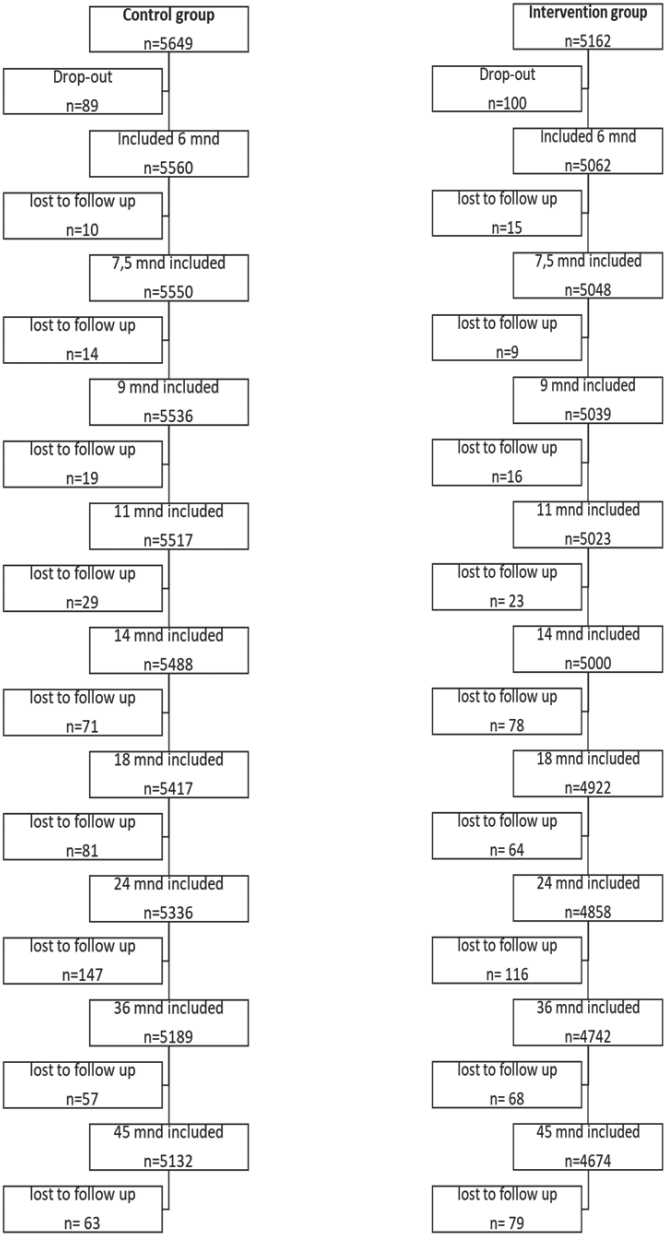
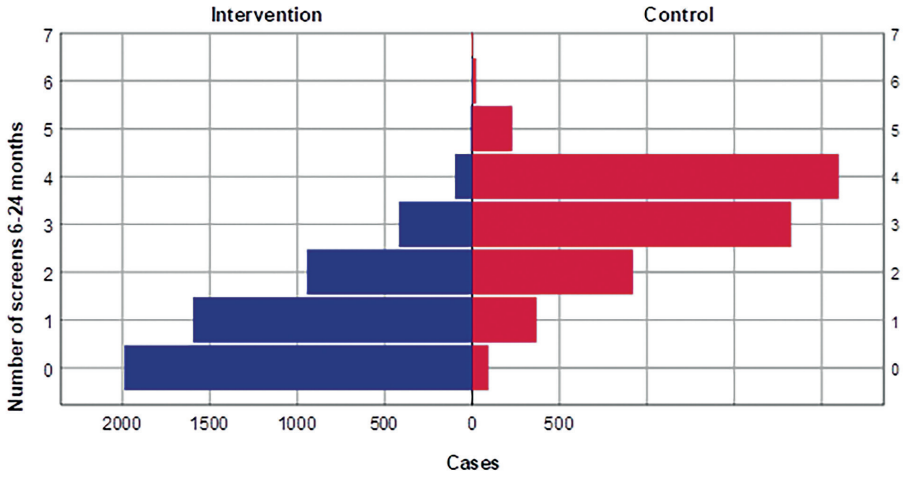


Figure 2. Number of orthoptic vision screenings performed between 6-24 months.



The national protocol in the control group indicated 2-4 orthoptic vision screenings during these moments. In the intervention group all the children were invited for general screening, but the vision screening was performed on indication only.

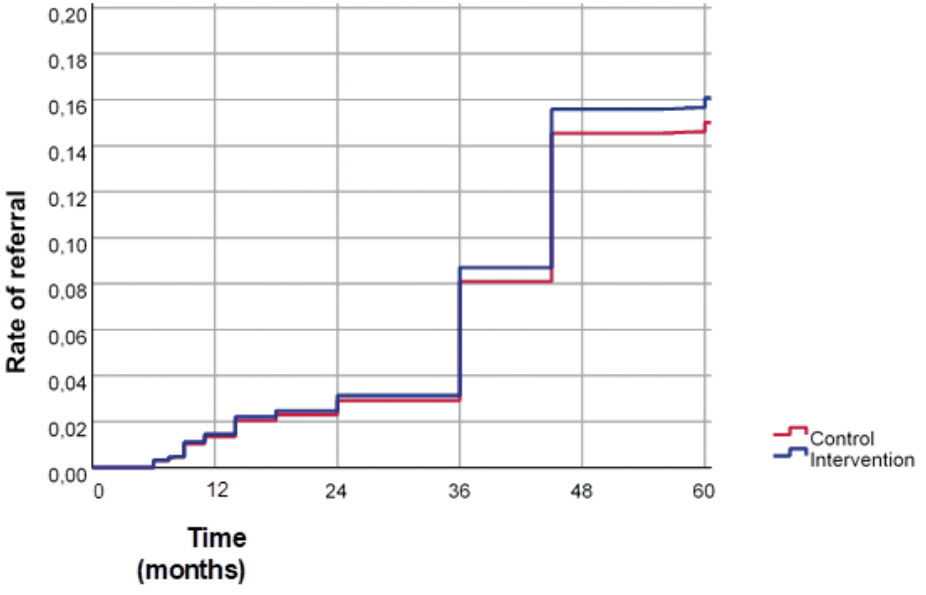
Referral

After screening at 6-24 months in the control group, 173 out of 5560 (3.1%) children were referred, versus 123 out of 5062 (2.4%) children in the intervention group (Relative Risk (RR) = 0.78 [95%CI 0.62, 0.98]). Observation of strabismus by either parents or screening physician was the referral reason, in 80 (46.2%) versus 57 (46.3%) children. A visually apparent problem as nystagmus, microphthalmos, ptosis, dacryostenosis, cyst, anisocoria was the reason for referral in 11 (6.4%) versus 22 (17.9%) children. The preverbal screening test itself, at 6-24 months, as primary screening instrument, led to a referral in 28 (16.2%) versus eight (6.5%) children. Whether the strabismus was detected by observation only, or by the screening test, could not be determined in 43 (24.9%) versus 32 (26.0%) children. Four children in both groups were referred due to positive family history (2.3% vs. 3.3%) and seven children in the control group for other causes (4.0%).

Visual acuity measurements at 36 months led to 258 (4.6%) versus 267 (5.3%) referrals. Visual acuity measurement at 45 months led to 308 (5.5%) versus 350 (6.9%) children were referred. Extra VA measurements at 60 months led to another 32 (0.6%) versus 15 (0.3%) referrals.

In total, 771 children (13.9%) in the control group were referred based on screening, as compared to 755 children (14.9%) in the intervention group (p 0.11) (Figure 3). Time to referral analysis, demonstrated no significant (p 0.161) difference between both groups (HR 1.08, 95%CI 0.97-1.19) (Figure 3).

Figure 3: Cumulative referral rate for vision screening between age 6-60 months.



Diagnosis and age of detection of amblyopia

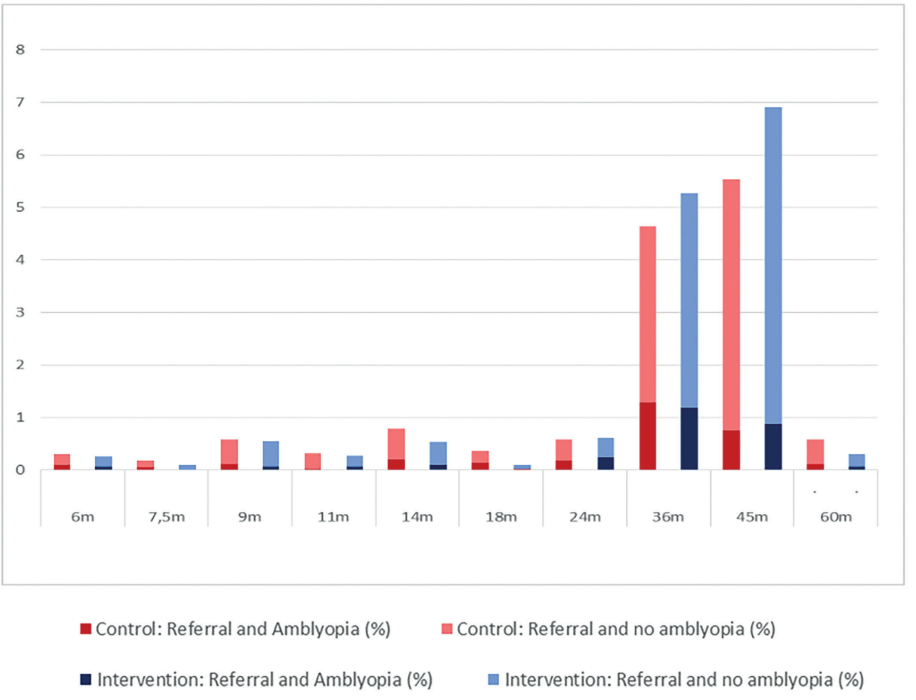
After screening at age 6-24 months, from the 173 versus 123 referrals, 44 out of 5560 (0.79%) versus 27 out of 5062 (0.53%) children were diagnosed with amblyopia (RR = 0.67 [95%CI 0.42, 1.09] (Table 3). Other eye disorders were diagnosed in 29 (0.52%) versus 21 (0.41%) children (Table 3 & Appendix).

After VA measurements, of the 598 referrals (out of 5560 children) 120 (2.2%) in the control group (36-60 months) were diagnosed with amblyopia versus 107 (2.1%) out of the 632 referrals (out of 5062 children) in the intervention group (Table 3). Other eye disorders were diagnosed in 31 (0.56%) versus 21 (0.41%) children (Table 3 & Appendix). Amblyopia detected outside screening, for instance, after referral by a GP or after self-referral, yielded 21 (0.38%) versus 25 (0.49%) cases of amblyopia (Table 3), and other eye disorders in 21 (0.38%) versus 32 (0.63%) children (Table 3 & Appendix).

In total, 185 (3.3%) children in the control group and 159 (3.1%) children in the intervention group were diagnosed with amblyopia (p 0.613) as a result of referral by CHC centres, 6-60 months screening and referrals made outside of screening (Table 3, Figure 4). Insufficient data was obtained in 234 (4.2%) in the control group versus 208 (4.1%) children in the intervention group. These children could not be classified as amblyopic because of insufficient or failed VA measurements twice and no available orthoptic data.

