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Can vision screening in Dutch Youth Health Care (YHC) be improved by adding an autorefraction test – a feasibility study

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Summary
BACKGROUND AND RELEVANCE
The primary goal of vision screening in young children is the detection of amblyopia, also referred to as "lazy eye", and risk factors for development of amblyopia requiring treatment. Amblyopia is a neurological deficit in vision that is estimated to affect 2-5% of children. Child vision screening, a task of preventive Youth Health Care (YHC) in the Netherlands, reduces the prevalence of amblyopia. Current Dutch vision screening is performed using charts with symbols. These tests are time consuming, difficult to administer in young children and probably of low prognostic value. Instrument-based vision screening by means of a autorefractive device on the other hand is quick, and requires minimal cooperation of the child and could therefore be more efficient. Several studies suggest that screening using an autorefractive device may be a useful strategy to detect amblyopia in young children. However, to date, none have studied the performance and costs in regular Dutch YHC practice, and compared these outcomes with current practice.

AIM
Aim of this research project is to establish whether the current Dutch vision screening in children aged 3-6 years old in YHC can be improved by using an autorefractive device, with regard to screening performance and costs. We also compare screening performances in specific subgroups of children (i.e. younger children, children with poor fluency of the Dutch language such as children with a migration background, and children with language difficulties or limited intellectual functioning). Finally, we assess the feasibility and acceptability of using an autorefractive device in daily YHC practice.

METHODS
Our population-based, cross-sectional cost-effectiveness study was performed at five YHC locations in The Hague. Children aged 3-6 years got the standard YHC vision screening, with the Amsterdam Picture chart (APK) at the age of 3 years (3y) and the Landolt-C (LC) at the ages of 3 years and 9 months (3y9m) and 5 or 6 years (5/6y). As part of standard care, in some children the VOV test (eye inspection and assessment of pupil responses, cornea light reflex, cover tests and eye movements) was also done. For the study, the children were additionally screened with an autorefractive device,

in this study the Plusoptix S12C Mobile Vision Screener® (PO). After an insufficient vision screening result or a 'refer' on the Plusoptix, children were referred for diagnosis by an orthoptist at Haaglanden Medical Center (HMC).
In a parallel part of this study, orthoptists in this clinic performed the current YHC vision screening tests as well as a test with the Plusoptix in other children aged 3-6 years who visited the clinic. These data were used to estimate the sensitivity of the tests.
Focus group discussions among YHC professionals and interviews of parents were performed to assess the feasibility and acceptability of using an autorefractive device in daily YHC practice.
The main target group of screening, i.e. children with amblyopia, was defined as having 'amblyopia' in the initial diagnosis, and/or having 'occlusion' in the therapy, and/or getting the diagnosis 'amblyopia' after a 13-weeks period of refractive adaptation.

RESULTS
At the YHC, 2,144 children were included. With the current YHC vision screening, 14% needed a referral for diagnosis at the clinic. 69% of the referred children arrived at the clinic, and 14% of the arrived children (29) were detected with amblyopia (lazy eye, all ages combined). With the Plusoptix test, less children (7%) needed a referral for diagnostics, a similar percentage (66%) arrived at the clinic, and 25% of children that arrived at the clinic (23) were detected with amblyopia.

Mean time needed for the screening tests was higher in younger than in older children, but at each age (3 years, 3 years and 9 months and 5/6 years, in short 3y, 3y9m and 5/6y) the Plusoptix test took on average less than half of the time needed for the vision chart tests (table S1).

Table S1. Average costs per child per test and per age group

	Mean time needed per test (minutes)		**Mean costs per child screened (€)**	
	First vision chart test	**Plusoptix**	**Current vision screening***	**Plusoptix**
3 years (n=788)	5.8	2.2	17.77	6.61
3 years 9 months (n=731)	5.2	2.0	20.39	7.51
5/6 years (n=625)	3.1	1.1	6.89	9.41

* including costs of clinical consultation, excluding an occasionally performed VOV test

Compared to the current vision screening, costs are less for the Plusoptix test at the ages of 3y and 3y9m, but higher at the age of 5/6y (table S1). In this older age group, the vision chart test is performed quicker than at younger age, and more often results in a sufficient outcome and thus no need for a follow-up visit at YHC or a referral for diagnostics, which both reduce the costs at 5/6y. Also, at 5/6y the Plusoptix screening devices were used less efficiently than at age 3y and 3y9m, as due to a different screening setting about half as many children per device were screened at age 5/6y. This explains the higher costs for screening with the Plusoptix at 5/6y.

As with both screening methods children with amblyopia remained undetected, we investigated if combining both ways of screening was worthwhile. The results of the VOV test did not lead to detection of children with amblyopia, therefore these test results and costs were omitted in this analysis.

3y. For children aged 3y current vision screening with the APK is not recommended for the detection of children with amblyopia, as total costs for screening this age group are high, and YHC physicians mentioned that the APK is often difficult to perform. Screening with the PO at 3y should be considered, especially if PO devices are already present at the YHC. If the costs of the PO are already attributed to the screening at age 3y9m, the costs for screening with the PO at the age of 3y

and thus detecting already part of the children with amblyopia are €562 per child detected with amblyopia at the early age of 3 years.

3y9m. A combination of both tests seems most attractive for children aged 3y9m. In this screening alternative named POLC1, all children are screened with the autorefractive device, and all children with a 'refer' result are referred to the orthoptist. Only children with a 'refer or try again' result (i.e. no 'pass' or 'refer' result could be obtained) get a vision chart test. Costs per child screened (€11.82) are far less than for the current vision screening (€20.39), and almost all children of who we know they have amblyopia were detected at costs of €570 per child detected. Also, with POLC1 only 61 children instead of 122 with the current vision screening would need a referral to the clinic for diagnosis.

5/6y. All calculated alternatives have higher costs than the current vision screening guideline. The alternative LC&PO, in which all children are tested with PO as well as Landolt-C, detected 2 children with amblyopia who were missed with the current vision screening (which detected 6 children). The incremental costs compared to the current guideline for finding these two children are €1,650 per child. Costs per child screened are €12.30 in this alternative, versus €6.89 in the current vision screening without the VOV-test. With LC&PO 68 would need a referral to the clinic for diagnosis, whereas this is 40 with the current vision screening.

Test characteristics.

The test characteristics of the current Dutch vision screening as well as the screening by Plusoptix to detect children with amblyopia were difficult to assess, because about one-third of the children who were test positive and thus needed a referral did not go for further diagnostic evaluation. Therefore, in these children the diagnosis of amblyopia (yes or no) was unknown. An overview of the test estimates is given in table 29. Sensitivity and the positive predictive value (PPV) of a single APK, Landolt-C and Plusoptix test to detect children with amblyopia are comparable, while specificity of the Plusoptix test is higher than specificity of the vision chart tests.

Table 29. Overview of estimated test characteristics to detect children with amblyopia, in %

	PPV best estimate (min-max)	Sensitivity* (95%CI)		Specificity min/max (95%CI) at prevalence of 3%
		Clinical study	Dev./language problems, clin. study	
APK	12.8 (4.8-67.3)	Not estimated	Not estimated	86.0 (83.2-88.5) / 87.2 (84.4-89.5)
LC	17.8 (10.3-52.4)	67 (51-80)	71 (30-95)*	86.9 (84.9-88.7) / 88.0 (86.1-89.7)
PO	25.0 (16.4-50.7)	63 (49-75)	75 (43-93)*	94.4 (93.3-95.3) / 94.9 (93.9-95.8)

LC: Landolt-C, PO: Plusoptix, PPV: positive predictive value.

*in children with a test result. Only about half (7 of 13) of the child with a developmental of language problem had a test result on the Landolt-C, whereas 12 of 13 had a result on the Plusoptix.

Background characteristics.

Age. The effect of age on vision screening results and costs is large, and therefore age-specific recommendations are needed.

Language and developmental problems. Based on 49 included children with language or developmental problems, screening with Plusoptix gives less false-positive test results that the current YHC vision screening.

Ethnic background. For children with a Western background (n=818) as well as for children with a non-Western background (n=951), at age 3y and 3y9m the Plusoptix more often had a sufficient result ('pass') than the vision chart test. For both ways of screening, more non-Western than Western children needed a referral for diagnostics. 1.3% of Western and 2.0% of non-Western children were detected with amblyopia, but this difference was not statistically significant (p=0.33).

Costs of screening and diagnosis were lower for Western children compared to the group of all children, for vision screening as well as for screening with the Plusoptix.
SES. As a marker for social-economic status (SES), we only have data on education of both parents. The percentage of insufficient results at the vision chart test and 'refer' on the Plusoptix is higher at a low maternal educational level than at a high education level at the ages of 3y and 3y9m, and for the Plusoptix also at 5/6y. However, there is no reason to develop SES-specific recommendations for vision screening.

Feasibility and acceptability.
Based on qualitative research methods among YHC professionals and parents, it seems that the Plusoptix is feasible and acceptable in practice.

DISCUSSION
In comparison to the current vision screening, more cost-effective alternatives using an autorefractive device are available for the age groups of 3 years and 3 years and 9 months.
For the interpretation of the study results, it should be kept in mind that the estimated costs of screening and diagnostics in an age group and the costs per screened child are based on a large number of children and are thus reliable. However, costs per child detected with amblyopia and incremental costs for detecting additional children with amblyopia while comparing various screening alternatives are less reliable, as the number of children detected with amblyopia is small.
In comparing various screening alternatives, especially the total costs per age group or costs per screened child are useful to compare, while it is good to have in mind that the performance of the screening in terms of number of children detected may deviate somewhat from our findings due to coincidence. Furthermore, costs per child for the autorefractive devices depend on the number of children screened per device. This likely will vary per YHC location.
Costs of screening and diagnosis were lower for Western children than for non-Western children. Because our study population has more children with a non-Western background (about 50%) in comparison to the Netherlands as a whole (about 16%), extrapolation of the costs to the Dutch population will result in lower costs per child screened than presented in our study.
Children with language and developmental problems may benefit from screening with the Plusoptix, as the vision charts caused more unnecessary referrals to the clinic than the Plusoptix.

The YHC guideline for vision screening is currently under revision. In the concept revised guideline, the APK test and VOV are being omitted. Our data support these changes. However, in the concept revised guideline, no screening is present at all at the age of 3y, and a vision chart test (E-hooks instead of Landolt-C) is recommended for all children aged 3y9m and 5/6y. Whereas our findings support using a vision chart test at the age of 5/6 years, we found alternatives that are more cost-effective compared to vision screening for the age group of 3y9m. In the best alternative at 3y9m all children are screened with the PO, and all children with a 'refer' result are referred to the orthoptist to get extensive vision diagnostic tests. Only children with a 'refer or try again' result get a vision chart test in the YHC setting. Children with a 'pass' on the PO do not get a vision chart test at the age of 3y9m, but all get it at a later age (5/6y). We heard hesitations for this recommendation from orthoptists and ophthalmologists, who prefer a functional vision test like the vision chart test for all children at the age of 3y9m as they are afraid that autorefraction tests will miss certain risk factors for amblyopia, like microstrabismus. However, our findings show that with our recommendation similar numbers of children with amblyopia are detected at much lower cost, and thus are a better alternative. And if part of the children with specific deviations are missed using autorefractive tests, they will get a vision chart test at the age of 5/6 y. We agree that it is better to detect the children at an earlier age, but our findings indicate that not many children aged 3y9m will get this delayed detection. However, screening with the PO at 3y should be considered, especially if PO devices are already present at the YHC, to already detect part of the children with amblyopia at a young age. Our recommendations are also in accordance with the recommendations of the USPSTF (2011) and

AAPOS (2012) to give each child at least one vision screening between the ages of 3 and 5 years, to detect the presence of amblyopia or its risk factors. These institutes indicate that at younger age autorefractive testing might be an alternative to vision charts at the age of 3 through 5 years.

Implementation of the recommended screening alternatives at 3y and 3y9m will require investments of the YHC organizations, as they will need to purchase the autorefractive devices. The cost savings are distributed over two parties. The YHC has cost savings as YHC professionals will need less time to perform the vision screening, but also insurance companies will save substantial costs as less children will need a referral to the clinic for diagnostic evaluation. Of the total costs for vision screening per age group, about half is caused by the clinical consultations. Thus, a successful implementation with cost savings is of interest for not only YHC, but also the insurance companies.

CONCLUSION AND RECOMMENDATIONS

Our results imply that vision screening in Dutch Youth Health Care can be improved by adding an autorefraction test. We recommend adaptation of the current vision screening as follows:

1) Omit the VOV test as a structural component of a vision screening protocol. Perhaps it has value when used on indication.
2) Omit the APK screening test. Instead use an autorefractive device at the age of 3 years to already detect part of the children with amblyopia.
3) Screen all children at the age of 3 years and 9 months with an autorefractive device. Refer all children with a 'refer' result to the orthoptist, and test the children with a 'refer or try again' result (i.e. no 'pass' and no ' refer') with a vision chart test like the Landolt-C test. If the result on the vision chart test is insufficient, refer to the orthoptist; if the result is 'doubtful', repeat vision screening at a second visit; and if the result is 'sufficient' no further action is needed. Also, if the result of the test with the autorefractive device is a 'pass', no further action is needed.
4) Screen all children at the age of 5 or 6 years with a vision chart test like the Landolt-C test (as in the current vision screening).

The results of this study will be shared with the developers of the update of the Vision Screening Guideline for YHC, which is scheduled to take place in 2016-2018.