Based on the intention to screen analysis, there was no significant difference (p 0.55) between both groups in their time to amblyopia diagnosis. The corresponding HR was 0.98 (95%CI 0.79-1.21). Most amblyopia diagnoses were made after the VA measurements at 36 and 45 months, with no advantage in time to diagnosis by screening performed up to 36 months (Figure 5a). A sensitivity analysis yielded an unchanged absence of a difference between both groups (i.e. no benefit of screening) after multivariate correction for the number of visits (HR adjusted (HRadj) 0.97, 95%CI 0.78-1.20), gender (HRadj 0.98, 95%CI 0.79-1.21) or children identified outside of the study (i.e. referred by general practitioners) (HRadj 0.97, 95%CI 0.78-1.20). The per protocol analysis, comparing those without any preverbal screening (n 2083) with children receiving ≥1 preverbal screening test (n 8539), also showed no significant difference (p 0.11) between both groups in their time to amblyopia diagnosis (HR 0.79, 95%CI 0.59-1.06) (Figure 5b).

Figure 4. Referral and amblyopia cases detected at each screening moment (percentages)



Positive predictive value

Vision testing performed at 36, 45 and 60 months yielded 3.2 times more amblyopia diagnoses (120 and 107 cases) than screening between 6-24 months (44 and 27 amblyopia cases, respectively). The positive predictive value between 6-24 months (i.e. a referral resulting in an amblyopia diagnosis) is 25.4% (95%CI 19.5-32.4%) for the control group and 22.0% (95%CI 15.6-30.1%) in the intervention group. The corresponding values for an amblyopia diagnosis based on referral after VA testing (36, 45 and 60 months) are 20.1% (95%CI 17.1-23.5%) versus 16.9% (95%CI 14.2-20.1%) respectively. When children diagnosed with amblyopia based on vision testing (reference standard) are compared with an aggregate of all 6-24 months preverbal screening moments (index test), than screening in the control group has a sensitivity, specificity, positive and negative predictive value of 26.8%, 97.6%, 25.4% and 97.8% respectively. Likewise, preverbal screening in the intervention group has a sensitivity, specificity, positive and negative predictive value of 20.1%, 98.1%, 22.0% and 97.8% respectively.

Figure 5a. Time to amblyopia diagnosis intention to treat analysis

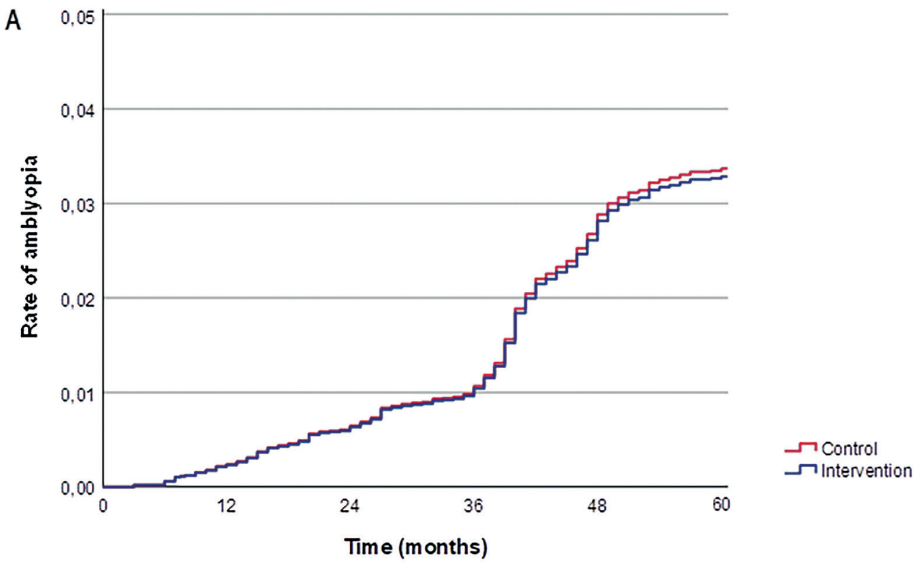


Figure 5b. Time to amblyopia diagnosis per protocol analysis

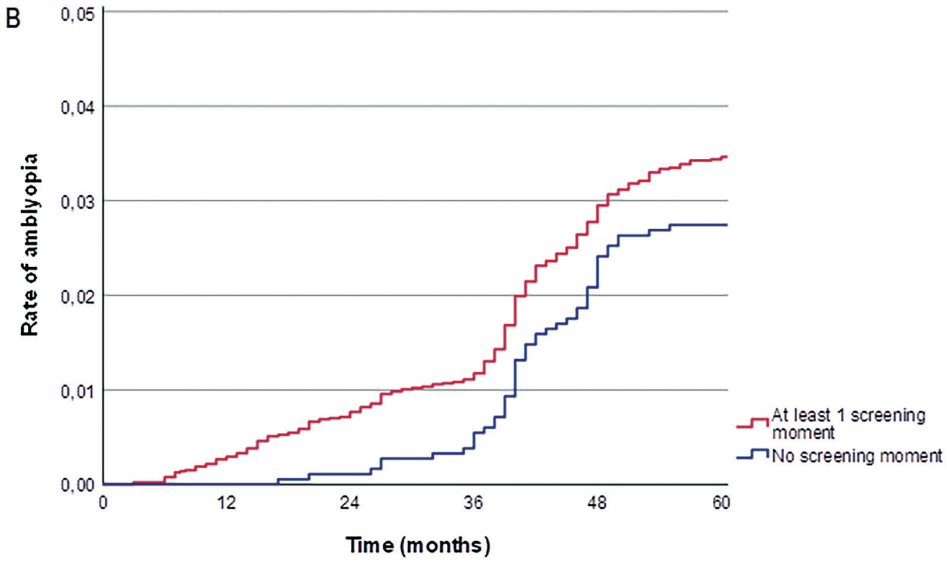


Table 3. Amount of referrals, amblyopia cases, the positive predictive value (PPV) of amblyopia, other diagnosed eye disorders (appendix 4) and the overall PPV of all diagnosed eye diseases (other and amblyopia).

	Age in months	Group	Referral, n	Amblyopia, n	PPV Amblyopia (%)	Eye disease, n	PPV all diagnoses (%)
Preverbal screening 6-24 months	6 months	Control	17	5		2	
		Intervention	13	3		2	
	7.5 months	Control	10	3		1	
		Intervention	5	0		0	
	9 months	Control	32	6		5	
		Intervention	28	3		5	
	11 months	Control	18	1		7	
		Intervention	14	3		3	
	14 months	Control	44	11		8	
		Intervention	27	5		7	
	18 months	Control	20	8		1	
		Intervention	5	1		0	
	24 months	Control	32	10		5	
		Intervention	31	12		4	
Total preverbal screening 6-24 months		**Control**	**173**	**44**	**25,4**	**29**	**42,2**
		Intervention	**123**	**27**	**22,0**	**21**	**39,0**
VA at 36-60months	36 months	Control	258	72		17	
		Intervention	267	60		12	
	45 months	Control	308	42		11	
		Intervention	350	44		8	
	60* months	Control	32	6		3	
		Intervention	15	3		1	
Total VA measurements 36-60 months		**Control**	**598**	**120**	**20,1**	**31**	**25,3**
		Intervention	**632**	**107**	**16,9**	**21**	**20,3**
Total all screening visits 6-60 months		**Control**	**771**	**164**	**21,3**	**60**	**29,1**
		Intervention	**755**	**134**	**17,7**	**42**	**23,3**
Referrals outside of screening		Control	47	21		21	
		Intervention	59	25		32	
Total screening 6-60 months and referrals outside of screening		**Control**	**818**	**185**	**22,6**	**81**	**32,5**
		Intervention	**814**	**159**	**19.5**	**74**	**28.6**

** Optional extra vision exam in case of exam failure at 45 months.*

Type of amblyopia

Strabismus amblyopia was detected in 50 versus 27 children, of whom 26 (52%) versus 12 (44%) were detected between 6-24 months, and 14 (28%) versus seven (26%) with VA measurements at 36-60 months. The other ten (20%) versus eight children (30%) were detected outside of screening.

Refractive amblyopia was detected in 60 versus 68 children, of whom five (8.3%) versus two (2.9%) with screening between 6-24 months and 54 (90%) versus 62 (91.2%) with VA measurements at 36-60 months. One (1.7%) versus four children (5.9%) were detected outside of screening.

Combined mechanism amblyopia was detected in 17 versus 16 children, of whom seven (41.2%) versus nine (56.3%) were detected between 6-24 months and four (23.5%) versus four (25%) with VA measurements at 36-60 months. Six (35.3%) versus three (18.8%) were detected outside of screening.

Bilateral amblyopia was detected in 49 versus 40 children, of whom five (10.2%) versus two (5%) with screening between 6-24 months and 40 (81.6%) versus 30 (75%) with VA measurements at 36-60 months. Four (8.2%) versus eight (20%) were detected outside of screening.

Deprivation amblyopia was detected in two versus four children. Both children in the control group were detected between 36-60 months. One child in the intervention group was detected between 6-24 months, one between 36-60 months and two outside of screening.

Type of amblyopia was unknown in seven versus four children.

There was no significant difference between the number of amblyopia cases between the two groups; 185 children (3.3%) in the control group versus 159 children (3.1%) in the intervention (p 0.613). There were slightly more strabismus and slightly less refractive amblyopia cases in the control group. Strabismus amblyopia was diagnosed earlier.

Figure 6. Type of amblyopia detected (y-axis, %) for each age of screening (x-axis, months) for the control and intervention group.

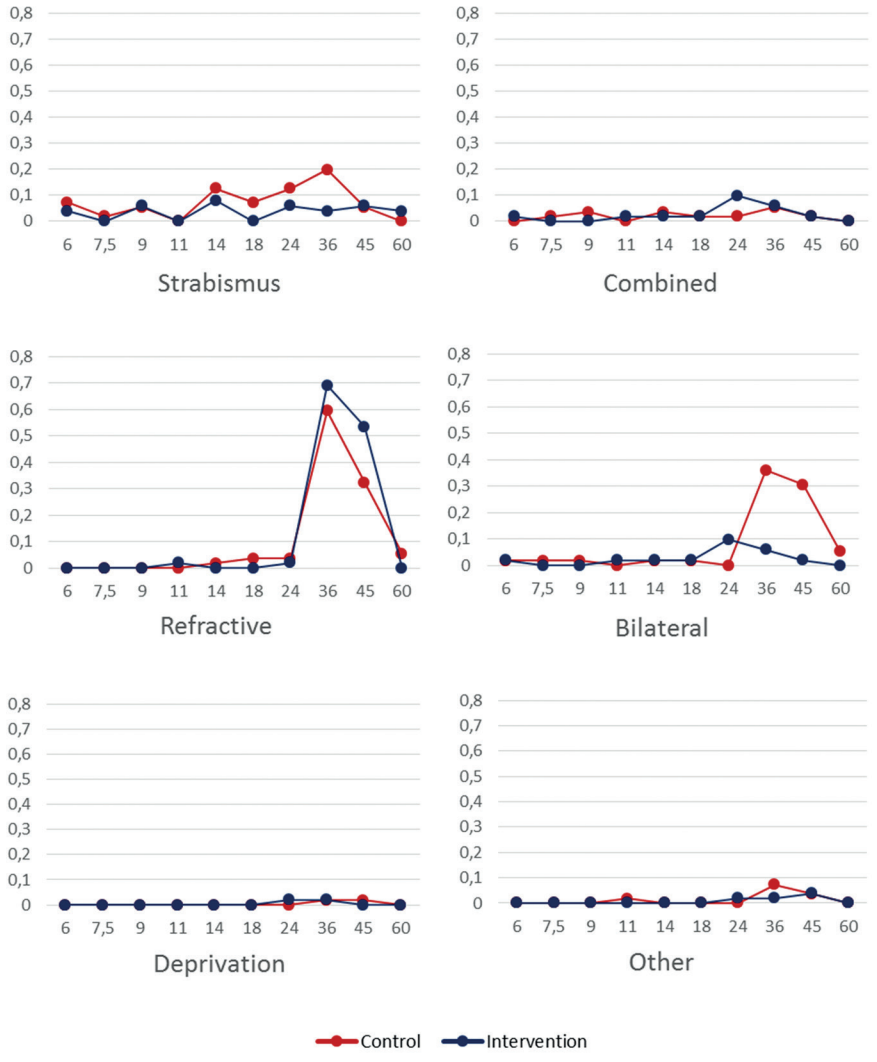
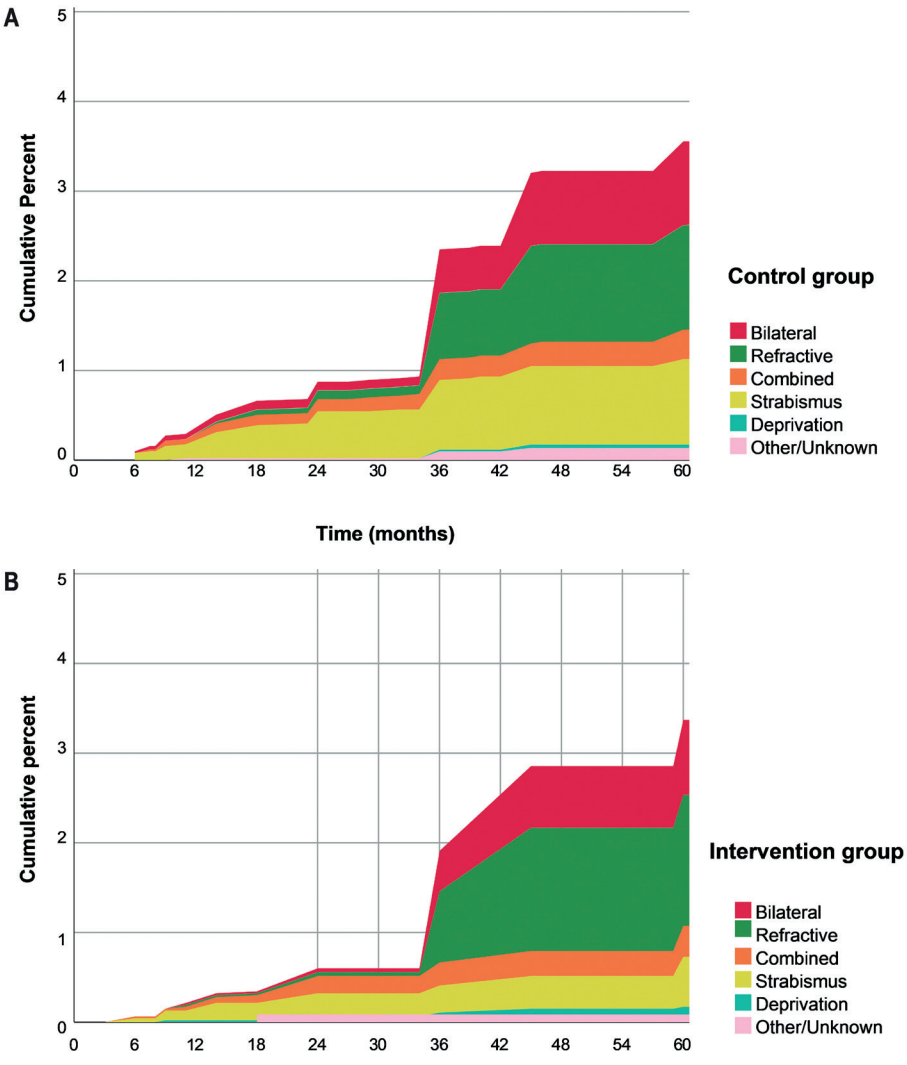


Figure 7. Cumulative percent of amblyopia detected separated for each type of amblyopia for each screening moment for the control group (a) and intervention group (b).



Severity of amblyopia

The LogMAR VA of the amblyopic eye was equally distributed between both groups (Figure 8). The LogMAR VA difference between both eyes was equally distributed between study groups (p 0.733, Mann-Whitney U test) (Figure 9).

Severe amblyopia (VA under the 0.25 decimal) was diagnosed in 55 versus 45 children. Moderate amblyopia (VA 0.25 - 0.5 decimal) was diagnosed in 83 versus 74 children. Mild amblyopia (VA higher than 0.5 decimal) was diagnosed in 15 versus 11 children. Severity was unknown in 32 versus 29 children.

There was no significant difference between both groups regarding the vision of the amblyopic eye in the severe amblyopia group (VA under 0.25 decimal, above 0.6 logmar)(p 0.274). There was no significant difference between both groups regarding the vision of the amblyopic eye in the moderate to severe amblyopia group (VA under 0.50 decimal, above 0.3 logmar) (p 0.549).

Figure 8. Frequencies of the visual acuity (logMAR) of the amblyopic eye for the intervention and control group.

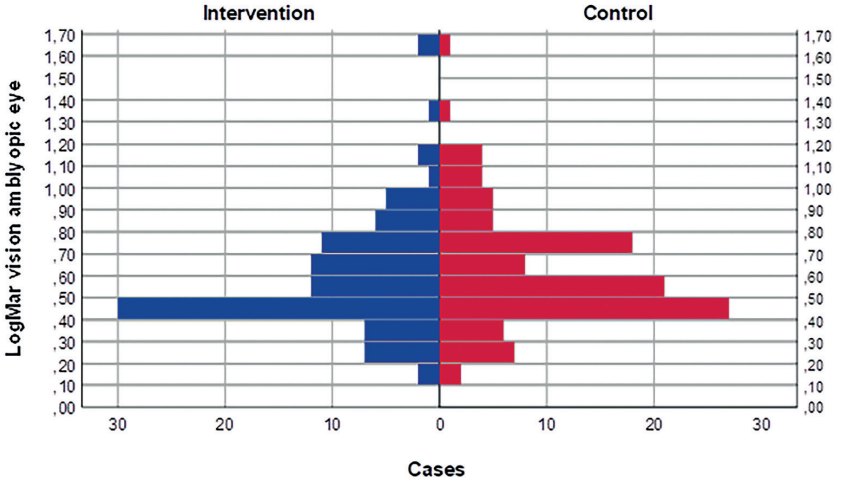
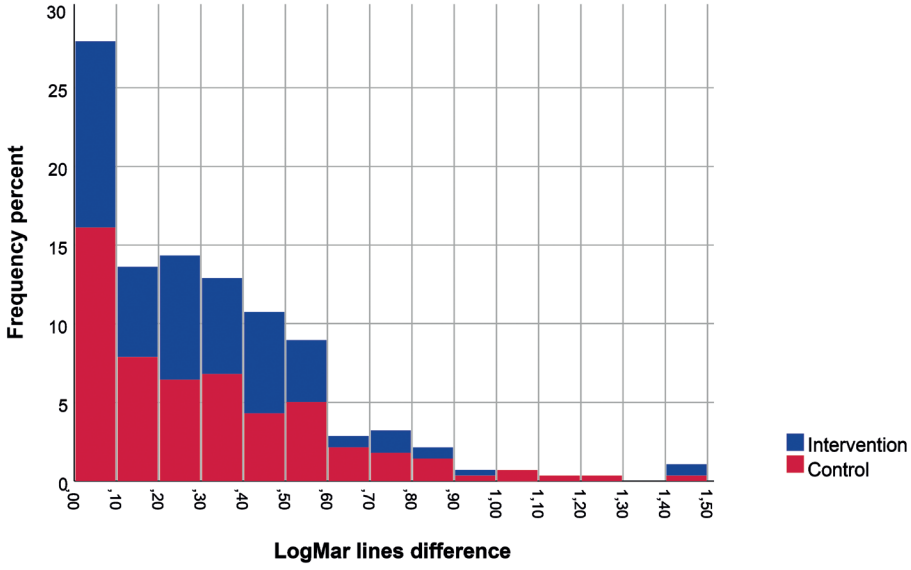


Figure 9. Stacked histogram of the LogMAR difference between eyes in children diagnosed with amblyopia.



DISCUSSION

This study demonstrated that omission of routine preverbal eye screening tests between the age of 6-24 months in the Netherlands did not lead to significant differences in amount of children referred, in total cases of amblyopia detected or in time of detection. Nor was there a significant difference in the severity of the detected amblyopia. The most important reason for referral at age 6-24 months was observed strabismus or a visually apparent eye disorder noticed by the parents. These disorders will be detected regardless of formal vision screening. Strabismus amblyopia was mainly detected before the age VA could be measured. Refractive amblyopia and bilateral amblyopia on the other hand were detected, almost exclusively, with the VA measurements between 36-60 months. Visual acuity measurements at 36-60 months yielded far more amblyopia cases compared to the screening between 6-24 months with even expenses. Only 0.8% from the 3.3% amblyopia in the control group and 0.5% from the 3.1% amblyopia in the intervention group were detected with preverbal screening. More strabismus amblyopia cases were detected in the control group. This difference only became apparent after the VA measurements.
Amblyopia is more responsive to treatment in children younger than seven years of age.[9] As there was no significant difference in time to referral and severity of amblyopia, omission of eye screening between 6-24 months does not seem to affect the effectiveness of amblyopia treatment. With the VA measurements at 45 months, children will be referred and receive treatment well before the age of seven. In ongoing research we will assess whether there is a difference in amblyopia treatment received between children referred from the control versus the intervention group.

The positive predictive value (PPV) was low for all screening moments. In the Netherlands, the general health screening is performed by youth health care physicians and nurses, which makes screening much cheaper than screening performed by orthoptists, but might lead to a lower PPV. Another factor that influences the PPV is the low prevalence of amblyopia. For the VA measurements at 45 months the low PPV might be an underestimation because children were already under orthoptic control due to the VA measurements at 36 months. Due to the higher age CHC personnel might have referred children quicker because of fear of missing amblyopia at this age and because they depend more on the VA measurements at 45 months. The high specificity and high negative predictive value can be explained by the large sample size and the low incidence rate of amblyopia.

There was a high response rate from the treating orthoptists (532 out of 771 referrals in the control group and 464 out of 755 referrals in the intervention group) which minimized the lost to follow up. Some information could not be retrieved because: (i) some children were first referred to their general practitioners and they might not have referred the child further to an orthoptist; (ii) parents were unaware of the referral; (iii) parents did not comply with the referral; (iv) some orthoptic clinics changed during the long follow-up.[10,11] With no received orthoptic information, we might have missed some amblyopic children. Children, who could not be classified as amblyopic due to two or more failed or insufficient VA measurements at the CHC centre without orthoptic information, hold the highest potential risk to be amblyopic. As this group was similar between groups 234 (4.2%) versus 208 (4.1%) we expect the amount to be the same in both groups. Because only the orthoptic information from the first measurement was analysed, the orthoptic assessment at a young age (i.e. before VA could be measured) might have missed some children with micro strabismus. Moreover, children with high anisometropic amblyopia might have had a micro strabismus which was not recognized at the first orthoptic visit. The high amount of children with bilateral amblyopia could be explained as only the orthoptic information of the first VA measurement was recorded. Therefore, the amblyopia diagnosis was based on the VA before glasses adaptation.

The small difference in type of amblyopia between the groups, slightly more strabismus amblyopia and slightly less refractive amblyopia in the control group, could be explained by the age of diagnosis. Children in the control group were diagnosed a bit earlier and because anisometropia tends to increase with age children in the control group were more likely to be classified as amblyopic due to strabismus than amblyopia due to refractive error. Also the same criteria for refractive amblyopia were used for all ages.

The strength of this study is the large sample size, (8% of the Dutch birth rate was included) with a long follow-up (37 722 patient-years exposure time) and high attendance rate. The incidence of amblyopia (3.3% versus 3.1%) is comparable to literature.[12]

A limitation of the study is that only the referred children had an orthoptic eye examination. Due to the large sample size, it was not possible to provide all children with an orthoptic examination. Most children had two VA measurements (36 and 45 months) at the CHC centres. The observational study by Sloot et al. showed a good performance of the VA measurements at the CHC centres.[13] Therefore, children with

a sufficient VA measurement at the CHC centre were classified as not amblyopic. As a consequence, very mild amblyopia could have been missed. Mild amblyopia, however, would have a much lower impact than moderate to severe amblyopia.