Contents

1. Introduction

1.1 Amblyopia

Amblyopia, also referred to as "lazy eye", is a neural deficit in vision that is estimated to affect 1.0% to 5.0% of children (Lola Solebo, 2015). In a Dutch study, amblyopia was diagnosed in 3.4% (95% CI 2.7–4.0) of children aged 0-7 years (Groenewoud, 2010). The origin of the condition is believed to be found in early visual development, where form deprivation or abnormal binocular interaction leads to cortically deprived vision (Flynn, 1991). Amblyopia can be caused by obscured images (e.g. from infantile cataracts, ptosis), misaligned images (e.g. from constant strabismus), or defocused images (e.g. from different refractive error between the eyes, termed anisometropia) (Ehrt, 2012). The hallmark of amblyopia is decreased visual acuity, typically monocular, for which no ocular structural disorder fully accounts and which cannot be counteracted by correction with glasses. Randomized clinical trials have shown that treatment, usually patching, improved visual acuity of the amblyopic eye among children with amblyopia risk factors (e.g., strabismus or anisometropia; Jonas, 2017).

1.2 Vision Screening

1.2.1 Goal of vision screening

The goal of child vision screening in general is to detect subnormal vision or risk factors that threaten visual development, preferably at a time when treatment can be initiated to yield the highest benefit. The primary goal of vision screening by Dutch Preventive Youth Health Care (YHC) in young children is the detection of amblyopia and risk factors for development of amblyopia requiring treatment (Coenen, 2010). Refraction errors are not especially targeted, but are inevitably detected during the process.

1.2.2 Role of Dutch Preventive Youth Health Care (YHC)

Vision screening reduces the prevalence of amblyopia in the Netherlands (Groenewoud, 2010). In the Netherlands, child vision screening is a task of preventive Youth Health Care (YHC).
Vision screening is performed according to a national guideline and consists of a series of consecutive screening examinations until the age of 7 years (www.NCJ.nl, Coenen 2010). Among children aged 3 to 6 years, YHC performs vision acuity screening with chart tests during the routinely performed health assessments at the ages of 3 years (3y), 3 years and 9 months (3y9m) and 5 to 6 years (5/6y). YHC refers children who are of concern to an orthoptist or ophthalmologist for clinical consultation. However, YHC professionals in the Netherlands find these tests time consuming. Also, inability of children to cooperate may limit the use of some tests, especially in the younger age groups and in children with a limited intellectual functioning (Jonas 2017, Iyer 2017 (in Dutch)). Other important issues about the current child vision screening include serious doubts about the prognostic value.

1.2.3 Autorefractive devices

In contrast to the current vision screening by means of a vision chart, instrument-based vision screening using an autorefractive device, is quick and requires minimal cooperation of the child, as the child only has to look to the device for a short period of time (AAP, 2012). This allows for earlier detection of risk factors that can lead to amblyopia in children, especially for those children who are unable or unwilling to cooperate. E.g. Salcido (2005) concluded that photoscreening is more time efficient than traditional screening and has a significantly higher positive predictive value (PPV) in 3- and 4-year-old children. A recent evidence report from the USPSTF shows promising diagnostic accuracy for autorefractors (Jonas 2017, supplemental etable 10). A disadvantage of autorefractive devices in comparison with chart tests is that the autorefractive device only measures eye characteristics like refraction, but not vision itself. Retinal and optic nerve abnormalities, as well as

disturbed signal transfer from the eye to the brain or signal processing in the visual cortex may remain unnoticed with autorefractive devices.

1.3 Research questions

To be effective, screening tests must be able to be administered successfully to a high proportion of children (high testability), be able to identify a high proportion of children who have a vision disorder (high sensitivity), and also be able to identify as normal a high proportion of children who do not have a vision disorder (high specificity). International studies with autorefractive devices have shown promising results. A cost analysis should be performed before broad-scale implementation can be considered.

Therefore, the aim of the current research project is to establish whether current Dutch vision screening in children aged 3-6 years old in YHC can be improved by using an autorefractive device, with regard to costs and effects. Also the effectiveness of both screening options for specific subgroups of children (i.e. younger children, children with poor fluency of the Dutch language such as children with a migration background, and children with language difficulties or limited intellectual functioning) is determined.

The research questions are:

1) What is the validity (sensitivity, specificity, positive predictive value) of the current Dutch vision screening as well as the screening by the autorefractive device Plusoptix (PO), in children aged 3y, 3y9m and 5/6y, to detect amblyopia or risk factors for amblyopia requiring treatment?
2) What are costs and effectiveness of using Plusoptix in YHC practice as compared to the current Dutch vision screening?
3) What is the feasibility and acceptability of using Plusoptix in YHC practice among professionals and parents, compared to current Dutch vision screening?
4) Is it possible to improve the current Dutch vision screening in specific subgroups of children (e.g. migrants, lower SES and intellectual disability, various ages) by screening with Plusoptix, with regard to costs and effects?
5) Is it possible to improve the current referral criteria as defined by the American Association for Pediatric Ophthalmology and Strabismus (AAPOS) to enhance screening performance of the Plusoptix in The Netherlands?

2. Methods

2.1 Design and setting

Our population-based, cross-sectional study was performed at five YHC locations in The Hague, with different population profiles. Two areas (Haagse Hout and Loosduinen) mainly have a native Dutch population, while in the other areas (Escamp, Centrum and Laak) a large part of the population has a non-Dutch ethnic background. Children received regular care, including standard vision screening (i.e. Amsterdam Picture chart (APK) or Landolt-C vision test), and were additionally screened with Plusoptix S12C Mobile Vision Screener® (abbreviated as Plusoptix in the rest of this document). If the results of the standard vision screening and/or the Plusoptix indicated the need for diagnostic evaluation by an orthoptist, children were referred to one of the three locations of Haaglanden Medical Centre and Bronovo-Nebo, also in The Hague (HMC). This first part of the study is called the cost-effectiveness study. Of all included children and their parents background variables are registered in order to be able to compare study group characteristics with national statistics to determine generalizability to the Dutch population.

Besides this cost-effectiveness study, in a different group of participants a clinical study was performed to determine the sensitivity of the tests. In this clinical study orthoptists from HMC performed the tests that were also performed by YHC, i.e. measurement with the Plusoptix device and the APK or Landolt-C vision test, in a clinical population of 3-6 year-olds, where (risk factors for) amblyopia are highly prevalent and already known in magnitude. Children that already participated in the cost-effectiveness study could not participate in the clinical study.

Lastly, focus group discussions and interviews were performed to determine the feasibility and acceptability of using the Plusoptix in practice and to determine the acceptability of the results from both types of screening. Two focus group discussions were held with YHC professionals, and the interviews were done by telephone with parents (see '2.6.6 Qualitative research methods' for more details).

2.2 Data collection

Among children aged 3 to 6 years, YHC routinely performs health assessments at the ages of 3 years (3y), 3 years and 9 months (3y9m) and 5 to 6 years (5/6y). During a period of 6 months, from 1 September 2016 to 10 March 2017, all parents of children aged 3 to 6 years who were invited for these regular YHC visits at the study locations were sent an information leaflet about the study together with the invitation. When they arrived, the YHC assistant informed them again about the study, and invited them to participate voluntarily. Children that had known eye or vision problems (e.g. wearing glasses or being already known at an eye clinic) and children whose parents did not give consent were excluded from the study. Parents of the study participants signed an informed consent form.
For the clinical study children aged 3-6 years who visited an orthoptist at the Haaglanden Medical Centre and Bronovo-Nebo were included when their parents/guardians gave written informed consent. Data about these children were collected for one year, from 19 September 2016 to 29 September 2017. The reason why these children visited HMC could be various, e.g. parents noticed possible eye or vision problems and obtained a referral from the general practitioner or the YHC physician, the standard vision screening by YHC at a location that did not participate in the study gave reasons for referral, or children were already seen earlier at HMC and returned as part of care. If the children were included in the cost-effectiveness study, they were excluded from the clinical study.

2.3 Screening

All participants of the cost-effectiveness study had the standard YHC child vision screening as well as a test with an autorefractive device, in this study the Plusoptix. At the ages of 3y and 3y9m the YHC assistant first performed the Plusoptix test, and registered the result in the YHC electronic database. The vision chart test was then performed by the YHC nurse for children aged 3y, and by the YHC physician for children aged 3y9m. These professionals were blinded for the Plusoptix result. In children aged 5/6 years blinding was not possible because both tests were performed by the assistant. Randomization of the order of performing the tests was not feasible in practice. We chose to perform the vision chart test first, and thereafter the test with the Plusoptix, because bias from knowing a previous test result was expected to be less for the Plusoptix test than for the vision test.

2.3.1 Current vision screening

Vision screening is part of the Preventive YHC and is routinely performed within the health assessments for children of ages between 0 – 7 years (Coenen, 2010). In the first three years, a test called "Vroegtijdige Opsporing van Visuele Stoornissen" (VOV), i.e. "Early detection of visual disorders", is used to get an impression of the vision of the child. The VOV test consists of eye inspection and assessment of pupil responses, cornea light reflex, cover tests and eye movements. During the health assessment at the age of 3 years, the Amsterdam Picture Chart (APK, Leeskaart APK-TOV 3m/5m transparent, figure 1) is used to examine monocular visual acuity at the YHC facility. The Landolt-C chart ("Leeskaart C-symbool transp. 46.5 x 35cm") is used during the health assessments at the ages of 3 years and 9 months and 5/6 years. If the child does not seem to understand the Landolt-C test, the APK test is used instead. Both charts are used on a light box, usually at a distance of 5 meter. For some children aged 3-6 years also a VOV test is performed by the YHC physician, depending on the chart test result (see "Criteria for additional testing and referral").

Figure 1. Amsterdam Picture Chart (APK, on the right) and Landolt-C chart (on the left) in use at YHC.

2.3.2 Autorefractive test

In our study, the Plusoptix S12C Mobile Vision Screener® (PlusoptiX GmbH; Nuremberg, Germany) was used (on loan from the manufacturer). It is a computer-aided, handheld digital device that measures refraction, pupil sizes and corneal reflexes (ocular alignment or gaze asymmetry) (Matta, 2008). The device is held 1 meter from the child. It makes noise and produces flashing lights to attract the child's attention. Measurements are obtained within a few seconds. An automated printout of refractive outcomes may be provided. Measurements are compared with preprogrammed referral criteria to determine a 'pass' or 'refer' for each screening. In case measuring circumstances have shortcomings (e.g. the light in the room) or if a complete image of both pupils cannot be made (e.g. because of an obstruction like a cataract or eye lashes, because the eyes are out of focus or because the child does not focus on camera), the test result is 'refer or try again'. The test requires hardly any cooperation of the child, thus allowing earlier detection of

conditions that may lead to amblyopia in children, especially in children who have difficulties to cooperate with routine acuity screening (e.g. young children and children with low levels of concentration, children with limited intellectual functioning and/or poor fluency in the Dutch language).
The project group has explored the possibility of including more than one type of autorefractive device in the study, but this would have complicated the organization of the screening at the YHC too much and increased the costs of the study. Therefore, we decided to choose only one screening device. From Schwartz et al (2014) we concluded that various devices were quite comparable. We choose Plusoptix because 1) it has been studied often, usually with satisfying results, 2) Flanders (Belgium) has chosen Plusoptix to screen 1- and 2-years old children, and 3) Plusoptix is mentioned in the YHC Dutch Vision Screening Guideline as an instrument in need of a cost-analysis.

2.3.3 Criteria for additional testing and referral

Current vision screening. For the standard YHC vision screening, the Dutch guideline was followed to decide which children needed a second vision screening or referral to the clinic for diagnostics. The Dutch guideline has age-dependent cut-off points for both APK and Landolt-C to determine whether the test result is sufficient, insufficient or doubtful (Coenen, 2010, figure 2). If the score on the APK or Landolt-C is doubtful or if it is not possible to get a test score, the Dutch guideline recommends to perform a VOV test. If the APK, Landolt-C or VOV test had an insufficient score children should be referred to the hospital for an eye examination. If it is not possible to get a test score or if the score on the APK or Landolt-C is doubtful, while the VOV-test is not insufficient, it is recommended to schedule an extra health assessment 2-3 months later. If at this extra health assessment the score on the APK or Landolt-C is still not sufficient, the child should be referred to the hospital.

Autorefractive test. For the Plusoptix test, table 1 shows age-specific cut-off criteria for referral that were set in collaboration with orthoptists from our project group and based on the "Amblyopia Risk Factor Targets Recommended by the American Association for Pediatric Ophthalmology and Strabismus" (Donahue, 2016; Simon, 2016). Recently, the US Preventive Services Task Forces (USPSTF) slightly adapted the risk factors for amblyopia (Jonas, USPSTF 2017, see the values between brackets in table 1 if different from our referral criteria). The Plusoptix test is only performed once at the first visit, and children were referred when the outcome of the Plusoptix was 'refer'. In case the Plusoptix had an outcome of 'refer or try again', the test was repeated. A 'refer or try again' outcome results if measuring circumstances have shortcomings (e.g. the light in the room) or if a complete image of both pupils cannot be made (see 2.3.2). Instructions were to try to get a result for maximally 5 minutes. In case 'refer or try again' remained the only outcome, it was decided to not refer the children to the orthoptist.

Table 1. Referral criteria used in this study for Plusoptix S12C Mobile Vision Screener®.

Age in months		ΔSE ΔCYL	CYL[&]	MYO[#]	HYP	Δpupil size	ASY
From	to	Anisometropia	Astigmatism	Myopia	Hyperopia	Anisocoria	Strabism
31	47	≥ 1.5 (> 2.0) D	≥ 2 D	≥ -2.5 (>-3.0)D	≥ +4 D	≥ 1mm (*)	≥10 (>8)°
48	300	≥ 1.5 D .	≥ 1.5 D	≥ -1.5 D .	≥ +3.5 D	≥ 1mm (*)	≥10 (>8)°

Between brackets: values of risk factors for amblyopia from USPSTF (Jonas, JAMA, 2017) if different from the values in the table that were used as cut-off values.
*: no value indicated by USPSTF.
Δ: difference between left and right eye.
[&]: in this study negative values for cylinder were used.
[#]: usual notation for myopia, not mathematical. If the absolute value is equal to or greater than the cut-off, the child is referred.
SE: sphere, CYL: cylinder, MYO: myopia, HYP: hyperopia, ASY: asymmetry, Δ: difference between left and right eye.

Figure 2. Criteria from the Dutch YHC vision screening guideline (Coenen, 2010) for sufficient (v=voldoende), insufficient (o=onvoldoende) or doubtful (t=twijfel) results of standard vision screening, for the charts and distance between child and chart (5 meter) that are used most often. In Coenen (2010), criteria are also given for charts that are less than 5 meter from the child. OD=right eye, OS=left eye.

Figure 2a. Interpretation of scores for Amsterdam Picture Chart (APK and APK-TOV) at 5 meter distance, children aged 3y.

Tabel 5: Controle- en verwijscriteria APK-TOV en APK, 3 jaar, 5 meter

	OD 5/30	5/20	5/15	5/10	5/6	5/5
OS						
5/30	o	o	o	o	o	o
5/20	o	o	o	o	o	o
5/15	o	o	o	o	o	o
5/10	o	o	o	t	t	o
5/6	o	o	o	t	v	t
5/5	o	o	o	o	t	v

In words: The result is 'sufficient' (v) if both eyes score 5/5 (comparable to 0.5 at the Snellen chart) or 5/6. If both eyes score 5/10 or if scores between the left and right eye differ one line at scores of 5/10, 5/6 or 5/5, the result is 'doubtful' (t). All other combinations of scores get the result 'insufficient' (o), i.e. scores of 5/30, 5/20 or 5/15 for one or both eyes, or 5/5 in one eye but 5/10 in the other eye (i.e. difference of 2 lines).

Figure 2b. Interpretation of scores for Landolt-C chart (LC) at 5 meter distance, children aged 3.5 to 5.0 years.

Tabel 6: Controle- en verwijscriteria Landolt-C, 3,6 tot 5,0 jaar, 5 meter

	OD 0,1	0,12	0,15	0,2	0,25	0,3	0,4	0,5	0,65	0,8	1,0
OS											
0,1	o	o	o	o	o	o	o	o	o	o	o
0,12	o	o	o	o	o	o	o	o	o	o	o
0,15	o	o	o	o	o	o	o	o	o	o	o
0,2	o	o	o	o	o	o	o	o	o	o	o
0,25	o	o	o	o	o	o	o	o	o	o	o
0,3	o	o	o	o	o	o	o	o	o	o	o
0,4	o	o	o	o	o	o	o	o	o	o	o
0,5	o	o	o	o	o	o	o	v	v	t	o
0,65	o	o	o	o	o	o	o	v	v	v	t
0,8	o	o	o	o	o	o	o	t	v	v	v
1,0	o	o	o	o	o	o	o	o	t	v	v

In words: The result is 'sufficient' (v) if both eyes score 0.5 or higher, or if the best eye scores 0.65 or higher while the other eye scores only one line less. If both eyes score 0.5 or higher but there is a difference of two lines in the scores, the result is 'doubtful' (t). All other combinations of scores get the result 'insufficient' (o), i.e. scores of 0.4 or less for one or both eyes, or 0.5 in one eye but 1.0 in the other eye (i.e. difference of three lines).

Figure 2c. Interpretation of scores for Landolt-C chart at 5 meter, children aged over 5.0 years.

Tabel 7: Controle- en verwijscriteria Landolt-C, vanaf 5,0 jaar, 5 meter

	OD 0,1	0,12	0,15	0,2	0,25	0,3	0,4	0,5	0,65	0,8	1,0
OS											
0,1	o	o	o	o	o	o	o	o	o	o	o
0,12	o	o	o	o	o	o	o	o	o	o	o
0,15	o	o	o	o	o	o	o	o	o	o	o
0,2	o	o	o	o	o	o	o	o	o	o	o
0,25	o	o	o	o	o	o	o	o	o	o	o
0,3	o	o	o	o	o	o	o	o	o	o	o
0,4	o	o	o	o	o	o	o	o	o	o	o
0,5	o	o	o	o	o	o	o	o	o	o	o
0,65	o	o	o	o	o	o	o	o	t	t	t
0,8	o	o	o	o	o	o	o	o	t	v	v
1,0	o	o	o	o	o	o	o	o	t	v	v

In words: The result is 'sufficient' (v) if one or both eyes score 0.8 or higher. If one eye scores 0.65 while the other eye scores 0.65 or higher, the result is 'doubtful' (t). All other combinations of scores get the result 'insufficient' (o), i.e. scores of 0.5 or less for one or both eyes.

Thus, children could get a referral to HMC for orthoptic examination on either the results of the vision screening as described in the guideline, a 'refer' result on the Plusoptix, or both.

2.4 Registration and main outcomes measures

The YHC professionals registered the study data in their YHC registration system (KD+), which was adapted for our study. Data from all visits to YHC was extracted for all study children from 1 September 2016 onwards. Data were anonymous but contained a YHC-ID number. Final data extraction from KD+ was performed on 20 June 2017. Background variables like education and country of birth of the parents, and language problems of the child were also extracted. The data were delivered by YHC in different excel-worksheets in one xls-file, and merged per YHC visit based on the YHC-ID number using R (R Development Core Team, 2008).

The test outcomes were registered as a conclusion in KD+, i.e. sufficient, doubtful or insufficient for the vision chart tests; sufficient, doubtful, insufficient or not succeeded for the VOV; and pass, refer, 'refer or try again' or -if the YHC professional did not perform the test- 'not performed' for the Plusoptix test. For most children more detailed information on the test results was also available. For the chart tests, the specific line of smallest symbols that the child could read (figures 1 and 2) was registered per eye using the line number. Also, the detailed test results as stored in the Plusoptix devices were matched to the KD+ data using the YHC-ID number that was entered into the device. These data include sphere, cylinder, axis and pupil size per eye (OD=right eye; OS=left eye), and gaze asymmetry. Outcomes of the VOV test components were also registered.

In this study, also the costs of screening and diagnostics are considered. To calculate costs of performing the screening, YHC professionals were also asked to measure the time needed for screening for both the standard screening and screening with Plusoptix and its preparation and registration, using a stopwatch. The time measurements were also entered in the KD+ registration system.

For children referred for orthoptic diagnosis, a special referral procedure was made for this study, in order to be able to recognize the study children at HMC. Data on diagnosis and therapy, as well as test results and background variables, were registered in a separate database by the HMC orthoptists. These data were matched to the YHC-data from KD+ based on the YHC-ID number. Diagnostic categories included 'no orthoptic/eye deviations', 'ophthalmologic deviations', 'strabismus', 'refraction error', 'amblyopia', 'media abnormality', 'anisocoria', and combinations of these. Therapeutic categories included 'glasses', 'occlusion therapy', 'both glasses and occlusion', 'no action, no follow-up', 'no action (yet), but follow-up within 3 months', and also for follow-up after 3-5 months, 6-12 months and over 1 year. The HMC files for study children referred by YHC and initially treated with glasses were reinvestigated on October 6, 2017, to check for the presence of refractive adaptation at about 13 weeks after initial diagnosis. The HMC orthoptist registered if initial therapy with glasses for children who may or may not have amblyopia resulted in better vision (i.e. no amblyopia) or no improvement (i.e. amblyopia).

The data for the clinical study were registered by the HMC orthoptists in a separate database, with similar content as described above.

2.5 Target group

The main target group of YHC vision screening, i.e. children with amblyopia, was defined as having 'amblyopia' at the initial clinical diagnosis, and/or having 'occlusion' (patching) in the therapy, and/or getting the diagnosis 'amblyopia' from the orthoptist after a 13-weeks period of refractive

adaptation. A diagnosis of amblyopia was given to children with a best corrected difference in vision between the left and right eye of 2 or more lines on the vision chart. If the vision could not be determined, a unilateral amblyopia was detected if there was a preference for fixating with one eye in a cover test. Bilateral amblyopia was diagnosed if the best corrected vision was less than 0.5.

Moreover, a broader target group, including also children with a significant refraction error, was defined. This group included all children in the amblyopia target group, as well as children with myopia $\geq$ -2.5 D, hyperopia $\geq$ +3.0 D, and/or astigmatism $\geq$ 2.0 D on at least one eye determined with cycloplegic retinoscopy. Results for this target group are given in the appendix.

2.6 Analysis

Using registered data on the type of chart used, the line numbers per eye that the child could still read and the criteria from the YHC vision guideline (Coenen, 2010), a conclusion of the standard vision screening per visit was calculated for both eyes combined. Information registered in words by the YHC professional about the test, e.g. "tried performing the test but child did not understand it", was also analyzed and used for the conclusion, e.g. 'tried, but no result'. The thus obtained conclusion was compared to the conclusion registered by the YHC professional, and used in further analysis, as in this way the effect of other cut-off values can be analyzed. Only if no conclusion could be drawn, e.g. because line numbers were not registered, the conclusion as registered by the YHC professional was used in the analyses.
Similarly, using the detailed data per eye on sphere, cylinder, pupil size and gaze asymmetry from the Plusoptix device in combination with the cut-off values used for this study, a conclusion for the Plusoptix device was calculated. While the device first rounds off the values to quarters of numbers (e.g. 2.25, 2.5. 2.75, etc.) we based our analyses and conclusions on the unrounded values. E.g. a sphere equal to 3.9 in a 3y old will get the outcome 'refer' from the device, as the values is rounded to 4.0 before making the conclusion, while in our calculations this value results in a 'pass', as it is below the cut-off value of $\geq$ 4.0.

For the standard vision screening, some children were tested at more than one visit, e.g. if the first test had a 'doubtful' result. A final conclusion was calculated by combining the results of these separate visits. Children with a 'sufficient' score on one of the vision screenings also scored 'sufficient' on the final conclusion. Children with one or more 'insufficient' scores, as well as children with two 'doubtful' scores or two test failures or a combination of 'doubtful' and a test failure, scored 'insufficient' on the final conclusion, as long as they did never have a 'sufficient' score. The score 'no conclusion' was given to all other children who were tested by using a vision screening chart, for example when only one doubtful result was obtained without getting a second test result, or in case no test results could be given because the child did not cooperate. The VOV outcomes were ignored for this conclusion on the standard vision screening (see Results, Standard YHC vision screening, text above tables 11a-c for the justification).
As the test with Plusoptix was only performed once, at the first visit, the final conclusion is similar to the conclusion for the first visit.

The background variables on education of the parents were categorized into low (i.e. no finished education, elementary school, trade degree), medium (i.e. high school, vocational degree) and high (i.e. college, university) following the definition of the Central Bureau of Statistics (CBS). We also distinguished Western and non-Western children by the country of birth of the parents. If one of the two parents was born in a non-western country, the child was defined as non-Western. Western countries are European countries (excluding Turkey), North-America, Oceania, Indonesia and Japan.

2.6.1 Calculation of costs

Costs were calculated based on the time needed for each of the screening tests (chart, VOV and Plusoptix) and the type of YHC professional who performed the test. Jeckmans (2011) published hourly rates for YHC professionals consisting of not only wages and taxes, but also including the costs of e.g. housing and supporting staff. These rates were indexed to 2017 euros by using the Consumer Price Index of the Central Bureau of Statistics (table 2). Costs of screening per visit were calculated by multiplication of the time needed and the hourly rate of the professional who performed the test. As screening with Plusoptix was performed only once, the costs were based on the time needed for this one test, while for the standard vision screening costs for a second or even third screening were also taken into account if these were performed. For visits without registration of any test result and for which also any indication lacked that the vision test was tried but failed (i.e. 'no data'), we assumed that the test was not performed, and thus no costs were attributed for these visits.

Table 2. Hourly rates (including wages, taxes, housing, supporting staff, etc) for YHC professionals (indexed to 2017€ from Jeckmans, HHM, 2011)

Euros (2017) per hour	**0-4 years old**	**5/6 years old**
YHC physician	96.46	106.16
YHC nurse	67.45	63.27
YHC assistant	43.56	47.50

The costs of a clinical consultation (€80,87, indexed to 2017 €; ZIN, 2015) were added to the costs if a child was diagnosed at the clinic. For children with a referral who did not follow-up the referral, no costs for a clinical consultation were taken into account. If a child visited the clinic because of a referral on only one way of screening, the cost of the visit were only taken into account for the screening that resulted in the referral. Thus, if a child had an insufficient score on the vision chart test, but a pass on the Plusoptix device, the costs for the clinical consultation were only taken into account when calculating the costs for the vision chart test.