Another limitation of the comparison was that all children did attend their regular screening visits at the CHC centres, and that physicians may have detected more cases than physicians who were not trained to perform eye examinations: (i) the physicians were used to specific eye screening within the general health screening examination; (ii) they actively had to omit eye screening in the intervention group; (iii) they had to exclude conspicuous eye disorders and a positive family history in the intervention group, all raising their level of attention for eye disorders.

Photoscreening is not part of the vision screening programme in the Netherlands. Photoscreening is used to detect risk factors for amblyopia and is in some countries suggested as a replacement for preverbal vision screening or even VA measurements. However, it is still unclear how much amblyopia will be prevented if glasses are prescribed early. The Pediatric Eye Disease Investigator Group did not find a significant reduction in the development of strabismus, nor better stereo acuity, nor better VA when prescribing glasses at age 1-2 years to moderate hypermetropic children (+3 up to +6) compared to no prescription of glasses.[14] In Flanders, Belgium, photoscreening has been introduced recently as an temporary add-on screening to VA measurements at one and two-and-a-half years of age. Implementation of photoscreening resulted in increase of prescriptions of glasses from 4.7% to 6.4%.[15]

The rate of failed VA measurements with the Landolt C at 45 months is currently assessed, as the VA measurements at 36 months already proved to be insufficient in 32.1% at 36 months with the APK.[11] Similar rates have previously been reported for Lea Symbols and HOTV.[16] Difference between VA measurement at 36 and 45 months will be further investigated as to compare the use of different VA charts, testability at different ages and diagnosis and treatment after referral. Preverbal vision screening is not only performed in the Netherlands but also in the majority of countries throughout Europe. Large differences, however, exist in type and amount of screening tests and screening personnel.[1] Our results could, therefore, be informative for other countries that want to evaluate, extent, implement or disinvest their own preverbal vision screening.

In conclusion, routine eye screening tests between the age of 6-24 months can be omitted without any negative impact on amblyopia detection or its severity. Strabismus

or visually apparent disorders were diagnosed regardless of formal preverbal vision screening. Refractive amblyopia is not discovered with preverbal eye screenings before the age VA can be measured.

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7

High rate of failed visual-acuity measurements with the Amsterdam Picture Chart in screening at the age of 36 months

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*both authors contributed equally to the study

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ABSTRACT

PURPOSE In the Netherlands, youth health care physicians and nurses screen all children for general health disorders at Child Health Care Centers. As part of this, the eyes are screened seven times, with the first visual acuity (VA) measurement at 36 months with the Amsterdam Picture Chart (APK). The suitability of the APK has been questioned.

METHODS Children born between July 2011 and June 2012 born in the provinces Drenthe, Gelderland and Flevoland and invited for screening at 36 months were eligible. Parents were sent the APK picture optotypes to practice with their children in advance. Data were collected from electronic screening records. The Dutch vision screening guideline prescribes that children with VA < 5/6, or one line interocular difference (not logMAR, however) should be retested or referred.

RESULTS Of 10 809 eligible children, 1546 did not attend and 602 attended but had no VA measurement at age 36 months, 247 of these were under orthoptic treatment. Of the 8448 children examined, VA was sufficient in 5663 (67.0%) and insufficient in 1312 (15.5%). In 1400 (16.6%), the measurement of VA itself failed. In 73 (0.9%), data were missing. Of the 216 children with 2 failed VA measurements, 150 (69%) were not referred, and measurement of VA was deferred to the next general screening examination at 45 months.

CONCLUSIONS Although most parents had practiced the APK picture optotypes at home with their children, the rate of failed APK measurements plus the measurements with insufficient visual acuity was 32.1% at 36 months. Similar rates have previously been reported for Lea Symbols and HOTV, permitting the conclusion that measurement of VA at the age of 36 months cannot be recommended as a screening test in the general population.

INTRODUCTION

In the Netherlands, child healthcare (CHC) physicians or nurses screen all children on general health disorders at Child Healthcare Centres (CHC's), where parents are invited to have their child examined. Coverage is between 95% and 100% in the first year, declining thereafter. The eyes of the children are screened seven times, at the ages of 1-2, 3-4, 6-9, 14-24, 36, 45 and 54-60 months. The vision screening programme has been shown to be effective in detecting amblyopia in the Rotterdam Amblyopia Screening Effectiveness prospective birth-cohort Study (RAMSES study).[1,2] Eye screening at 0-4 months includes inspection of the anterior segment, Hirschberg test, pupillary reflexes and the fundus red reflex. At 6-24 months eye screening also comprises cover test, alternating cover test, eye motility and monocular pursuit movements. At 36, 45 and 54-60 months, visual acuity (VA) is measured. At 36 months the Amsterdam Picture Chart (APK) is used.[3] At 45 and at 54-60 months Landolt-C optotypes are used.[3]

The APK was developed in the early 1950s in Amsterdam and has eleven different pictures (Figure 1). These eleven pictures were found recently to have different thresholds.[4] In contrast with Landolt-C and Snellen's E-optotypes, the width of the lines of the APK optotype is not one-fifth, but one-tenth of the size of the optotype. The width of the lines of the Lea Symbols is one-seventh of the size of the optotype. The APK has been favoured by many Dutch orthoptists over years, because children can be tested at the age of 3 successfully in most cases, provided the measurement of VA is done by an orthoptist.[5] However, many of the APK pictures are archaic and may be unfamiliar to modern or non-European children.

As the quality of the APK as a psychophysical measurement was found to be low in a previous study by Engin et al.,[4] we studied the VA measurement at the age of 36 months in a large birth-cohort study, and found high rates of measurements with insufficient VA and of failed measurements.

MATERIALS AND METHODS

This study is part of the Optimization of Amblyopia Screening study that compares two sequential birth cohorts, with and without eye screening tests between 6 and 24 months of age.[6,7] In the RAMSES observational birth-cohort study, it had been found that cases of amblyopia detected before age 36 months, were not detected by screening and had strabismus in most cases.[1] Moreover, the quality of the screening examinations between 6 and 24 months of age was shown to be moderate in a semi-structured observational study.[8]

Visual acuity (VA) was measured with the APK (Figure 1) in 36-months-old children at CHC's. Children born between 1st July 2011 and 30th June 2012 in the region with CHC's of the family health care providers Icare and the Municipal Health Service in the provinces Drenthe, Gelderland and Flevoland, who were invited for screening at 36 months, were eligible. Youth Health Care (YHC) physicians and nurses of Icare, one of the organisations for preventive health care, screen 8% of the Dutch birth figure. Together with the invitation, parents were sent the APK picture optotypes to practise with their child in advance. VA was measured by YHC physicians or nurses. They receive one day of eye-examination training by a teaching orthoptist every five years. The VA measurement was rated as sufficient VA, insufficient VA or failed measurement (Table 1). The VA measurement was rated insufficient when the VA did not reach the threshold. The VA measurement failed when the measurement carried out by a particular YHC physician or nurse failed, when only binocular VA was measured or when only the VA of one eye was measured. If the child already wears glasses and is under treatment of an orthoptist or ophthalmologist, the VA measurement should only be performed if there is a specific reason to do so, according to the Dutch guideline.[3] Data were collected from electronic screening records from the CHC's.

The Dutch vision screening guideline prescribes retesting after six weeks in case of failed VA measurement and in case of threshold VA designated as "doubtful" VA. This is defined as a VA of one eye of 5/10 or when there is one line interocular difference (not logMAR, however: 5/5, 5/6, 5/10, 5/15, etc.). Note that, according to the current Dutch guideline, a VA 5/6 and 5/5 is designated as "doubtful". Note also that the interval between 5/10 and 5/6 is approximately 2logMAR lines. If the VA at the retest is not better than the first measured VA, the child is referred. Children with a VA lower than 5/10 for one eye or two lines interocular difference at the first measurement, are referred directly.[3] It must be noted however, that for this study, the Dutch guideline

category "doubtful", or threshold VA and the Dutch guideline category "referred directly" are both designated in this study as insufficient VA.

Figure 1. Amsterdam Picture Chart with eleven different optotypes.

When used at 5 m, the measured visual acuity is 5/30, 5/20, 5/15, 5/10, 5/6 or 5/5.
The height of the optotypes of D = 5 is approximately 10 min of arc when viewed at 5 m.

Table 1. Criteria for referral or repeat measurement, according to the Dutch national guideline for vision screening, for sufficient, insufficient or failed measurement at age 36 months.[3]

	Visual Acuity (VA) measured with APK
Sufficient	Monocular VA ≥ 5/6 for both eyes
Insufficient	Monocular VA < 5/6 for one or both eyes One line interocular difference (not logMAR, however: 5/5, 5/6, 5/10, 5/15, etc.)
Failed measurement	The measurement failed Only binocular VA obtained VA was measured of one eye only

RESULTS

A flow-chart of the distribution of the eligible children is presented in Figure 2. Of the 10,809 eligible children aged 36 months, 1,546 children did not attend, 247 children attended but were not screened as they were already being treated by an orthoptist. Another 355 children attended but had no measurement of VA for unknown reasons. General screening time is limited, and there may have been other priorities. VA was measured in 8,661 eligible children at 36 months, in 8,448 with the APK, in 19 with the Landolt-C and in 194 children with the E-optotypes. Because of the low number in the subsets measured with Landolt-C and with E-optotypes, these were excluded from analysis.

Figure 2. Flow-chart of the eligible children, the drop-outs and children with and without visual acuity measurement at 36 months.