Costs for using the Plusoptix devices were estimated per child screened. The price of the Plusoptix S12C Mobile Vision Screener® is €6,710 excluding taxes, i.e. €8,119 including 21% BTW. Additionally, a yearly replacement of batteries (€21.72 including taxes) is included in the price. The useful life time of the devices is estimated at 7 years. Following the methodology for depreciation of the Guideline for performing economic evaluations in health care, yearly costs per device are €1,385 (interest rate of 4.2%; ZIN, 2015).
In 6 months, more than 2,144 children were screened using nine devices, thus resulting in an estimation of a yearly number of children screened with one device in Dutch YHC of about 475, and average costs for the device per child screened of about €2.90. However, use of the devices was distributed uneven: the 1519 study children aged 3y and 3y9m were screened by 5 devices, while the 625 children aged 5/6y were screened by 4 devices. Therefore, for children aged 3y and 3y9m costs for the device per child screened were estimated at about €2.30, while this was about €4.40 for children aged 5/6y.
If the Plusoptix test is only performed in children aged 3y9m, but not in children aged 3y, we took into account that the 5 devices were used to screen only about 731 children in 6 months. In that case, costs for the device per child of 3y9m screened are about €4.70.

Imputation of missing values of time registration.
In order to obtain good insight in the costs of the screening tests, missing time entries for all three tests (standard vision screening, VOV and Plusoptix) were dealt with by multiple imputation. In

multiple imputation, missing values are replaced multiple times using the observed time entries, results on the screening tests, and background variables. The background variables that were included in the imputation procedure were sex of the child, age of the child, education of the parents and whether at least one of the parents was born in a non-Western country. The multiple imputation procedure was performed in SPSS version 24 with the predictive mean matching algorithm using 20 iterations and resulted in 50 imputed datasets.

2.6.2 Optimizing YHC vision screening – screening alternatives investigated

For the current Dutch vision screening (chart test and VOV) as well as for screening once at each age (3y, 3y9m and 5/6y) with the Plusoptix without further screening, the effectiveness and monetary costs were calculated and compared. The yield of the screening is the number of children in the target group that was detected by the screening, where children with amblyopia are considered to be the main target group (see above).

Based on the current or revised YHC vision screening guideline, screening alternatives to improve the current Dutch vision screening were defined by combining screening with the Plusoptix test and the vision chart test in various ways for children aged 3y9m and 5/6y, see table 3. For children aged 3y the study results did not give reasons to evaluate alternatives combining the APK test with other tests.

Table 3. Screening alternatives for YHC vision screening.

Screening alternatives for children aged 3 years and 9 months and 5/6 years		
Start with Plusoptix 1 (POLC1)	Start with Plusoptix: • Refer → refer to clinic for diagnostic follow-up • Pass → no further action • Refer or try again → Landolt-C • Not performed / no data → Landolt-C	Landolt-C: • Insufficient → refer to clinic for diagnostic follow-up • Sufficient → no further action • Doubtful → second YHC screening • Tried, but no result → second YHC screening • No data → second YHC screening
Start with Plusoptix 2 (POLC2)	Start with Plusoptix: • Refer → refer to clinic for diagnostic follow-up • Pass → Landolt-C • Refer or try again → Landolt-C • Not performed / no data → Landolt-C	Landolt-C: Similar to POLC1 (above)
Start with Landolt-C (LCPO)	Start with Landolt-C: • Insufficient → refer to clinic for diagnostic follow-up • Sufficient → no further action • Doubtful → Plusoptix • Tried, but no result → Plusoptix • No data → Plusoptix	Plusoptix: • Refer → refer to clinic for diagnostic follow-up • Pass → no further action • Refer or try again → second YHC screening • Not performed / no data → second YHC screening
Landolt-C & Plusoptix (LC&PO)	Perform both tests in all children: • If at least one test is insufficient/refer → refer to clinic for diagnostic follow-up • If the Landolt-C is sufficient and the Plusoptix is **not** 'refer', or if the Plusoptix is 'pass' and the Landolt-C is **not** insufficient → no further action • If neither of the above described situations apply → second YHC screening	

The screening alternatives are compared based on monetary costs (total costs for the age group, costs per detected child in the target group, and the costs per screened child), the number of detected children in the target group, and the number of children referred. The main target groups presented are children with amblyopia. Results for the target group of amblyopia or significant refraction error are presented in the appendix. When calculating the costs for children aged 3y9m, costs for the Plusoptix device were based on use for children at this age only, but in the footnote costs are also mentioned in case the devices are also used for children aged 3y.

2.6.3 Optimizing cut-off values of the Plusoptix

In order to optimize the cut-off values for the Plusoptix, only data from children in the target groups (i.e. diagnosed with amblyopia, and diagnosed with amblyopia or significant refraction error) who were not detected by the Plusoptix device are used. Based on these data we investigated whether the referral criteria of the Plusoptix device can be improved.

2.6.4 Subgroup analyses

Analyses for performed for subgroups. We distinguished Western and non-Western children by the country of birth of the parents. In addition, a subgroup of children with language and developmental problems was defined from the registration of these problems by the YHC professionals in the YHC registration system KD+. The matched registration by the HMC orthoptist was used for additional information on language and developmental problems.

2.6.5 Estimation of test characteristics

In this study, we used three instruments: the APK was used in the 3y old children, the Landolt-C for 3y9m and 5/6y, and the Plusoptix device was used in all ages. For these instruments, the positive predicted value (PPV), the sensitivity and specificity of performing one test were approximated. The calculations for obtaining these estimates can be done by using table 4. Table 4 contains the test results in the rows and the diagnostic information in the columns. With a positive test result, we mean that the children should be referred due to the test; the remainder of children will be in the negative test result row.

Table 4. Table used to estimate test characteristics

	Disease			
	+ (present)	- (absent)	? (unknown)	Total
Test +	a	b	e	a+b+e
Test -	c	d	f	c+d+f
Total	a+c	b+d	e+f	N=a+b+c+d+e+f

If the category ? (unknown) is not present (e=0 and f=0), test characteristics are calculated as:
Sensitivity = a / (a+c)
Specificity = d / (b+d)
PPV (positive predictive value) = a / (a+b)

The *positive predictive value (PPV)* of a test is the proportion of positive results in a test that is true positive. Thus, it is the proportion of the children that are referred to the orthoptist who actually belong to the target group (i.e. have the disease, amblyopia). This statistic is calculated using the data from the YHC (cost-effectiveness study). Children who needed a referral but did not visit the orthoptist are a difficulty in the estimation as their diagnosis is unknown (cell e).
A minimum PPV is calculated under the assumption that all these children with unknown diagnosis do not have amblyopia (i.e. PPV=a/(a+b+e)). A maximum PPV is calculated under the assumption that all these children with unknown diagnosis do have amblyopia (i.e. PPV=(a+e)/(a+b+e)). The best estimate of the PPV is made by using only data from the children with a positive test who do have a diagnosis (i.e. PPV=a/(a+b)).

The *sensitivity* of a test is the probability that the test will indicate 'disease' among those with the disease. Sensitivity of the vision chart tests and Plusoptix were calculated from the clinical study at HMC. Children in the target group (i.e. have the disease, as diagnosed by the orthoptist) were selected. In these groups, the percentages with an insufficient result (chart tests) or 'refer' (Plusoptix) on their first test were determined, as this is the sensitivity of a test. Children with a 'doubtful' result on the vision screening or in which no results could be obtained ('tried but no result', or 'refer or try again' on Plusoptix) complicate this analysis, as they are not clearly positive or negative on the test. We decided to classify these children as test negative, therefore our estimate of the test sensitivity is the minimal sensitivity.

The *specificity* of a test is the probability that the test indicates 'no disease present' among those without the disease. It is the proportion of negatives (i.e. 'sufficient' or 'pass') that are correctly identified as such (e.g. the percentage of healthy people who are correctly identified as not having the condition). In this study, children were only sent to an orthoptist if one of the tests was positive (insufficient for the vision screening after one to three visits, or refer for the Plusoptix). Hence, it is difficult to estimate the specificity, as most children with a negative test result were not seen by an orthoptist.
The specificity was estimated from the children in the cost-effectiveness study under assumption of a fixed prevalence of 3% for the prevalence of amblyopia. With this prevalence and the total number of children with a test result (N), it can be calculated how many children have the disease (N*prevalence for cell a+c) and how many do not have the disease (N*(1-prevalence) for cell b+d). With these column totals, specificity was estimated twice under different assumptions. The first is that children with a positive test result but an unknown diagnosis of amblyopia have the same probability of having amblyopia as the children with a positive test result who did get a diagnosis. The specificity is then equal to (N*(1-prevalence)- (b+e*(b/(a+b)))) / (N*(1-prevalence)). The second assumption is that all children with unknown diagnosis do not have amblyopia. The specificity is then (N*(1-prevalence)-(b+e)) / (N*(1-prevalence)). In results section 3.9 'Test characteristics' it is shown how the estimations are done, using the data.

2.6.6 Qualitative research

Focus groups. To determine the acceptability and feasibility of the Plusoptix among professionals and parents, qualitative research methods were used. Two focus group discussions were held with YHC professionals to determine the feasibility of using the Plusoptix in practice and to determine the acceptability of the results from both types of screening. One focus group was conducted among YHC assistants who worked with the Plusoptix device. All 22 assistants were invited. The second focus group was conducted among YHC physicians who participated in the study. This focus group was conducted via Whatsapp. Eight YHC physicians were invited to participate.

Interviews with parents. Interviews with parents were performed by telephone. From the database with children whose parents agreed to participate in the study and who were referred to the hospital, data from the children who had missing values on the result of the standard vision screening and on the YHC location were removed. After this, the first nine children with the most recent visit per YHC location were selected. The assistants of the seven locations called the parents of the first three children. If one of these parents did not answer or refused to participate, they called the next parent, until three parents agreed to participate. The phone numbers of these three parents were sent to the researcher. If needed, parents were called at least four times at different times and days.
The following questions were asked before it was revealed on the basis of which test the child was referred: what is the opinion of parents about the vision screening in general, and more specifically about the Plusoptix and the standard vision screening? Which test has their preference? Also they were asked if they expected their child to need glasses in advance of their visit to the hospital. After

the revelation of which test caused the referral, parents were asked again which test has their preference.

2.7 Ethical approval

The study plan, parent information and informed consent forms were assessed by the Medical Ethical Committee Southwest Holland. They judged that this study does not fall under the Medical Research (Human Subjects) Act. National legislation was followed in this study. Participants were well informed, participated voluntarily and could withdraw from the study at any time. They signed informed consent forms.

3. Results

3.1 Inclusion

In total 2488 children were invited to participate in the cost-effectiveness study. From these 2488 children, 194 children (7.8%) were excluded from the study because they were already under supervision of an orthoptist or wearing glasses. Moreover, 150 parents (6%) did not give consent to participate in the study. Hence, in total 2144 children are included in the study (table 5).

Table 5. Inclusion and exclusion from the study.

	Participants included		**Wearing glasses / visiting clinic for eye/vision**		**No parental consent**		**Total**
	n	*%*	*n*	*%*	*n*	*%*	***n***
3 years	788	91.1%	26	3.0%	51	5.9%	**865**
3 years and 9 months	731	86.3%	77	9.1%	39	4.6%	**847**
5/6 years	625	80.5%	91	11.7%	60	7.7%	**776**
Total	2144	86.2%	194	7.8%	150	6.0%	**2488**

3.1.1 Background characteristics

Background characteristics of non-participants were not available.
In our study group, slightly more girls than boys were present. Education and land of birth of the parents of the participants was available for 66.7% and 82.5% of the cases for at least one parent, respectively (table 6).

Compared with the Dutch population of about the same age (25-45 years; CBS statline data of first quarter of 2017), our sample was slightly lower educated: 37.6% in our sample had a high level of education, compared to 43.9% in the standard Dutch population. The percentage of low educated parents was comparable to the Dutch population (i.e. 16.7% and 15.5%, respectively).
The ethnic background of the children in our sample differed largely from the general Dutch population. Our population contained more non-Western children compared with the general Dutch population (i.e. 45.5% and 16.4%, respectively) and less Dutch children (i.e. 37.9% and 72.4%, respectively). This discrepancy can be explained by the YHC locations that were included in the study: in three of our five study locations in The Hague a large part of the population has a non-Dutch ethnic background. The large difference in ethnic background may have consequences for the generalizability of the results to the general Dutch population. For that reason we also analyzed the data for subgroups of Western and non-Western children separately.

Table 6. Number of participants and background characteristics of the parents per age group.

		Total		**3y**		**3y9m**		**5/6 y**	
		N	%	N	%	N	%	N	%
Number of participants		2144	100	788	36.8	731	34.1	625	29.2
Gender	N with data	2144	100	788	36.8	731	34.1	625	29.2
	boy	1043	48.6	381	48.4	363	49.7	299	47.8
	girl	1101	51.4	407	51.6	368	50.3	326	52.2
Education of mother	N with data	1279	59.7	571	72.5	498	68.1	210	33.6
	low	205	16.0	97	17.0	74	14.9	34	16.2
	medium	586	45.8	248	43.4	220	44.2	118	56.2
	high	488	38.2	226	39.6	204	41.0	58	27.6
Education of father	N with data	1112	51.9	477	60.5	454	62.1	181	29.0
	low	194	17.4	91	19.1	74	16.3	29	16.0
	medium	507	45.6	209	43.8	200	44.1	98	54.1
	high	411	37.0	177	37.1	180	39.6	54	29.8
Land of birth mother	N with data	1695	79.1	651	82.6	597	81.7	447	71.5
	Netherlands	663	39.1	300	46.1	262	43.9	101	22.6
	Other Western	303	17.9	103	15.8	111	18.6	89	19.9
	Non-Western	729	43.0	248	38.1	224	37.5	257	57.5
Land of birth father	N with data	1582	73.8	579	73.5	554	75.8	449	71.8
	Netherlands	579	36.6	251	43.4	231	41.7	97	21.6
	Other Western	244	15.4	86	14.9	83	15.0	75	16.7
	Non-Western	759	48.0	242	41.8	240	43.3	277	61.7

3.2 Standard YHC vision screening

In table 7 the number of visits children needed for vision screening is presented. For all ages combined, 21% of participants had a second visit in which vision screening and/or VOV was performed. This percentage was highest in the youngest age group (about one-third). A small fraction even got a third visit in practice, although this is not conform protocol. In most of these cases no result could be obtained on at least one earlier test.

Table 7. Number of children receiving a vision screening.

	First visit	Second visit		Third visit	
	n	*n*	*%*	*n*	*%*
3 year	788	275	34.9%	24	3.0%
3 year and 9 months	731	132	18.1%	14	1.9%
5-6 years	625	42	6.7%	0	0%
Total	2144	449	20.9%	38	1.8%

Results of the first vision test by age-related YHC assessment are shown in table 8. For 1872 children this outcome was calculated based on the line numbers that the child could still see on the chart, while for 72 children this was not registered but the YHC professional registered a conclusion in KD+ which we used.

For the APK test at age 3y, only about half of the children has a sufficient result at their first screening test, 18.9% had a doubtful result, while 13.2% has an insufficient score. For 8.8% of the three year-olds YHC professionals tried to perform the test, but no results could be obtained. Moreover, no data were available for 7%: for these children registration of any test result as well as any indication that the vision test was tried but failed, lacked. At the older ages, relatively more sufficient results were obtained with the Landolt-C test, while the percentage with insufficient results decreases with age.

Table 8. Results of vision test at first visit.

	Sufficient	Doubtful	Insufficient	Tried, but no result	No data	Total
3 years (APK)	409	149	104	69	57	788
	51.9%	18.9%	13.2%	8.8%	7.2%	100%
3 years and	496	13	151	24	47	731
9 months (LC)	67.9%	1.8%	20.7%	3.3%	6.4%	100%
5/6 years (LC)	549	39	34	1	2	625
	87.8%	6.2%	5.4%	0.2%	0.3%	100%
Total	1454	201	289	94	106	2144
	67.8%	9.4%	13.5%	4.4%	4.9%	100%

Moreover, table 9 shows the differences between the conclusions registered by the YHC professionals in KD+ and the recalculated conclusion based on the line numbers. Note, that only for 1739 children the professional noted the conclusion of the vision chart test. There was agreement on the sufficient, doubtful and insufficient results in 92.5% of the children, however in 37 children a sufficient result was registered by the YHC professional, while the line numbers indicated an insufficient or doubtful outcome. Most of these cases (*n* = 28) were children aged 3y who were screened with the APK chart at 3 meter, and scored on both eyes either line 6 or 5. On the APK chart at 5 meter this would have been sufficient, however for the APK chart at 3 meters this is insufficient or doubtful.

Table 9. Results of vision test at first visit: comparison of registration by YHC professional in KD+ with result calculated using the registration of the chart line numbers.

Recalculated vision chart result	**Vision chart result from KD+**			
	Insufficient	*Doubtful*	*Sufficient*	*Total*
Insufficient	231	41	9	281
Doubtful	42	119	28	189
Sufficient	1	6	1208	1215
Tried, but no result	40	13	1	54
Total	314	179	1246	1739

Reasons registered for not getting a sufficient result on the vision screening are presented in table 10. For children aged 3y one or more reasons per child were often registered. The reasons that were most often registered were not practicing the test in advance, not knowing the pictures, and lack of concentration. The registration was less complete for children aged 3 years and 9 months.

Lack of concentration was also registered relatively often at this age, as well as the impression that the children were really not able to see the symbols. For children aged 5/6y the registration of reasons was very incomplete: while 76 children did not get a sufficient result, only 6 reasons were registered.

Table 10. Reasons for not getting a sufficient result on the vision test, by age.

	3 years		**3 year 9 months**		**5/6 years**	
All	N=788		N=731		N=635	
Vision test not sufficient	N=379		N=235		N=76	
Reason for failure	*n*	*% of all*	*n*	*% of all*	*n*	*% of all*
Language	27	3.4	7	1.0	0	0
Attitude parent	9	1.1	2	0.3	0	0
Does not know the pictures	65	8.2	17	2.3	1	0.2
Concentration problems	89	11.3	42	5.7	2	0.3
Did not practice in advance	77	19.8	17	2.3	0	0
Unreliable	7	0.9	1	0.1	0	0
Too young	0	0	2	0.3	0	0
Too young in development	9	1.1	5	0.7	0	0
Too young in development (Van Wiechenscore)	2	0.3	2	0.3	0	0
Shy	53	6.7	6	0.8	0	0
Does not want cover glasses	45	5.7	6	0.8	0	0
Is not able to see it	51	6.5	52	7.1	3	0.5
Sum of above	434		159		6	

A VOV test should be performed according to the YHC guideline if the results of the vision test is doubtful, and children with an insufficient VOV result should be referred to the orthoptist.
Tables 11a-c show that in practice, the VOV test is not always performed when indicated (performed or tried after ‘doubtful’ result of the vision test in 40%, 15% and 62% of the children at ages 3y, 3y9m and 5/6y, respectively: blue italic numbers), while the VOV is also performed on indication if the vision test has a result other than doubtful (mainly after an insufficient or failing vision test). As this indicates that the VOV test is mostly done upon the professional judgement of its necessity instead of on indication according to the guideline, we conclude that for the VOV test, the vision guideline is not followed.

Moreover, 6 of the 8 children with an insufficient VOV result already needed a referral to the orthoptist because of an insufficient vision test result. One child with an insufficient VOV test had a sufficient vision screening and was not referred. The last child with an insufficient VOV test had a doubtful first vision screening and no second vision screening, and was referred to the clinic. Thus, in maximally 1 of 2,144 children the VOV might have been the reason for referral for diagnostic investigation, and this referral resulted in a diagnosis of no significant problem. Therefore, for the analysis of the performance of the guideline, i.e. the need of a referral to the clinic, the VOV test results are not used. This did not affect the study results. Costs of the VOV were taken into account to estimate the costs of the current guideline, but also an estimation without the VOV costs was made.

Table 11. VOV test results by vision test result.

Table 11a. VOV test results by vision test result, age group 3y.

3 year		Vision test result					
		Insufficient	*Doubtful*	Sufficient	Tried, but no result	No data*	total
VOV	Tried, no result	0	*0*	0	2	0	2
	Insufficient	4	*1*	0	0	0	5
	Doubtful	2	*3*	0	0	0	5
	Sufficient	30	*40*	6	14	4	94
	Not performed*	0	*3*	1	0	0	4
	Sum	36	*47*	7	16	4	110
	% of total	26.9%	*39.5%*	1.7%	23.2%	7.0%	14.0%
	No data	96	*74*	402	53	53	678
total		134	*119*	409	69	57	788

*E.g. physician was not available

Table 11b. VOV test results by vision test result, age group 3y9m.

3 year 9 months		Vision test result					
		Insufficient	*Doubtful*	Sufficient	Tried, but no result	No data	total
VOV	Tried, no result	0	*0*	0	2	0	2
	Insufficient	2	*0*	1	0	0	3
	Doubtful	3	*0*	0	0	0	3
	Sufficient	54	*2*	49	6	9	120
	Sum	59	*2*	50	8	9	128
	% of total	39.1%	*15.4%*	10.1%	33.3%	19.1%	17.5%
	No data	92	*11*	446	16	38	603
total		151	*13*	496	24	47	731

Table 11c. VOV test results by vision test result, age group 5/6y.

5/6 year		Vision test result					
		Insufficient	*Doubtful*	Sufficient	Tried, but no result	No data*	total
VOV	Insufficient	0	*0*	0	0	0	0
	Doubtful	1	*3*	0	0	0	4
	Sufficient	15	*21*	2	0	0	38
	Sum	16	*24*	2	0	0	42
	% of total	47.1%	*61.5%*	0.4%	0.0%	0.0%	6.7%
	No data	18	*15*	547	1	2	583
total		34	*39*	549	1	2	625

*E.g. physician was not available

According to the YHC guideline the child should be referred to the clinic after an insufficient first screening test. In practice, these children are often screened by YHC for a second time, especially at age 3y (in 48% of children with an insufficient score) and age 3y9m (in 42%). Also, if the first test was doubtful or no result was obtained, a second screening needs to be done. The final conclusion of 1 to 3 visits combined on vision screening is given in table 12. For the APK test at age 3y, 70.9% gets a sufficient result, while 16.8% has an insufficient score and needs referral to the orthoptist. In 9.9% no conclusion could be provided, and of 2.5% we did not get any data on the vision test outcome.

At the older ages, more sufficient results are obtained with the Landolt-C test: almost 80% at age 3y9m and more than 90% at age 5/6y. The percentages with insufficient results and 'no conclusion' decrease with age. In addition, only very few children have no data at all on the vision tests.

For all ages combined, 294 children with an insufficient vision test result (insufficient or 2x doubtful/tried but no result) needed a referral to the orthoptist, according to the guideline (table 12). The children with 'no conclusion' did not return to YHC for a second visit, and thus were not referred.

Table 12. Result of vision test after 1 to 3 visits.

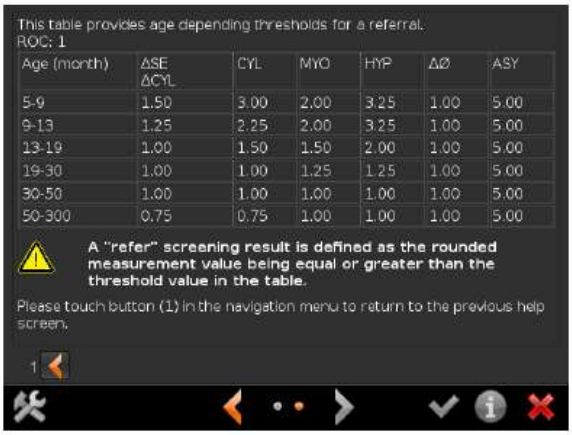
	Sufficient*	Insufficient*	No conclusion*	No data	Total
3 years (APK)	559 70.9%	132 16.8%	78 9.9%	19 2.5%	788 100%
3 years and 9 months (Landolt-C)	579 79.2%	122 16.7%	18 2.5%	12 1.6%	731 100%
5/6 years (Landolt-C)	572 91.5%	40 6.4%	12 1.9%	1 0.2%	625 100%
Total	1710 79.8%	294 13.7%	108 5.0%	32 1.5%	2144 100%

* Sufficient: 'sufficient' (=voldoende) at least one visit
Insufficient: 'insufficient' (=onvoldoende), or 2x 'doubtful'(=twijfel)/'tried, but no result'(=niet gelukt), AND not sufficient
No conclusion: not sufficient or insufficient, e.g. only one doubtful result, or no test result because child did not cooperate

3.3 Screening with the Plusoptix device

YHC used 9 Plusoptix devices to screen the children: 5 at four locations for children aged 3 to 4 years, of which 1 was only used for a period of 2.5 months, and 4 at three locations for children aged 5/6y. For the study, specific cut-off criteria were entered in the PO devices (table 1). However, by accident a predefined set of other referral criteria (called ROC 1) was used in two PO devices for a period of 2 and 4 months respectively. Thus, for 261 children other, more strict, criteria than those in the table were used (figure 3, bottom two lines). This other set of age-specific threshold values has led to an unintended 'refer'-conclusion in KD+ in 75 children. Among these children, one child aged 3y had amblyopia. This child would have been missed on the PO with the intended referral criteria we used in the study. It had an insufficient first vision screening.

Figure 3. Predefined set of cut-off criteria for a 'refer' result (called ROC 1), used by accident.



In addition, in some children the result from PO device differed from our manual calculation. These differences exist because the device first rounds off the values to quarters of numbers before the

conclusion ‘pass’ or ‘refer’ is drawn, while we use unrounded numbers in our analyses. Due to this, 21 children had an unintended ‘refer’ from the device, while our manual calculation resulted in a ‘pass’. None of them were diagnosed with amblyopia. On the other hand, 8 children had an unintended ‘pass’ from the device, while our manual calculations resulted in a ‘refer’. One of them (aged 3y9m) was diagnosed with amblyopia.

Results of the PO test are shown in table 13. For 2033 children this outcome was calculated based on the detailed results from the devices on sphere, cylinder, axis and pupil size per eye, and gaze asymmetry (i.e. independent of the set of criteria used by the PO device), while for 102 children this was not available but the YHC professional registered a conclusion in KD+ which we used.
The percentage of children having a ‘pass’ result at their first PO test increases with age from 79% at age 3y to 88% at age 5/6y. This effect of age is smaller than for the vision test (table 8). The percentage with ‘refer’ is 6-7%, while in 5-15% the outcome was ‘refer or try again’, the latter decreasing with age. In very few children the PO test was not performed or no data were registered. For all ages combined, 140 children had a ‘refer’ on the test with the Plusoptix and thus needed a referral to the orthoptist. In the paragraph ‘3.7 Optimizing cut-off values of the Plusoptix’ the cut-off criteria that caused these refers are given (table 22).

Table 13. Result of Plusoptix test.

	Pass	Refer or try again*	Refer	Not performed*	No data*	Total
3 years	620 78.7%	114 14.5%	49 6.2%	4 0.5%	1 0.1%	788 100%
3 years and 9 months	620 84.8%	62 8.5%	47 6.4%	2 0.3%	0 0%	731 100%
5/6 years	549 87.8%	30 4.8%	44 7.0%	0 0%	2 0.3%	625 100%
Total	1789 83.4%	206 9.6%	140 6.5%	6 0.3%	3 0.1%	2144 100%

* A ‘refer or try again’ outcome results if measuring circumstances have shortcomings (e.g. the light in the room) or if a complete image of both pupils cannot be made, e.g. because of an obstruction like a cataract or eye lashes, because the eyes are out of focus or because the child does not focus on camera.
Not performed: YHC professional registered in KD+ that the PO-test was not performed.
No data: no outcome on the PO test is registered in KD+, and the YHC-ID number was not found back in the data files from the devices.