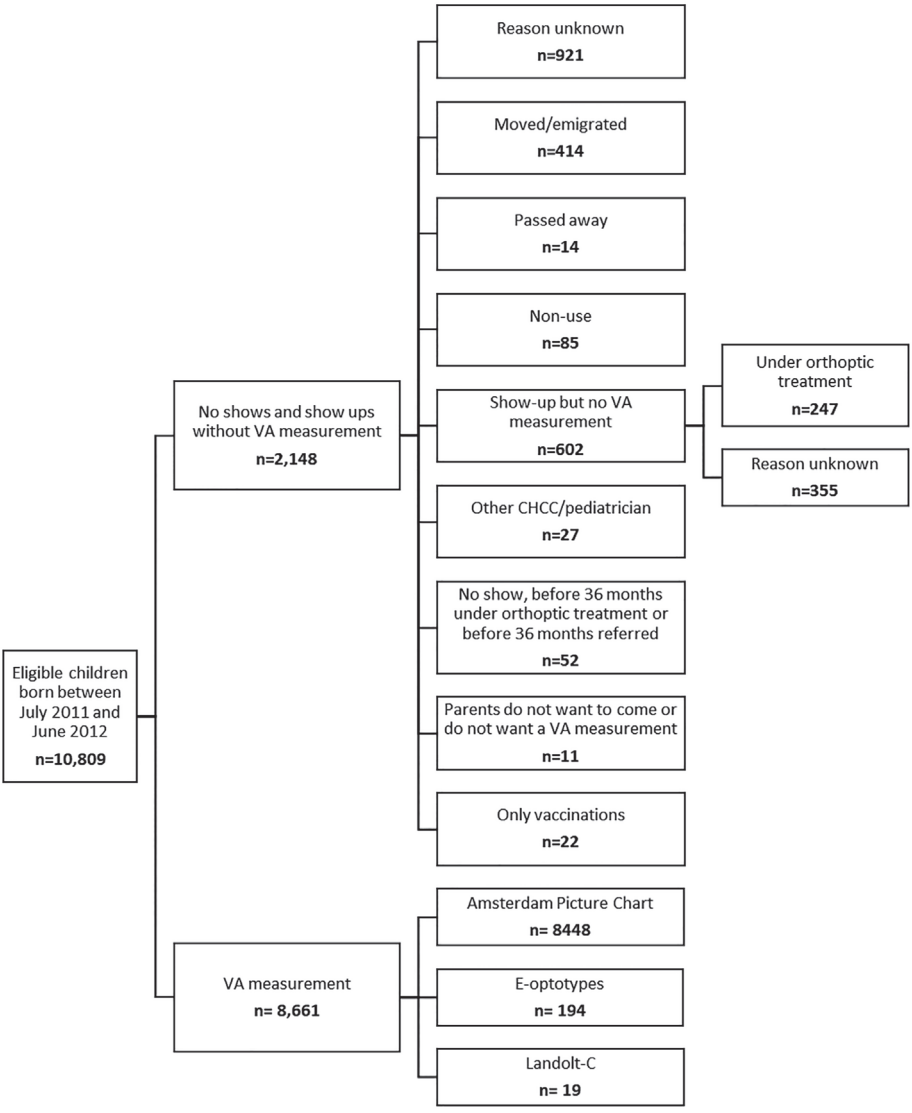
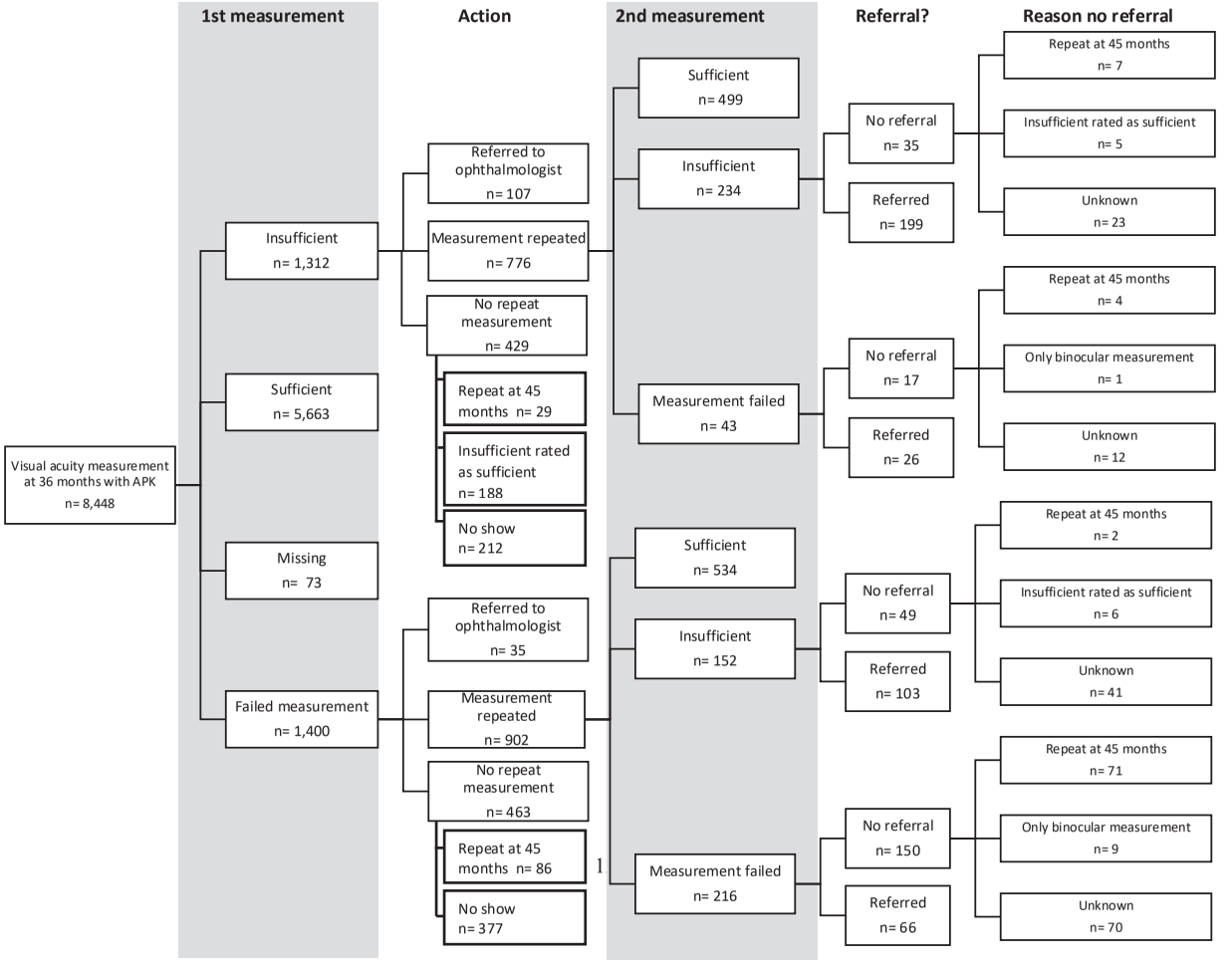


Figure 3. Flow-chart of visual acuity measurements with the Amsterdam Picture Chart at 36 months, the first measurement, action undertaken after the first measurement, the second measurement, the referral and the reason for no referral after the second measurement.



First measurement

A flow chart of the results of the first measurement and repeated measurements is presented in Figure 3. In 5,663 (67.0%) of the 8,448 children measured VA was sufficient with the APK, in 1,312 (15.5%) insufficient. In 1,400 (16.6%), the measurement failed and in 73 children (0.9%), data were missing. Of the 1,312 children with an insufficient VA, 107 were directly referred to an orthoptist or ophthalmologist. The VA measurement was repeated in 776 children at the CHC's. The VA measurement was not repeated, nor was the child referred, in the other 429 children, (i) because the VA that was insufficient according to the Dutch guideline was incorrectly rated as sufficient (188 children, many of these had VA 5/6 and 5/5/), (ii) the parents or physician decided to measure again at the next general screening exam at age 45 months according to notes in the records (29 children), or (iii) because they did not attend for unknown reason (212 children). Of the 1,400 children with a failed measurement, 35 were directly referred to an orthoptist or an ophthalmologist. The VA measurement was repeated in 902 children at the CHC's. The VA measurement was not repeated, nor was the child referred, in the remaining 463 children because (i) the parents or physician decided to re-measure at the next general screening exam at age 45 months according to notes in the records (86 children) or because (ii) they did not attended for unknown reason (377 children).

Repeated VA measurement after insufficient first VA measurement

In 776 children with an insufficient VA measured the first time, the measurement was repeated, and in 234 of these the VA was insufficient, of which 35 children were not referred. In 43 children the second measurement failed, of which 17 children were not referred. Reasons for non-referral are listed in Figure 3.

Repeated VA measurement after failed first VA measurement

In 902 children with a failed measurement, the measurement was repeated, and in 152 of these, the VA was insufficient, of which 49 were not referred. In 216 children, the second measurement failed, of which 150 (69.4%) children were not referred. In at least half of these children, measurement of VA was deferred to the next general screening examination at 45 months. Reasons for non-referral are listed in Figure 3.

DISCUSSION

In this birth cohort study, measured VA was insufficient in 15.5% of the children, while the VA measurement failed in another 16.6% of the children, although parents had practised the APK picture optotypes at home with their children in advance.
One could argue that the rate of failed VA measurements would have been lower when using the Lea symbols, but in a systematic study by Becker et al.,[5] it was shown that the failure rate using Lea symbols in general-population screening was even higher than in our study: 44% at the age of 31-36 months and 24% at the age of 37-48 months. In that study, the failure rates were much lower for VA measurements when carried out by orthoptists.[5] To have VA measured in all children in the Netherlands by orthoptists would be prohibitively expensive, however. In a Swedish study, measurement of VA using both HOTV and Lea symbols at 36 months and 48 months was evaluated. For both charts, at the age of 36 months, the test failed in 20% of the children apart from the children who did not reach the threshold, as compared to around 10% at the age of 48 months.[9]

As compared with the Lea Symbols and HOTV, the failure rate of the APK in our study at the age of 36 months is only slightly better, but still too high for it to be used to measure VA in general screening at 36 months. If 16.6% of the VA measurements fails and another 15.5% of the children does not reach the VA threshold, 32.1% should either be retested after six weeks or referred according to the Dutch guideline. For screening in the general population this becomes prohibitively expensive.

In addition, it seems possible that the large number of failed measurements and of measurements with insufficient VA may have kept YHC physicians and nurses from referring children in accordance with the Dutch vision screening guideline at the age of 36 months. It has been found previously by Tjiam et al. that, in some cases, YHC physicians or nurses deviate from the Dutch guideline, when they consider a repeat measurement as unlikely to be successful, for instance when caused by a language barrier.[10]

Accordingly, YHC physicians and nurses were more inclined to refer a child when the measurement of VA was insufficient as compared to a failed measurement of VA. This is evident from the number of children who were not referred after two failed measurements, 150 (69.4%) of 216 children. According to notes in the records, in at least half of the children with two failed measurements, instead of referral, the decision

was taken to repeat the measurement at the next general screening exam nine months later, at age 45 months.

In conclusion, measurement of the VA at the age of 36 months cannot be recommended as a screening test in the general population, considering the high rate of failed VA measurements for the APK and the previously reported failure rates for the Lea Symbols and HOTV.

Compliance with Ethical Standards

The Medical Ethical Committee of the Erasmus Medical Centre declared that the Medical Research Involving Human Subjects Act did not apply to this research proposal as it concerned population-based prevention and that the 'Besluit Publieke Gezondheid'
(Public Health Decision, Ministry of Health 2008) applied, where only permission from the health inspectorate must be obtained to deviate from the national screening guidelines (reference number MEC-2012-003). This permission was granted. The research adhered to the tenets of the Declaration of Helsinki.

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General discussion

In the Netherlands, Child Health Care (CHC) centres exist since 1901. The first CHC centre was an initiative of the Dutch paediatrician Dr. Plantenga, who was inspired by Pierre Budin, an French obstetrician, who had opened the first baby clinic in 1892 in Paris. Babies were examined, weighed and instructions and advices were given to mothers about hygiene and breastfeeding.[1,2,3] This first private initiative was followed by other organizations and eventually became nationwide implemented in the Netherlands. Vision screening, primarily for the detection of amblyopia, was added to general health screening at the CHC centres after 1960 and included inspection, testing of ocular alignment, monocular visual acuity (VA) and stereo acuity testing in children aged three years and older. [4,5] At that time children were diagnosed with amblyopia at approximately age six or seven and treatment started at that age is much less effective and successful than when started at age four or five.
Vision screening was extended with the preverbal orthoptic vision screening Early Detection of Visual Disorders (Vroegtijdige Onderkenning Visuele stoornissen: VOV) test after 1980, because it was assumed that amblyopia should be diagnosed and treated as early as possible. At 0-6 months of age this screening comprised inspection of the eyes, pupillary reflexes, red fundus reflex and eye motility to detect congenital eye disorders like cataract, retinoblastoma and congenital glaucoma. At 6-24 months, this preverbal screening comprised also Hirschberg test (corneal light reflex), cover test for detection of strabismus, and pursuit movements.[6,7] Initially, these tests were intended to be performed by orthoptists at the CHC centres, but in the end these tests were performed by CHC physicians, after instructions given, in courses, by orthoptists.

To evaluate the effectiveness of the amblyopia screening in the Netherlands, the Rotterdam Amblyopia Effectiveness Study (RAMSES), an observational birth-cohort study (N=4624) was started in 1996. Three thousand children were followed form birth up to the age of seven. Children were examined at age seven and this study showed that preverbal screening contributed little to the detection of refractive amblyopia, while strabismus amblyopia was detected by the parents in approximately half of cases.[8] If strabismus is first detected by the parents because it is visually apparent, screening is, in that case, not necessary. As stated above, preverbal vision screening with orthoptic tests at age 6-24 months was added to detect and treat amblyopia at an even younger age, assuming that amblyopia should be detected and treated as early as possible. The RAMSES study showed, however, that these tests mostly detected strabismus amblyopia, which is visually apparent.