Also for the Plusoptix device the professionals of the YHC registered the reasons why the measurement with the device did not result in a ‘pass’. Table 14 provides an overview of these reasons for all test outcomes. We did not select on test result, as reasons were also given in cases where the device at first gave a ‘refer or try again’ test result, and the professional redid the test leading to a ‘pass’ or ‘refer’ result. This table clearly shows that professionals registered very few reasons for children at the age of 5/6 years. Concentration problems are most often mentioned, especially for the younger children.

Table 14. Reasons for not getting an immediate 'pass' on the Plusoptix test, by age.

	3 year		3 year 9 months		5/6 year	
	N=788		N=731		N=635	
Reason for failure	*n*	*%*	*n*	*%*	*n*	*%*
Operating device	15	1.9	8	1.1	7	1.1
Language	5	0.6	1	0.1	0	0
Concentration problems	58	7.4	19	2.6	5	0.8
Does not want to cooperate	43	5.5	12	1.6	1	0.2
Measuring circumstances	20	2.5	19	2.6	4	0.6
Parent disturbs	0	0	1	0.1	0	0
Device did not properly	2	0.3	0	0	0	0
Shy	5	0.6	4	0.5	2	0.3
Sum of above	148		64		19	

3.4 Diagnostic results of study children referred by YHC

For all ages combined, 294 children with an insufficient vision test result (insufficient or 2 times doubtful/tried but no result) needed a referral to the orthoptist, according to the guideline, i.e. 13.7% or about 1 per 7 children (1:7.3). Less children (140) children needed a referral because they had a 'refer' on the Plusoptix test, i.e. 6.5% or 1 per 15 children (1:15.3). Table 15 shows the combination of results of both screenings: only 64 children had a need for referral from both the vision screening protocol as well as the Plusoptix test. The percentage agreement between the vision screening and the Plusoptix test, considering sufficient/pass, no conclusion/refer or try again, and insufficient/refer, was 74.8%.

Table 15. Results on vision screening (1 to 3 visits) and Plusoptix, all children.

Vision test after 1 to 3 visits	**Plusoptix**					
	Pass	Refer or try again*	*Refer*	Not performed*	No data*	Total
Sufficient**	1499	140	***66***	2	3	1710
No conclusion**	84	11	***10***	3	0	108
*Insufficient***	***181***	***48***	***64***	***1***	***0***	***294***
No data	25	7	***0***	0	0	32
Total	1789 83.4%	206 9.6%	***140*** ***6.5%***	6 0.3%	3 0.1%	2144 100%

* A 'refer or try again' outcome results if measuring circumstances have shortcomings (e.g. the light in the room) or if a complete image of both pupils cannot be made, e.g. because of an obstruction like a cataract or eye lashes, because the eyes are out of focus or because the child does not focus on camera.
Not performed: YHC professional registered in KD+ that the PO-test was not done.
No data: no outcome on the PO test is registered in KD+, and the YHC-ID number was not found back in the data files from the devices.
** Sufficient: 'sufficient' (=voldoende) at least one visit
Insufficient: 'insufficient' (=onvoldoende), or 2x 'doubtful'(=twijfel)/'tried, no result'(=niet gelukt), AND not sufficient
No conclusion: not sufficient or insufficient, e.g. only one doubtful result, or no test result because child did not cooperate

The diagnostic results of children needing a referral are shown in table 16. Data are provided for the children referred based on the YHC vision screening protocol (1-3 visits) and separately for the

children referred based on the Plusoptix test. For both groups, about two-third arrived at the clinic and got a diagnosis.
The vision screening detected 29 children with amblyopia (target group 'amblyopia' in the initial diagnosis and/or 'occlusion' in the therapy and/or 'amblyopia' after a period of refractive adaptation). This is 14.3% of children who arrived at the clinic. The Plusoptix test detected a smaller absolute number of children, i.e. 23. However, as the percentage of referred children was smaller than for vision screening, the relative percentage of children with a target group diagnosis of amblyopia was larger for the PO (25.0% of children who arrived at the clinic, $X^2(df)=4.2(1)$, $p<0.05$).

These percentages are the estimated positive predictive values (PPV): for the vision screening protocol (guideline, 1-3 visits) the PPV to detect amblyopia is estimated at 14.3%, and for a single test with the Plusoptix this is 25.0%. The APK had a PPV of 11.3%, as 9 of 80 children that arrived at the clinic had amblyopia. For the Landolt-C the PPV was estimated at 16.2% (14 of 92 at 3y9m and 6 of 31 at 5/6y). In the Plusoptix group, relatively more of the referred children had a diagnosis indicating some kind of vision/eye problem (69.6% compared with 42.9% in the vision screening group) and immediate therapy (66.3%, compared with 37.9% in the vision screening group).
Overall, of the 2,144 study children 29 children with amblyopia were detected by vision screening, i.e. 1.4% of 1 in 74. For screening with Plusoptix, these numbers are 23 detected with amblyopia, i.e. 1.1% or 1 in 93.

Table 16. Diagnostic results of children needing a referral, for YHC vision screening and Plusoptix.

Diagnostic results	**YHC vision screening**		**Plusoptix**	
	Number	**%**	**Number**	**%**
Number referred (% of total children)	294	13.7	140	6.5
Total arrived (% of children referred)	203	69.0	92	65.7
Number in target group amblyopia (% of children arrived: PPV)	29	14.3	23	25.0
Diagnostic conclusion	203		92	
No significant problem	116	57.1	28	30.4
Amblyopia (incl. other problems)	25	12.3	21	22.8
Strabismus (without amblyopia)	0	0.0	0	0.0
Refraction error (without amblyopia)	51	25.1	38	41.3
Other	11	5.4	5	5.4
Therapy	203		92	
Immediate treatment: Occlusion (with/without glasses)	5	2.5	4	4.3
Immediate treatment: Glasses (without occlusion)	72	35.5	57	62.0
Diagnostic follow-up (1-12m)	36	17.7	4	4.3
No therapy, or follow-up >1 y	90	44.3	27	29.3
Other	0	0	0	0

In total, 35 children were detected with amblyopia by either the current vision screening, the PO test, or both. 11 were detected at 3y, 16 at 3y9m and 8 at 5/6y.

In table 17, the results of both ways of screening are shown for these children with amblyopia (all ages combined). For the vision test protocol, 5 of the 6 children that remained undetected had a

sufficient score on at least one visit (2 at 3y, 1 at 3y9m, 2 at 5/6y), while 1 (3y9m) had no conclusion. For the Plusoptix test, 5 of the 12 children that remained undetected had a 'pass' (1 at 3y, 1 at 3y9m, 3 at 5/6y), while in 1 (3y) the test was not performed. 6 had the result 'refer or try again', i.e. the test did not give a conclusion (3 at 3y, 2 at 3y9m, 1 at 5/6y). In contrast to the vision test protocol, a visit for a second Plusoptix test was not protocolized in this study. The percentage agreement between the vision screening and the Plusoptix test for children detected with amblyopia, considering sufficient/pass, no conclusion/refer or try again, and insufficient/refer, was 50.0%.

Table 17. Results on vision screening (1 to 3 visits) and Plusoptix, for children detected with amblyopia.

Vision test after 1 to 3 visits	**Plusoptix**				
	Pass	Refer or try again*	*Refer*	Not performed*	Total
Sufficient**	0	0	*5*	0	5
No conclusion**	0	0	*1*	0	1
*Insufficient***	*5*	*6*	*17*	*1*	*29*
Total	5	6	*23*	1	35

* A 'refer or try again' outcome results if measuring circumstances have shortcomings (e.g. the light in the room) or if a complete image of both pupils cannot be made, e.g. because of an obstruction like a cataract or eye lashes, because the eyes are out of focus or because the child does not focus on camera.
Not performed: YHC professional registered in KD+ that the PO-test was not done.
No data: no outcome on the PO test is registered in KD+, and the YHC-ID number was not found back in the data files from the devices.
** Sufficient: 'sufficient' (=voldoende) at least one visit
Insufficient: 'insufficient' (=onvoldoende), or 2x 'doubtful'(=twijfel)/'tried, no result'(=niet gelukt), AND not sufficient
No conclusion: not sufficient or insufficient, e.g. only one doubtful result, or no test result because child did not cooperate

3.5 Costs of current YHC vision screening and test with Plusoptix

To calculate the costs of the current YHC vision screening the costs of each consultation was calculated by multiplying the time needed for the screening and the hourly wage of the professional. For the first visit, the time needed was often registered: in 70% for the vision test, 56% for the VOV and 96% for the Plusoptix test (all ages combined). For the second visit, the time needed was less often registered: 22% for the vision test, and 15% for the VOV. In order to obtain the average time needed with the corresponding standard deviation, missing time registrations were imputed.
In table 18, the average time needed for the tests are presented. On average the tests take longer at the age of 3 years; the screening at 5/6 years seems to go quicker and there was less variability in the time needed within this group.

Table 18. Mean time needed for the different screening tests by age group, and standard deviation (sd), in minutes. Calculations are based on imputated data if time measurements are lacking.

	3y				**3y9m**				**5/6 y**			
	N	N_{time}	mean	sd	N	N_{time}	mean	sd	N	N_{time}	mean	sd
First vision chart test	730	556	5.8	2.7	684	433	5.2	2.1	623	430	3.1	1.1
First VOV	106	69	2.2	1.8	128	58	1.4	1.7	42	29	1.1	0.7
Plusoptix	782	746	2.2	1.5	727	697	2.0	1.4	620	592	1.1	0.9
Second vision chart	275	72	6.0	2.6	132	21	6.2	2.9	42	5	4.8	1.8
Second VOV	24	4	2.2	0.5	13	2	2.3	0.6	4	0	2.4	0.2

N: number of children with a test result.
N_{time}: number of children with a time registration, for the other children time duration was estimated using the imputation technique described in the Methods section.

Table 19 gives the average costs per child for each test and each age group, with and without the VOV test, and with and without taking the costs for clinical consultations into account. The costs for the clinical consultation were only taken into account when the child had an insufficient test score and actually showed up at the clinic. Thus, if a child had an insufficient score on the vision chart test, but a pass on the Plusoptix device, the costs for the clinical visit were only taken into account when calculating the costs for the vision chart test.
For children aged 3y and 3y9m screening the average costs per child for screening with the Plusoptix are less than for screening with the current vision tests, whereas this is the other way around for children aged 5/6y.

Table 19. Average costs per child per screening method and per age group based on the imputed time registrations

Mean costs per child (€)	Current vision screening	Curr.vision screening +VOV	Plusoptix	Current vision screening	Curr.vision screening +VOV	Plusoptix
	Without clinical consultation			With clinical consultation (€80.87)		
3 years	8.85	9.46	3.92	17.77	18.37	6.61
3 years 9 months	9.95	10.39	3.73	20.39	20.80	7.51
5/6 years	2.74	2.90	5.36	6.89	7.04	9.41

Table 20 (first two columns) gives an overview of the results on screening performance and costs of the standard YHC vision screening (without costs of the VOV test) and screening with Plusoptix, by age group. Total costs including costs for the VOV are €100-500 higher per age group. These are presented in one of the footnotes of the table. Costs of the PO devices were distributed over the age groups as performed in practice in our study, i.e. 5 devices for age 3y and 3y9m combined, and 4 devices for age 5/6y.

3 years. For the total study group at the age of 3y, costs of screening with the Plusoptix and clinical consultation (€5,167) was less than half of the costs with the current vision screening (€13,718 without VOV, €14,184 with VOV). The number of children detected with amblyopia was 6 for screening with the PO versus 9 for the current vision screening, and costs per child detected were €861 for the Plusoptix screening and €1,524 for the current vision screening (€1,576 with VOV). The number of children needing a referral to the orthoptist was 3 times higher for the current vision screening compared to screening with the Plusoptix. The incremental costs for detecting 3 additional children with the current vision screening

Table 20. Screening performance and costs, for target group amblyopia, by age group. All study children. In table 3 the screening alternatives are explained.

	Study protocols			**Screening alternatives***			
Amblyopia target group	**Current vision screening^**	**Only PO&**	**Only PO&&**	**POLC1**	**POLC2**	**LCPO**	**LC&PO**
3 years							
Total costs (incl. clinical consultation; €)*	13,718^	5,167					
N with test performed	772	782					
N of children with amblyopia detected	9	6					
N of children with amblyopia missed	2	5					
N of children arrived at the clinic	83	26					
N of children who needed a referral to the clinic	132	49					
Costs per child screened (euro)*	17.77	6.61					
Costs per child detected with amblyopia (€)*	1,524	861					
3 years 9 months							
Total costs (incl. clinical consultation; €)*	14,704^	5,463	7,257	8,557	18,991	17,451	19,125
N with test performed	721	727		724	710	720	717
N of children with amblyopia detected	14	13		15	16	15	16
N of children with amblyopia missed	2	3		1	0	1	0
N of children arrived at the clinic	92	34		42	101	86	94
N of children who needed a referral to the clinic	122	50		61	186	158	174
Costs per child screened (euro)*	20.39	7.51	9.98	11.82	26.75	24.24	26.67
Costs per child detected with amblyopia (€)*	1,050	420	558	570	1,187	1,163	1,195
5/6 years							
Total costs (incl. clinical consultation; €)*	4,300^	5,831		6,236	9,244	6,791	7,613
N with test performed	624	620		620	619	624	619
N of children with amblyopia detected	6	4		4	8	6	8
N of children with amblyopia missed	2	4		4	0	2	0
N of children arrived at the clinic	31	32		32	54	27	49
N of children who needed a referral to the clinic	40	44		44	74	41	68
Costs per child screened (euro)*	6.89	9.41		10.06	14.93	10.88	12.30
Costs per child detected with amblyopia (€)*	717	1,458		1,559	1,155	1,132	952

^Without costs of VOV. As the current vision screening includes VOV tests, we also calculated total costs including costs for VOV for each age group. These were €14,184 for 3y, €15,041 for 3y9m and €4,396 for 5/6y. Costs per child screened including costs for VOV are presented in table 19.

& With costs for the PO devices distributed over the age groups as performed in practice in our study, i.e. 5 devices for age 3y and 3y9m combined, and 4 devices for age 5/6y.

&& The costs for age group 3y9m, when the costs of the five PO devices are all attributed to children aged 3y9m only (and not to age 3y). At 3y9m, these costs can be compared to the screening alternatives.

* With costs for the five PO devices for 3y and 3y9m attributed to the age group of 3y9m only. This causes higher costs for the screening alternatives at age 3y9m. When the Plusoptix devices are also used for the 3 year old children, the costs for the devices can be divided over the two groups. Then, the costs for 3y9m become € 5463, 6760, 17177, 14313, and 17313 for 'Only PO', POLC1, POLC2, LCPO and PO&LC respectively. The costs per child screened: € 7.51, 9.34, 24.19, 19.88, and 24.15, and the costs per detected child: € 420, 451, 1074, 954, and 1082, respectively.

(without VOV) compared to screening with the Plusoptix is €2,850 per extra child detected with amblyopia.

3 years and 9 months. For the total study group at the age of 3y9m, costs of screening with the Plusoptix and clinical consultation (€5,463) was also far less than these costs with the current vision screening (€14,704). The number of children detected with amblyopia was similar for both ways of screening (13 with PO, 14 with current vision screening), and costs per child detected with amblyopia were €420 for the Plusoptix screening and €1,050 for the current vision screening. The number of children needing a referral to the orthoptist was again about 3 times higher for the current vision screening compared to screening with the Plusoptix. The incremental costs for detecting 1 additional child with the current vision screening compared to screening with the Plusoptix are €9,241 per extra child detected with amblyopia.

5/6 years. For the age of 5/6y, the pattern is different than for the younger age groups. Total costs of screening is less for the current vision screening (€4,300) than for screening with the Plusoptix (€5,831). The number of children detected with amblyopia was 4 for screening with the PO versus 6 for the current vision screening, and costs per child detected were €1,458 for the Plusoptix screening and €717 for the current vision screening. The number of children needing a referral to the orthoptist was similar for both ways of screening. At this age, the current vision screening detects more children with amblyopia at lower costs than screening with the PO.

All ages. By using only the current vision screening guideline, in each age group two children of who we know they have amblyopia remained undetected. Thus, by making use of the Plusoptix device six extra children with amblyopia were detected who were missed by the current vision screening guideline. On the other hand, using only PO without vision screening left 12 children of who we know they have amblyopia undetected. This implies that combining both ways of screening may be worthwhile.

3.6 Screening alternatives

To determine if the YHC vision screening can be optimized using PO (research question 4), results are presented for combinations of screening with the vision chart tests and PO, for children aged 3y9m and 5/6y (table 20; see 2.6.2 and table 3 for explanation). These can be compared to the results from the current vision guideline and screening with only PO in the first columns. However, when calculating the costs for children aged 3 years and 9 months for the screening alternatives, costs for the five Plusoptix devices used for 3y and 3y9m combined were recalculated as if they were used for children aged 3y9m only, as it might be an option not to perform any vision screening at all at age 3y. In the footnote of the table, costs for 3y9m are also presented in case the devices are also used for children aged 3y. These costs are lower than those presented in the table, as in the footnote the costs for the devices are shared between more children over two age groups. To be able to compare the results of 'Only PO' with the other screening alternatives at 3y9m, we make the same distribution of the costs of the devices (attributed to 3y9m only) in a new 'Only PO' column.

It should be kept in mind that the estimated costs of screening and diagnostics in an age group and the costs per screened child are based on large numbers and thus reliable, however, costs per child detected with amblyopia and incremental costs for detecting additional children with amblyopia while comparing various screening alternatives are less reliable, as the number of children detected with amblyopia are small. In comparing various screening alternatives, especially the total costs per age group or costs per screened child use useful to compare, while it is good to have in mind that the performance of the screening in terms of number of children detected may deviate somewhat from our findings due to coincidence.

3.6.1 Screening alternatives at 3 years and 9 months

Also without using the PO at the age of 3y, the costs per child aged 3y9m with amblyopia detected are lowest for the scenario 'Only PO' (i.e. without a vision chart test): €558. With this screening 13 children with amblyopia were detected. 'Only PO' also has the lowest number of children with a referral to the clinic of all screening alternatives. In the alternative POLC1 (see table 3) 2 extra children with amblyopia are detected for an extra €1300, resulting in incremental costs for these children of €650 per child detected. This scenario is dominant over the current vision screening, as the latter detects one child less while the costs are much higher. The two screening alternatives that detect most children with amblyopia, POLC2 and LC&PO, have much higher costs. In POLC2, the incremental costs to detect one extra child with amblyopia compared to POLC1 are €10,400.
Thus, the screening alternative POLC1 seems most attractive for children age 3y9m, as it detects 15 children with amblyopia at costs of €570 per child detected. In this alternative, all children are screened with the PO, and all children with a 'refer' result are referred to the orthoptist. Only children with a 'refer or try again' result and children in which PO is not performed get a Landolt-C test.
In case the PO devices are also used for all children aged 3y, the costs for this screening alternative are even less, i.e. €6,760 for the total age group, €9.34 per child screened, and €451 per child detected with amblyopia.

The yield of screening at 3y9m may increase if no screening is performed at the age of 3y: it can be expected that part of the 11 children with amblyopia that were detected at 3y will then be detected at the age of 3y9m. However, obviously, the average age at detection will increase without screening at the age of 3y. If the costs of the PO are already attributed to the screening at age 3y9m, the costs for screening with the PO at the age of 3y and thus detecting already 6 children with amblyopia at 3y will be €3,374 (€1,268 for cost of YHC time and €2,106 for visits to the clinic), i.e. €562 per child aged 3y detected with amblyopia.

Other considerations. Other considerations relevant for the choice of the optimal screening alternative may be the number of children needing a referral to the clinic (current vision screening: 122, 'only PO': 50, POLC1: 61) and the age of detection of children with amblyopia.

3.6.2 Screening alternatives at 5/6 years

The costs for the current vision screening (without the costs for the VOV) were €4,300 for this cohort and it detected 6 children with amblyopia, which results in costs per detected child of €717 (see also table 20). All calculated alternatives have higher costs than the current vision screening guideline, as can be seen in table 20. The alternative LC&PO has the lowest costs per detected child of the alternatives (€952) and detects 8 children with amblyopia. Hence, also at age 5/6y the current vision screening guideline missed two children with amblyopia. The incremental costs compared to the current guideline for finding these two children are €1,650 per child.
Other considerations. Other considerations relevant for the choice of the optimal screening alternative may be the number of children needing a referral to the clinic (current vision screening: 40, 'only PO': 44, PO&LC: 68).

3.6.3 Optimal screening to detect children with amblyopia or significant refractive error

The results for the current vision guideline and the screening alternatives for the broader target group that includes not only children with amblyopia but also children with significant refractive error are presented in the appendix.
At the age of 3y, also for this target group costs per detected child are less for screening with the PO (€344) compared to the current vision screening (€528 without costs of VOV), but of the 31 children in the target group that are detected, only 15 are detected by the PO while the current vision

screening detects 26 of them. Incremental costs per extra detected child for the current vision screening compared to screening with the Plusoptix are €777.
At the age of 3y9m, results are similar to those at age 3y, although incremental costs using vision screening instead of the cheaper PO screening are now €1,320 per additionally detected child. The screening alternative POLC1 again seems attractive at this age, as 3 more children are detected at relatively low additional costs compared to 'Only PO' (3 additional children, at €433 per extra detected child).
At the age of 5/6y, results for this broader target group are similar to the results at this age for the more constrained target group of children with amblyopia.

In conclusion:
For screening at 3y, current vision screening with the APK is not recommended for the detection of children with amblyopia, as it gives high incremental costs compared to screening with the Plusoptix. Screening with the PO at 3y is recommended, especially if PO devices are already present at the YHC. If the costs of the PO are already attributed to the screening at age 3y9m, the costs for screening with the PO at the age of 3y and thus detecting already 6 children with amblyopia at 3y are €562 per child detected with amblyopia at the early of age 3y.

For screening at 3y9m, current vision screening with the Landolt-C is not recommended for the detection of children with amblyopia, as it gives high incremental costs compared to screening with the Plusoptix. Screening with the PO at 3y9m detects a similar number of children with amblyopia at much lower costs.
The screening alternative POLC1 seems most attractive for children age 3y9m, as it detects 15 children with amblyopia at costs of €570 per child detected. In this alternative, all children are screened with the PO, and all children with a 'refer' result are referred to the orthoptist. Only children with a 'refer or try again' result and children in which PO is not performed get a Landolt-C test.

For screening at 5/6y, current vision screening with the Landolt-C is preferable over screening with the PO, as costs are lower and the number of children detected with amblyopia are higher.
With the screening alternative LC&PO, in which all children are screened by the Landolt-C and the Plusoptix, 2 more children with amblyopia are detected, however incremental costs compared to the current guideline for finding these two children are €1,650 per child. Therefore, based on the study results the current vision screening without PO is recommended.

The target group of children with amblyopia or refraction error does not give reasons to change these conclusions.

3.7 Optimizing cut-off values of the Plusoptix

To determine whether the cut-off values of the Plusoptix can be optimized, the data from the Plusoptix device of the 12 children with amblyopia who did not get a refer from the device were checked. Of these 12 children, 6 children had a 'refer or try again' result (i.e. no satisfying measurement available) and 1 child did not have data from the Plusoptix device. The data of the other 5 children are given in table 21 below. None of the measurements are close to the threshold values (see table 1), i.e. this does not give a clue for optimization of the cut-off values.

Table 21. Children with amblyopia who were not identified by the Plusoptix device.

Age group	Sphere OD	Sphere OS	Cylinder OD	Cylinder OS	Gaze asymmetry
5/6y	0.48	0.27	-0.59	-0.45	1.33
5/6y	0.93	0.36	-1.04	-0.33	1.48
5/6y	0.85	1.47	-0.51	-0.50	0.94
3y9m	0.84	1.40	-0.48	-0.67	2.39
3y	0.61	1.95	-0.48	-1.57	3.57

To check if unneeded 'refer' results on the Plusoptix can be prevented, we also determined why children got a 'refer' result from the Plusoptix, i.e. what cut-off value was responsible for the 'refer' (table 22). In more than 60% astigmatism, i.e. the value for the cylinder, caused the 'refer', sometimes in combination with cut-off values for hyperopia or anisometropia. The reason for the 'refer' on the Plusoptix was also determined for the children who had a diagnostic investigation at

Table 22. Reason for a 'refer' result at the Plusoptix (first columns), and outcome of diagnostic investigations by the orthoptist in relation to the reason for the 'refer' (second part). Estimation of minimum and maximum positive predictive value (PPV) by reason for 'refer' (last two columns).

All children with 'refer' on Plusoptix					**Referred by PO and arrived at clinic**			**PPV**	
Reason for refer by Plusoptix	**Age**							**PPVmin**	**PPVmax**
	3y	**3y9m**	**5/6y**	**Total (a)**	**no ambl.**	**amblyopia (b)**	**Total (c)**	**b/a**	**b/c**
myopia	3	1	3	7	3	1	4	14,3%	25,0%
	6,7%	2,1%	7,3%	5,3%	4,3%	4,3%	4,3%		
hyperopia	0	1	1	2	0	1	1	50,0%	100,0%
	0,0%	2,1%	2,4%	1,5%	0,0%	4,3%	1,1%		
astigmatism (cyl)	26	21	25	72	42	8	50	11,1%	16,0%
	57,8%	44,7%	61,0%	54,1%	60,9%	34,8%	54,3%		
anisometropia	7	6	5	18	5	5	10	27,8%	50,0%
	15,6%	12,8%	12,2%	13,5%	7,2%	21,7%	10,9%		
anisocoria	1	3	1	5	2	0	2	0,0%	0,0%
	2,2%	6,4%	2,4%	3,8%	2,9%	0,0%	2,2%		
strabismus	2	3	1	6	3	0	3	0,0%	0,0%
	4,4%	6,4%	2,4%	4,5%	4,3%	0,0%	3,3%		
combination of hyp., astigm. and anisometropia	1	2	2	5	3	1	4	20,0%	25,0%
	2,2%	4,3%	4,9%	3,8%	4,3%	4,3%	4,3%		
combination of hyp. and astigm.	1	5	1	7	2	3	5	42,9%	60,0%
	2,2%	10,6%	2,4%	5,3%	2,9%	13,0%	5,4%		
combination hyp. and anisometropia	1	0	1	2	1	1	2	50,0%	50,0%
	2,2%	0,0%	2,4%	1,5%	1,4%	4,3%	2,2%		
combination astigm. and anisometropia	3	5	1	9	4	3	7	33,3%	42,9%
	6,7%	10,6%	2,4%	6,8%	5,8%	13,0%	7,6%		
no data from device, refer from KD+					4	0	4		
					5,8%	0,0%	4,3%		
Total (7 of 140 missing)	45	47	41	133	69	23	92	16,4%	25,0%

the clinic. The number of children is small in most rows, but we can see that referrals because of astigmatism resulted in the detection of 8 of the 23 children with amblyopia, and that we know that 42 of the 72 children who needed a referral for this reason did not belong to the target group. The PPV for this reason is thus estimated between 11-16%. Also for anisometropia the numbers are >5: the cut-off for anisometropia helped detecting 5 of 23 children with amblyopia at a PPV between 28% and 50%. Refers for anisocoria and strabismus never caused detection of children with amblyopia, but the number of children that got diagnosed is too small to draw the conclusion that referral for these reasons is not needed. In conclusion, this exercise does not give indications for improvement of the cut-off values.