Therefore the effectiveness of preverbal, orthoptic vision screening before the age of three years is the central theme of this thesis. It was primarily investigated with a large disinvestment study of the preverbal part of the vision screening, the Optimisation of Amblyopia Screening (OVAS) study. In this study two large sequential birth cohorts, that underwent general health screening, with and without preverbal orthoptic vision screening were compared. The question was whether, and to what extent, omission of preverbal vision screening with orthoptic tests as part of general health screening between the age of 6-24 months would affect the detection of strabismus-, refractive- and combined-mechanism amblyopia and to confirm whether the omission of routine orthoptic vision screening tests between age 6-24 months would have no significant negative impact on the total number of cases and the severity of the detected amblyopia.

Preverbal orthoptic vision screening tests and measurement of VA at age 3-5 years are primarily aimed at the detection of amblyopia. Photoscreening has been recently added to regular vision screening in, for example, Flanders at the age of 1-2 years. Photoscreening aims, however, to detect risk factors for the development of amblyopia, instead of the detection of amblyopia itself. The most important risk factor that can be detected by photoscreening is high refractive error. Early prescription of glasses for high refractive errors that are detected by photoscreening will reduce the prevalence of amblyopia at the age of 4-6 years, but it is unknown to what extent. Photoscreening is beyond the scope of this thesis.

First, we compared the very extensive vision screening programme in the Netherlands with other vision screening programmes in Europe. We developed a questionnaire for a survey. We received answers from 36 countries. We found that vision screening programmes in Europe are very diverse. Large differences exist in age of screening, screening tests used and number of screening tests. In most European countries, infants are screened at age 0-4 months, mainly with inspection of the eyes and the red pupil reflex test. Preverbal vision screening with orthoptic tests at age 6-30 months is also (partially) performed in most European countries, but these tests are rarely performed by orthoptists. This preverbal screening consists of a combination of two or more of the following tests; inspection of the eyes, fixation, red reflex testing, Hirschberg test (cornea light reflex), Bruckner test, Cover test, pupillary reflexes, monocular pursuit and motility. In all European countries VA is measured to detect amblyopia with high sensitivity and specificity, but the age of the first measurement varies between three and seven years of age. In a third of countries VA is tested once, in one third twice

and in one third more than two times. The large diversity in screening programmes is caused by the lack of cost-effectiveness studies, lack of data collection and quality monitoring due to the development of practise bases screening protocols separate for all countries and to the lack of competion in preventive healthcare. Comparison of vision screening programmes is hampered by insufficient data collection and monitoring, that impedes comparison and again perpetuates their diversity.

The Dutch vision screening programme is very extensive with seven exams. Comparison and evaluation of existing screening programmes is difficult, especially for programmes with repeated screens. When only one measurement of VA is performed the specificity, sensitivity and attendance can be estimated and the cost-effectiveness calculated, but with repeated screens this calculation is difficult. A established method to compare the cost-effectiveness of screening programmes is the use of micro-simulation models (MISCAN). With a micro-simulation model, the effectiveness of introduction, modification or disinvestment of (components of) a screening programme can be calculated, provided that very detailed data is available. We used the detailed data from the RAMSES birth cohort study for a micro-simulation model. In the calculation with the model the uncertainty of the age of onset of amblyopia proved to be important. As the incidence curve of amblyopia is unknown, we made an estimation based on approximation of the observational data from the RAMSES study in conjunction with experts' estimations and literature. For each type of amblyopia, deprivation, strabismus, refractive error and combined strabismus and refractive error, the mean actual sensitivity was estimated. The preverbal orthoptic vision screens had lower sensitivity than the VA measurements. Using the incidence curves and the mean sensitivity per screen, we estimated the effect per screen. The finding in the RAMSES birth cohort study that orthoptic tests at age 6-24 months yielded very few cases of amblyopia was confirmed by the micro-simulation model. The sensitivity and specificity of the entire screening programme was not appreciably affected by the omission of the preverbal vision screens. The observations in the RAMSES study, that orthoptic vision screening tests contributed little to the detection of refractive amblyopia, while strabismus amblyopia was detected by the parents, was confirmed by the results of the model simulation.

The disappointing yield of the preverbal vision screening test was reason for on-site evaluation of all vision screening tests in the child healthcare (CHC) setting. Three sources were used for this evaluation, the screening records, questionnaires and semi-structured observations of all vision screening tests, as defined in the national

CHC screening guideline. The semi-structured observations showed that tests that were performed at a very young age, like the Hirschberg test for the detection of strabismus, and the fundus red reflex, were performed in accordance with the CHC screening guideline and orthoptic practise. Preverbal vision screening consisting of more typical orthoptic tests, like the cover-uncover test, the alternating cover test and the eye motility tests, performed by non-orthoptists, were not performed according to the guideline and orthoptic practise. Eye motility was in most cases not tested in all directions of gaze and pupillary reflexes were often not tested because room lights could not be dimmed. In the majority of children the monocular pursuit movements were not tested. Monocular smooth pursuit movement at the age of 6-24 months is an indirect indicator of good VA of that eye. CHC physicians were often unaware of the true purpose of this test. The observations were presented to the participating CHC physicians and a majority of the CHC physicians stated that they indeed had difficulty with the performance and interpretation of the cover-uncover test, alternate-cover test, and monocular pursuit. Visual acuity measurements in children aged 36- 45 months were, by and large, performed in accordance with the guidelines and orthoptic and ophthalmologic practise. We concluded that the orthoptic tests are not suitable to be carried out by non-orthoptists in a screening setting.

From the results of the RAMSES study, the micro-simulation model and the on-site observations the impetus came for a disinvestment study. The Optimisation of Amblyopia Screening study (OVAS) was designed to assess whether the omission of orthoptic vision screening tests between age 6-24 months would have no significant negative impact on the severity and total cases of amblyopia detected. The study aimed to improve the cost-effectiveness of vision screening in the Netherlands without deterioration of the quality of care. Two sequential birth cohorts were recruited at the age of 6 months and followed up until the VA measurements at 45 months. The children were seen at general healthcare screening visits at 134 CHC centres of the CHC organization of Icare, serving the provinces of Drenthe, east Flevoland and mid Gelderland. At these general healthcare screening visits, children born July-December 2011 were vision screened at 6, 9, 14 and 24 months of age with inspection, pupillary reflexes, eye motility, Hirschberg test, cover test and monocular pursuit test. Children born January-June 2012 were vision screened at these general screening visits only in case of visually apparent abnormalities or a positive family history. Visual acuity was measured in all children at 36 and 45 months. Those children who had been referred by CHC physicians for diagnosis and treatment to an orthoptist or ophthalmologist were evaluated for cause and severity of amblyopia or other eye disorders.

In the OVAS study we found that at the age of 6-9 months most children were referred by CHC physicians to an orthoptist or ophthalmologist because of observed strabismus or visually apparent disorders, that was most often noticed first by the parents. At 6-9 months the detection rate of amblyopia was very low and amblyopia was caused by strabismus or strabismus combined with refractive disorder, none solely by refractive disorder, confirming the results of the RAMSES study. The total study population consisted of 10,622 children with 37,722 patient-years of on study exposure time and a 5 year follow-up. At the age of 6-24 months strabismus amblyopia and visually apparent eye disorders were mainly detected by the parents and were detected regardless of formal vision screening. Omission of routine preverbal eye screening tests between the age of 6-24 months did not lead to significant differences in amount of children referred, in total number of cases of amblyopia detected or in the severity of the detected amblyopia. Visual acuity measurements at 3-5 years yielded 3.2 times more amblyopia cases as compared to the screening between 6-24 months. Refractive amblyopia and bilateral amblyopia were detected almost exclusively by measurement of VA at the age of 36-60 months. The small difference in type of amblyopia between the groups, slightly more strabismus amblyopia and slightly less refractive amblyopia in the control group, could be explained by the age of diagnosis of amblyopia: children in the control group were diagnosed a bit earlier and because anisometropia tends to increase with age, children in the control group were more likely to be classified as amblyopic due to strabismus than amblyopic due to refractive error. These results have led to disinvestment of preverbal vision screening with orthoptic tests in the Netherlands as formulated in the revised CHC vision screening guideline.[9]

With the VA measurements, children will be referred and receive treatment well before the age of seven.[10] The quality of the VA measurements is of high importance to detect children in time for treatment. In the previous CHC vision screening guideline VA was measured by CHC physicians at 36 months with the Amsterdam Picture Chart (APK) and with Landolt C optotypes at 45 and 60 months according to thresholds formulated in the guideline. Visual acuity measurements at 36 months with the Amsterdam Picture Chart (APK) were analysed further because many considered the VA measurements with the APK as unreliable. Others believed that the percentage of failed VA measurements at the age of 36 months was too high. The latter proved to be correct. Visual acuity was measured in 8,661 eligible children from the OVAS sequential birth cohorts at 36 months. The measured VA was insufficient in 15.5% of children, whereas in another 16.6% the measurement failed altogether. If CHC doctors and nurses would have acted completely according to the CHC guideline, 32,1% of VA tests at 36

months of age should have been re-tested within 3 months. In practise re-testing was often postponed to the regular screen nine months later, at 45 months of age. This indicated non-adherence to the CHC guideline. Measurements of VA at the age of 36 months by CHC physicians cannot be recommended as a screening test in the general population. When these VA measurements would be performed by orthoptists, the failure rate would be lower, but this would however, be prohibitively expensive.

Due to the new insights provided by the model simulation, the OVAS disinvestment study and the large diversity in screening programmes, we were able to start the European Horizon-2020 study, EUSCREEN, to compare the cost-effectiveness of vison screening programmes in Europe. In this study the cost-effectiveness model is developed further and, guided and informed by the model, an implementation study of vision screening was started in Cluj Romania, where no population-wide vision screening exists. Out of 12,795 eligible four- and five-year-old children, 7,876 were screened. Screening in the cities was performed by resident nurses at the Kindergartens. Screening in rural areas was performed by GP nurses. The most conspicuous finding in the implementation study was that vision screening in rural areas was much more difficult than in urban areas. Cities in Romania have large kindergartens and all kindergartens have nurses, who were able to successfully measure VA at age 4 and 5 years. For nationwide implementation of vision screening in Romania, finding a feasible way to screen in rural areas is imperative, because 46% of the country's population lives in rural areas.

IMPACT

As a result of our study the following changes have been made to the Dutch vision screening guideline:

- In the age category 0-3 months pupillary reflexes are no longer assessed

- In the age category 6-24 months only Hirschberg (corneal light reflex), cover test and monocular pursuit are assessed. Eye motility, pupillary reflexes and alternating cover test are no longer performed. More emphasis is placed on the anamnesis

- At the age of 36 months the VA measurement is only performed on indication. The APK is no longer used, but replaced by the Lea Hyvarinen chart

- At the age of 45-60 months VA measurement is performed with the Tumbling E chart instead of the Landolt C chart

FUTURE RESEARCH

The VA measurements at 36 months are now only performed on indication. Orthoptists in the Netherlands have indicated that in the former screening guideline half of their referrals were due to the screening with VA measurements at 36 months and the other half were due to the VA measurements at 45 months. In ongoing research we will further evaluate the VA measurements at 45 months at the CHC centres with emphasis on the depth of amblyopia, because it is possible that the VA measurements at 36 months would have detected more deep amblyopia earlier.
Screening programmes throughout Europe are also under further investigation in the EUSCREEN study, as well as the further development of the model for optimisation, disinvestment or implementation of vision screening.

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English summary

Nederlandse samenvatting

ENGLISH SUMMARY

Vision screening programmes in Europe are very diverse. Large differences exist in age, tests used and frequency of testing (number of tests). To make an inventory of the current vision screening programmes in Europe, we developed a questionnaire, which we presented to vision screening experts in 36 countries in Europe. In most European countries infants aged 0-4 months are examined with inspection of the eyes and red reflex testing. In most European countries children aged 6-30 months are screened with a combination of two or more of the following tests; inspection of the eyes, fixation, red reflex testing, Hirschberg test, Bruckner test, Cover test, pupillary reflexes, monocular pursuit and motility, but these tests are seldomly performed by orthoptists. In all European countries visual acuity (VA) in children is measured, but the age of the first measurement varies between three and seven years of age. In a third of countries VA is tested once, in one third twice and in one third more than two times **(chapter 2)**.

In comparison with other vision screening programmes in Europe the Dutch vision screening programme stands out because of the number of screens performed. We modelled the effect of introduction, modification or disinvestment of a screening programme or its components with a micro-simulation model, with very detailed data from the RAMSES birth cohort study. The previous finding in the RAMSES birth cohort study that orthoptic tests at age 6-24 months yielded very few cases of amblyopia was confirmed by the micro-simulation model: The sensitivity and specificity of the entire screening programme was not appreciably affected by the omission of the 24 months screen **(chapter 3)**.

The fact that few children with amblyopia are detected by orthoptic tests, performed by non-orthoptists, at 6-24 months of age gave us the incentive to perform semi-structured observations of all vision screening tests, as defined in the Child healthcare (CHC) screening guideline, performed by CHC physicians. Tests that were more often performed at a very young age, like the Hirschberg test and the fundus red reflex, were performed in accordance with the guideline. Preverbal vision screening consisting of (alternating) cover test, pupillary reflexes, monocular pursuit and motility were not performed according to the guideline. Visual acuity measurements in older children (36- 45 months) were, by and large, performed in accordance with the guideline **(chapter 4)**.

To examine how many cases of amblyopia are detected by orthoptic test at 6-24 months the Optimisation of Amblyopia Screening study (OVAS) assessed whether the omission of orthoptic vision screening tests between age 6-24 months would impact the frequency, severity and age of detection of amblyopia. In this study two sequential birth cohorts, with and without vision screening, were followed up from six to 45 months of age. At the age of 6-9 months most children were referred to an orthoptist or ophthalmologist because of observed strabismus or visually apparent disorders, most often noticed by the parents. The detection rate of amblyopia was very low and concerned amblyopia caused by strabismus or caused by strabismus combined with refractive disorder, none solely caused by refractive disorder **(chapter 5)**.

The main outcome of this study was that at the age of 6-24 months strabismus amblyopia and visually apparent eye disorders are mainly detected by the parents before the age VA could be measured and are detected regardless of formal vision screening. Omission of routine preverbal eye screening tests between the age of 6-24 months in the Netherlands did not lead to significant differences in amount of children referred, in total number of cases of amblyopia detected or in the severity of the detected amblyopia. Refractive amblyopia and bilateral amblyopia are detected, almost exclusively, with the VA measurements between 36-60 months (**chapter 6)**.

As a secondary outcome of our study we analysed the effectiveness of VA measurements at 36 months with the dated Amsterdam picture chart (APK). Measured VA at 36 months with the APK did not reach threshold in 15.5% of the children, and the measurements themselves failed altogether in another 16.6% of the children. Referral or repeat testing of 1/3 of children is not feasible and on that basis VA measurements at 36 months are no longer performed routinely (**chapter 7**).

Inspired by the success of the disinvestment study of selected parts of the screening we initiated a pan-European comparison of vision screening programmes in all countries in Europe. Aim of this study is to develop the micro-simulation model further. Guided by and alongside the development of this model an implementation study of vision screening was started, with VA measurement at four and five years, in county Cluj, Romania, where no vision screening is performed routinely yet. The most conspicuous finding in this implementation study was that vision screening in rural areas was much more difficult than in urban areas. In urban areas the kindergartens have resident nurses and the children could be easily screened by these nurses, that they know and trust. In rural areas the kindergartens do not have nurses, the number

of children per village is small, healthcare is much less developed than in cities and the awareness of the usefulness of preventive healthcare among parents is low. For nationwide implementation of vision screening in Romania and other low and middle income countries that have no vision screening yet, screening in rural areas is the most important stumble bloc, for which a solution must be found (chapter 8).

NEDERLANDSE SAMENVATTING

In **Hoofdstuk 1** wordt in een algemene introductie amblyopie, de concepten van screening en het Nederlandse oogheelkundige screeningssysteem beschreven. Daarnaast wordt de RAMSES studie beschreven, welke de aanleiding vormde voor de optimalisatie van amblyopie screening (OVAS) studie.

Oogscreeningsprogramma's in Europa zijn erg divers. Grote verschillen bestaan in leeftijd, type screeningstest en aantal tests. We hebben een vragenlijst ontwikkeld om een overzicht te kunnen maken van de huidige oogscreeningsprogramma's in Europa, welke door experts uit 36 landen in Europa werd ingevuld. In de meeste Europese landen worden kinderen op de leeftijd van 0-4 maanden onderzocht door middel van inspectie van de ogen en het testen van de rode fundus reflex. In de meeste Europese landen worden kinderen in de leeftijd van 6-30 maanden gescreend door middel van een combinatie van twee of meer van de volgende (orthoptische) tests: inspectie van de ogen, fixatie, rode fundus reflex, Hirschberg test (cornea licht reflex), Bruckner test, (alternerende) Cover test, pupil reacties, monoculaire volgbeweging en motiliteitstest. Deze tests worden echter zelden uitgevoerd door orthoptisten. In alle landen in Europa wordt bij kinderen de visus gemeten, de leeftijd van de eerste meting verschilt echter tussen drie en zeven jaar oud. In een derde van de landen wordt de visus één keer gemeten, in een derde twee keer en in een derde van de landen drie keer **(hoofdstuk 2).**

In vergelijking met andere oogscreeningsprogramma's valt het Nederlandse screeningsprogramma op door de hoeveel tests die worden uitgevoerd. Met een micro-simulatie model hebben we het effect van introductie, verandering en disinvestering van (delen van) het oogscreeningsprogramma gemodelleerd, gebruik makend van de gedetailleerde gegevens uit de RAMSES geboortecohort studie. De eerdere uitkomst van de RAMSES geboortecohort studie dat orthoptische tests op de leeftijd van 6-24 maanden weinig gevallen van amblyopie (lui oog) opspoorden werd bevestigd door de model simulatie: de sensitiviteit en de specificiteit van het gehele oogscreeningsprogramma werd nauwelijks beïnvloed door het weglaten van de screening op de leeftijd van 24 maanden **(hoofdstuk 3)**.

Het feit dat weinig kinderen met amblyopie ontdekt werden door de orthoptische tests, uitgevoerd door niet orthoptisten, op de leeftijd van 6-24 maanden was voor ons de aanleiding om semi-gestructureerde observaties uit te voeren van

alle oogscreeningstests uitgevoerd door artsen en verpleegkundigen op het consultatiebureau, zoals beschreven in de richtlijn Jeugdgezondheidzorg. Tests die meestal uitgevoerd werden op een hele jonge leeftijd, zoals de Hirschberg en de rode fundus reflex tests, werden uitgevoerd conform de richtlijn. Preverbale oogscreening, bestaande uit de (alternerende) Cover test, pupilreacties, monoculaire volgbeweging en motiliteitstest werden niet uitgevoerd conform de richtlijn. De visus metingen in oudere kinderen (36-45 maanden) werden over het algemeen wel uitgevoerd conform de richtlijn **(hoofdstuk 4)**.

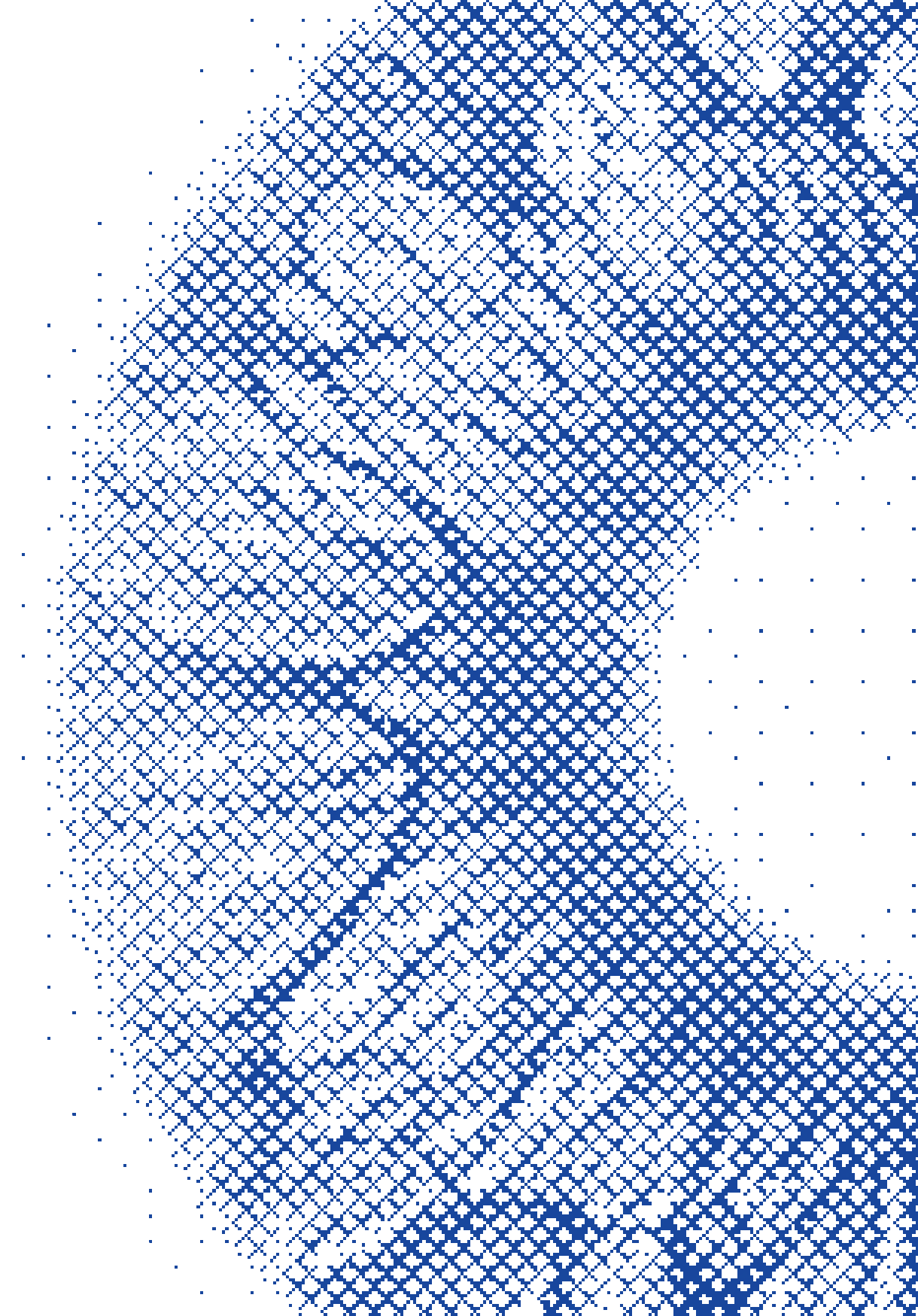
Om te onderzoeken hoeveel gevallen van amblyopie ontdekt worden door de orthoptische tests op de leeftijd van 6-24 maanden heeft de Optimalisatie Van Amblyopie Screening (OVAS) studie onderzocht of het weglaten van de routinematige screening op de leeftijd van 6-24 maanden geen negatief effect zou hebben op de ernst, leeftijd van diagnose en gevonden aantallen van amblyopie. In deze studie werden twee opvolgende geboortecohorten, met en zonder specifieke oogscreening, gevolgd van de leeftijd van 6 tot 45 maanden op het consultatiebureau. Op de leeftijd van 6-9 maanden waren de meeste verwijzingen naar een orthoptist of oogarts vanwege strabismus (scheelzien) of andere zichtbare oogafwijkingen, meestal opgemerkt door de ouders. Er werden maar weinig gevallen van amblyopie ontdekt en alle amblyopie bleek veroorzaakt door strabismus of door strabismus gecombineerd met refractie (brilsterkte verschil) amblyopie. Geen enkele amblyopie werd veroorzaakt door alleen een brilsterkte afwijking **(hoofdstuk 5)**.

De belangrijkste uitkomst van de OVAS studie was dat op de leeftijd van 6-24 maanden, de leeftijd voordat een visusmeting gedaan kan worden, strabismus amblyopie en andere zichtbare oogafwijkingen vooral opgemerkt werden door de ouders, los van formele oogscreening. Het weglaten van de routinematige preverbale oogscreeningstests op de leeftijd van 6-24 maanden in Nederland heeft niet geleid tot een significant verschil in de hoeveel verwezen kinderen, het totale aantal ontdekte gevallen van amblyopie of de ernst van de ontdekte amblyopie. Refractie amblyopie en bilaterale amblyopie werden bijna uitsluitend ontdekt door de visus metingen tussen 36 en 60 maanden **(hoofdstuk 6)**.

Als een tweede uitkomst van de studie hebben we de effectiviteit van de visus metingen met de verouderde Amsterdamse plaatjeskaart (APK) op de leeftijd van 36 maanden bestudeerd. In 15.5% van de visus metingen op de leeftijd van 36 maanden werd de drempel niet gehaald. In 16.6% mislukt de gehele visusmeting. Verwijzing of

herhaling van 1/3e van de visusmetingen is niet haalbaar en op grond daarvan wordt deze meting niet langer meer routinematig uitgevoerd op het consultatiebureau (**hoofdstuk 7**).

Geïnspireerd door het succes van de desinvesteringsstudie OVAS zijn we gestart met een Europese vergelijking van oogscreeningsprogramma's in heel Europa. Het doel van deze studie is om het micro-simulatie model verder te ontwikkelen. Begeleid door en gelijktijdig met de ontwikkeling van het model werd een implementatie studie gestart om visus metingen uit te voeren op de leeftijd van vier en vijf jaar in Cluj, Roemenië, waar nu nog geen screening plaatsvindt. De meest opvallende bevinding in deze implementatie studie was dat het implementeren van visus metingen in rurale gebieden veel moeilijker bleek te zijn dan het invoeren van visus metingen in stedelijke gebieden. In stedelijke gebieden zijn verpleegkundigen verbonden aan de kinderdagverblijven en deze verpleegkundigen konden makkelijk kinderen screenen omdat de kinderen deze verpleegkundigen al kenden en ze vertrouwden. In rurale gebieden waren geen verpleegkundigen verbonden aan de kinderdagverblijven, het aantal kinderen per dorp was laag, de gehele gezondheidszorg was veel minder ontwikkeld dan in de steden en de kennis over preventieve gezondheidszorg was laag bij ouders. Voor landelijke implementatie van visus metingen in Roemenië en andere landen met een laag en midden inkomen waar nog geen oogscreening bestaat, is het opzetten van screening in de rurale gebieden het grootste struikelblok waar een oplossing voor gevonden moet worden (**hoofdstuk 8**).



Appendices

ABOUT THE AUTHOR

Frea Sloot was born on the 3th of January 1986 in Haarlem, the Netherlands. She graduated from secondary school at Mendelcollege, Haarlem in 2004. The same year she started medical school at Utrecht University. During her fourth year she completed an internship in gynaecology at Dr. Horacio E. Oduber Hospital, Aruba. In her sixth year a corneal crosslinking project was her first real research encounter under supervision of dr. N.G. Tahzib and dr. A. van der Lelij. After obtaining her medical degree in 2010 she worked at the Central Military Hospital in Utrecht as a Ophthalmology resident (ANIOS) (supervision: colonel dr. D.F. Schaling).

In December 2012 she started the work described in this thesis at the department of Ophthalmology at the Erasmus Medical Center in Rotterdam under the supervision of prof. dr. H.J. Simonsz. She has presented her work at several national and international meetings. She actively participated in the granted Horizon 2020 EUSCREEN research application and in the revision of the national child healthcare vision screening guideline.
In October 2016 she started her residency in Ophthalmology at the department of Ophthalmology at the Erasmus Medical Center, headed by prof. dr. J.R. Vingerling.

PHD PORTFOLIO

Summary of PhD training and teaching

Name PhD student: F. Sloot
Erasmus MC Department: Ophthalmology
PhD period: Dec 2012 – Dec 2020
Promotor(s): Prof. dr. H.J. Simonsz, prof. dr. Vingerling
Supervisor: Prof. dr. H.J. Simonsz

1. PhD training

	Year	Workload (ECTS)
General courses		
- Statistics: Biostatistical Methods I: Basic Principles Part A (CC02A), NIHES	2013	2.0
- Systematic literature and Endnote Medical Library	2013	1.0
- Biomedical English Writing and Communication	2014	3.0
- Research Integrity	2014	0.3
Specific courses		
- Planning and Evaluation of Screening (HS05), NIHES	2013	1.4

Presentations at (Inter)national conferences		
- Nederlands Oogheelkundig Gezelschap (NOG) annual meeting, Groningen, the Netherlands: oral presentation	2013	1.0
- Association for Research in Vision and Ophthalmology (ARVO) annual meeting, Seattle, USA: poster presentation	2013	1.0
- Bielschowsky Gesellschaft, Leipzig, Germany: oral presentation	2013	1.0
- Child Vision and Research Society (CVRS) meeting, Waterloo, Canada: poster presentation	2013	1.0
- Turkish Ophthalmology Society 47th National Congress, Antalya, Turkey: oral presentation	2013	1.0
- Dutch Ophthalmology PhD students (DOPS) congress, Nijmegen, the Netherlands: oral presentation	2014	1.0
- Nederlands Oogheelkundig Gezelschap (NOG) annual meeting, Maastricht, the Netherlands: oral presentation	2014	1.0
- Association for Research in Vision and Ophthalmology (ARVO) annual meeting, Orlando, USA: oral presentation	2014	1.0
- Dutch Ophthalmology PhD students (DOPS) congress, Nijmegen, the Netherlands: oral presentation	2015	1.0
- Nederlands Oogheelkundig Gezelschap (NOG) annual meeting, Groningen, the Netherlands: oral presentation	2015	1.0
- Association for Research in Vision and Ophthalmology (ARVO) annual meeting, Denver, USA: poster presentation	2015	1.0
- European Strabismological Association (ESA) meeting, Venice, Italy: oral presentation	2015	1.0
- Child Vision and Research Society (CVRS) meeting, Prague, Czech Republic: oral presentation	2015	1.0
- Nederlands Oogheelkundig Gezelschap (NOG) annual meeting, Maastricht, the Netherlands: oral presentation	2016	1.0
- Association for Research in Vision and Ophthalmology (ARVO) annual meeting, Seattle, USA: oral presentation	2016	1.0
- World Society of Paediatric Ophthalmology and Strabismus (WSPOS) meeting, Copenhagen, Denmark: oral presentation	2016	1.0
- Nederlands Oogheelkundig Gezelschap (NOG) annual meeting, Maastricht, the Netherlands: oral presentation	2017	1.0
- Child Vision and Research Society (CVRS) meeting, Coleraine, Northern Ireland, oral presentation	2017	1.0

(Inter)national conferences, seminars and workshops		
- Bielschowsky Gesellschaft, Germany	2012 & 2014	1.0
- Nederlands Oogheelkundig Gezelschap (NOG) annual meeting, Maastricht, the Netherlands	2019	0.5
Other Presentations		
- Weekly ophthalmology meetings, Erasmus MC Rotterdam, the Netherlands, 2 oral presentations		1.0
- MGZ seminar, Erasmus MC Rotterdam, the Netherlands, oral presentation		0.5
Teaching: Supervising practicals (medical students)		
- Ophthalmology practical medical students, twice	2013 & 2014	0.3
- Supervision two Orthoptic students of the University of Applied Sciences Utrecht, dept. of Orthoptics, NL	2013	3.0
Other		
- Horizon 2020	2014-2020	25.0
- Richtlijn JGZ	2015-2019	5.0

LIST OF PUBLICATIONS

1. Sloot F, Soeters N, van der Valk R, Tahzib NG. Effective corneal collagen crosslinking in advanced cases of progressive keratoconus. J Cataract Refract Surg. 2013 Aug;39(8):1141-5
2. Paes EC, Mink van der Molen AB, Muradin MS, Speleman L, Sloot F, Kon M, Breugem CC. A systematic review on the outcome of mandibular distraction osteogenesis in infants suffering Robin sequence. Clin Oral Investig. 2013 Nov;17(8):1807-20
3. Sloot F, Hoeve HL, de Kroon ML, Goedegebure A, Carlton J, Griffiths HJ, Simonsz HJ; EUS€REEN Study Group. Inventory of current EU paediatric vision and hearing screening programmes. J Med Screen. 2015 Jun;22(2):55-64
4. Sloot F, Sami A, Karaman H, Benjamins J, Loudon SE, Raat H, Sjoerdsma T, Simonsz HJ. Effect of omission of population-based eye screening at age 6-9 months in the Netherlands. Acta Ophthalmol. 2015 Jun;93(4):318-21
5. Sloot F, Heijnsdijk E, Groenewoud JH, Goudsmit F, Steyerberg EW, de Koning HJ, Simonsz HJ. The effect of omitting an early population-based vision screen in the Netherlands: A micro-simulation model approach. J Med Screen. 2017 Sep;24(3):120-126
6. Sloot F, Sami A, Karaman H, Gutter M, Benjamins J, Sjoerdsma T, Simonsz HJ. Semistructured Observation of Population-based Eye Screening in The Netherlands. Strabismus. 2017 Dec;25(4):214-221
7. Telleman MAJ, Sloot F, Benjamins J, Simonsz HJ. High rate of failed visual-acuity measurements with the Amsterdam Picture Chart in screening at the age of 36 months. Acta Ophthalmol. 2019 Feb;97(1):24-28
8. Raat H, Schalij-Delfos NE, Simonsz HJ, Lanting CI, Sloot F, Sami A, van den Toren SJ. Richtlijn Opsporen oogafwijkingen. Nederlands Centrum Jeugdgezondheid 2019
9. Sloot F, Telleman MAJ, Benjamins SJ, Sami A, Hoogendam JP, Simonsz HJ, Orthoptic research group. Effectiveness of routine population-wide orthoptic preschool vision screening tests at age 6-24 months in the Netherlands. Acta Ophthalmol. 2021 April. Online ahead of print
10. Kik J, Nordmann M, Cainap S, Mara M, Rajka D, Ghițiu M, Vladescu A, Sloot F, Vladutiu C, Horwood A, Fronius M, Simonsz HJ. Implementing vision screening in urban and rural Cluj County in Romania. Submitted
11. Verkleij ML, Heijnsdijk EAM, Bussé AML, Carr G, Goedegebure A, Mackey AR, Qirjazi B, Uhlén IM, Sloot F, Hoeve HLJ, de Koning HJ, on behalf of Country-Committees Joint-Partnership of EUSCREEN Study Consortium. Cost-effectiveness of neonatal hearing screening programs: a micro-simulation modelling analysis. Ear Hear 2020 Nov Online ahead of print