Moreover, with the broader target group, including children with amblyopia and refraction error, 31 children were missed by the Plusoptix device (12 with amblyopia already discussed above, 19 with refraction error only). Again, some of the additional 19 children had a 'refer or try again' result with the Plusoptix device, namely 7 children. The data of the other 12 children are given in table A22 in the appendix. Again, no possibilities for improvements of the cut-off values became clear.

3.8 Subgroup analyses

3.8.1 Ethnic background

For 1769 of 2144 (82.5%) children the ethnic background could be determined by the country of birth of their parents. These consisted of 818 (46.2%) children with a Western background and 951 (53.8%) children with a non-Western background. Of the 35 children detected with amblyopia, 11 had a Western background, 19 a non-Western, and 5 had an unknown ethnic background. Thus, the percentage of children detected with amblyopia of the total number of screened children is lower in Western (1.3%) than in non-Western children (2.0%), but this difference is not significant (X^2(df)=0.77(1), p=0.38). In Western children, the 11 children with amblyopia were all detected at either 3y (5) or at 3y9m (6), but non at 5/6y. For non-Western children, detection of amblyopia also took place at 5/6y (3y: 5, 3y9m: 8, 5/6y: 6).

Screening. For children with a Western background as well as for children with a non-Western background, at age 3y and 3y9m the Plusoptix more often had a sufficient result ('pass') than the vision chart test (tables 23 and 24).
At the first visit, 62.0% of the non-Western children scored sufficient on the vision test whereas this is higher in the Western children (73.7%) (table 23). In younger children the vision test resulted more often in 'no data' in the non-Western children compared with the Western children (9.6% and 4.8%, respectively; X^2(df)=5.19(1), p<0.05) or was more often tried without a result (10.6% and 7.0%, respectively; X^2(df)=2.19(1), p=0.14). This might indicate that performing the vision test was more difficult in non-Western children, but there are many possible reasons for 'no data', so we cannot be certain. For Plusoptix, the 'refer or try again' result also occurred significantly more often in non-Western children in the 5/6 year group (X^2(df)=11.14(1), p<0.001). In the other age groups there were no significant differences.
This means that in the non-Western children, more children need a second visit or a referral to the orthoptist. The non-Western children were more often referred based on the total YHC vision screening (1-3 visits) compared with the Western children (17.5% versus 9.8%; X^2(df)=21.0(1), p<0.001, table 25), and Western children more often scored sufficient for the visits combined (84.8% versus 75.6%, not in table).
Similar results were found for the Plusoptix test, where 79.3% of the non-Western children passed the Plusoptix test compared to a higher percentage of 87.4% Western children. 9.0% of the non-Western children scored a 'refer' compared with 4.3% of the Western children (table 24). Thus, also for screening with the Plusoptix, more non-Western than Western children needed a referral for diagnostics (Plusoptix: X^2(df)=14.9(1), p<0.001).

Table 23. Results of vision test at first visit for Western children and for non-Western children.

Western children	Sufficient	Doubtful	Insufficient	Tried, but no result	No data	Total
3 years (APK)	224 63.1%	54 15.2%	35 9.9%	25 7.0%	17 4.8%	355 100%
3 years and 9 months (LC)	237 76.5%	7 2.3%	44 14.2%	10 3.2%	12 3.9%	310 100%
5/6 years (LC)	142 92.8%	5 3.3%	6 3.9%	0 0%	0 0%	153 100%
Total	603 73.7%	66 8.1%	85 10.4%	35 4.3%	29 3.5%	818 100%
Non-Western children						
3 years (APK)	128 41.0%	72 23.1%	49 15.7%	33 10.6%	30 9.6%	312 100%
3 years and 9 months (LC)	187 59.9%	3 1.0%	86 27.6%	12 3.8%	24 7.7%	312 100%
5/6 years (LC)	275 84.1%	29 8.9%	22 6.7%	0 0%	1 0.3%	327 100%
Total	590 62.0%	104 10.9%	157 16.5%	45 4.7%	55 5.8%	951 100%

Table 24. Result of Plusoptix test at first visit for Western children and for non-Western children.

Western children	Pass	Refer or try again*	Refer	Not performed*	No data*	Total
3 years	293 82.5%	43 12.1%	16 4.5%	2 0.6%	1 0.3%	355 100%
3 years and 9 months	276 89.0%	18 5.8%	14 4.5%	2 0.6%	0 0%	310 100%
5/6 years	146 95.4%	2 1.3%	5 3.3%	0 0%	0 0%	153 100%
Total	715 87.4%	63 7.7%	35 4.3%	4 0.5%	1 0.1%	818 100%
Non-Western children						
3 years	234 75.0%	51 16.4%	25 8.0%	2 0.6%	0 0%	312 100%
3 years and 9 months	251 80.4%	34 10.9%	27 8.7%	0 0%	0 0%	312 100%
5/6 years	269 82.3%	23 7.0%	34 10.4%	0 0%	1 0.3%	327 100%
Total	754 79.3%	108 11.4%	86 9.0%	2 0.2%	1 0.1%	951 100%

* A 'refer or try again' outcome results if measuring circumstances have shortcomings (e.g. the light in the room) or if a complete image of both pupils cannot be made, e.g. because of an obstruction like a cataract or eye lashes, because the eyes are out of focus or because the child does not focus on camera.
Not performed: YHC professional registered in KD+ that the PO-test was not done.
No data: no outcome on the PO test is registered in KD+, and the YHC-ID number was not found back in the data files from the devices.

Diagnosis. The percentage of children with a referral that also visited the clinic is comparable in both ethnic backgrounds (63-71%, table 25). For vision screening, also the percentage with a diagnosis of amblyopia is comparable in both groups (i.e., 14.5% of the Western children and 13.6% of the non-Western children; table 25), but for screening with PO this differed (40.9% vs 20.3%), however, due to small numbers this difference is not statistically significant (p=0.11).

Table 25. Diagnostic results of children needing a referral, for YHC vision screening and screening with Plusoptix for Western children and for non-Western children.

	YHC vision screening		Plusoptix	
Western children (N=818)	**Number**	**%**	**Number**	**%**
Number referred (% of total children)	80	9.8	35	4.3
Total arrived (% of children referred)	55	68.8	22	62.9
Number in target group ambl/occl (% of children arrived: PPV)	8	14.5	9	40.9
Non-Western children (N=951)				
Number referred (% of total children)	166	17.5	86	9.0
Total arrived (% of children referred)	118	71.1	59	68.6
Number in target group ambl/occl (% of children arrived: PPV)	16	13.6	12	20.3

Costs. For the current vision screening (including costs of VOV and including costs of clinical consultations) costs per screened child are lower for Western children compared to the group of all children (€14.17 vs €18.37) at the age of 3 years. Also at the age of 3y9m (Western €15.99; all €20.80) and at 5/6y (Western €5.32; all €7.04) costs per screened child are lower for Western children. For screening with the Plusoptix, these differences are also present, but smaller (3y: Western €5.99, all €6.61; 3y9m: Western €6.22, all €7.51; 5/6y Western €6.96; all €9.41).

As a large part of the population in the Netherlands is Dutch (72.4%) or other Western (11.2%), costs per screened child will likely be less for the population in the Netherlands, compared to the results presented in this study, in which Western and non-Western children were about equally distributed.

3.8.2 Language or developmental problems

49 out of 2144 (2.3%) children were registered as having language or developmental problems (16 at age 3y, 7 at 3y9m, 26 at 5/6y). Only 51% of these children scored sufficient at the first vision test, compared with 67.8% of all children. For the Plusoptix 85.7% of the children with language and developmental problems passed the Plusoptix, which was comparable to 83.4% for all children. Furthermore, 34% of the children with language and developmental problems needed a referral from the YHC vision screening whereas this was 8% for the Plusoptix screening (X^2(df)=4.5(1), p<0.05). Although in both groups all children but one got diagnosed, none of these children were diagnosed with amblyopia.
Although the sample is relatively small, we conclude that in children with language or developmental problems, screening with Plusoptix gives less false-positive test results that the current YHC vision screening.

3.8.3 Socioeconomic status (SES)

Indicators for socio-economic status are education, income and profession (www.volksgezondheidenzorg.info). Of these, we only have data on education of both parents. We assessed the relation between education of the mother and the first test result for the vision chart test and Plusoptix, and the results of vision screening after 1-3 visits, by age group. For the ages of 3y and

3y9m the percentage of insufficient results at the vision chart test and 'refer' on the Plusoptix, as well as the number of referrals after 1-3 screenings, is higher at a low educational level than with high education. At the age of 5/6y this effect still exists for the Plusoptix, but for the vision chart tests is had disappeared.

3.9 Test characteristics for detection of amblyopia

To answer research question 1, for the three tests used in the study (PO, APK and LC) the test characteristics for a single test were estimated. In table 26 the results of the first test are presented in the column 'total'. Children without data on the test were excluded from the table, whereas unclear test results on the vision tests ('doubtful' and 'tried, but no result') were combined into the outcome '?'.

Table 26. Data from cost-effectiveness study for estimation of test characteristics.

All children, Plusoptix		**Target group amblyopia**				**PPV**		
		+ (yes)	-(no)	*unknown*	*Total*	PPV_{min}	PPV_{max}	PPV_{best}
Plusoptix	+ (refer)	23	69	48	140	16.4	50.7	25.0
	- (pass)	5	178	1606	1789			
	? (refer or try again)	6	26	174	206			
		Prev*N	(1-prev)*N		N*: 2135			
3y, APK		**Target group amblyopia**						
		+ (yes)	-(no)	*unknown*	*Total*			
APK	+ (insuff)	5	34	65	104	4.8	67.3	12.8
	- (suff)	2	14	393	409			
	? (doubt/tried, but no result)	3	58	157	218			
		Prev*N	(1-prev)*N		N*: 731			
					788			
3y9m & 5/6y combined, LC		**Target group amblyopia**						
		+ (yes)	-(no)	*unknown*	*Total*			
Landolt-C	+ (insuff)	19	88	78	185	10.3	52.4	17.8
	- (suff)	3	44	998	1045			
	? (doubt/tried, but no result)	1	24	52	77			
		Prev*N	(1-prev)*N		N*: 1307			
					1356			

*N with a test result: 9 children did not have a PO result, 57 did not have an APK result and 49 did not have a landolt-C result.

3.9.1 Positive predictive value (PPV)

The positive predictive value (PPV) was estimated from the children with a positive, i.e.'+', test result (top row). A difficulty in the estimation is that the diagnosis of amblyopia (yes or no) is often unknown. The minimum PPV is calculated under the assumption that all these children with unknown diagnosis do not have amblyopia ($PPV_{min}=N_+$ / total, e.g. 23/140 for the PO). A maximum PPV is calculated under the assumption that all these children with unknown diagnosis do have amblyopia ($PPV_{max}=(N_+ + N_{unknown})$ / total, e.g. (23+48)/140 for the PO). The best estimate of the PPV is made by using only data from the children with a positive test who do have a diagnosis ($PPV_{best}=N_+ /(N_+ + N-)$, e.g. 23/(23+69) for the PO).

Thus, for the PO we estimated the PPV at 25.0% (range 16.4-50.7%), for the APK at 12.8% (range 4.8-67.3%) and for the Landolt-C at 17.8% (range 10.3-52.4%). These differences are not significant (X^2(df)=3.0(2), p=0.218).

For the APK and LC these values are somewhat higher than the estimates of the PPV for the vision screening protocol (guideline, with 1-3 visits with vision screening combined): the PPV to detect amblyopia with a series of APK tests had a PPV of 11.3%, while for the Landolt-C (1-3 visits) this was 16.2% (text above table 16).

3.9.2 Sensitivity

Sensitivity: Results from clinical study

The sensitivity was estimated from the data of the clinical study. In this study, 459 children who visited the HMC for vision or eye problems were included. The test results for APK, Landolt-C and Plusoptix (with the same cut-off criteria as used in the cost-effectiveness study in YHC) for all children are given in tables 27a and 27b, and separately for 61 children with amblyopia among them in tables 28a and 28b.

The sensitivity is calculated by dividing the children with amblyopia (in table 28) who got a positive test result (i.e. an insufficient test score for the APK or Landolt-C or a 'refer' on the Plusoptix) by the total number of children with amblyopia who had a test result.

Table 27. Results vision charts and Plusoptix all children clinical study.

Table 27a. Results of APK and Landolt-C (LC) vision test, all children in clinical study

	Vision test				
	Insufficient	Doubtful	Sufficient	No data	Total
APK, 3y (≤42 months)	9	17	12		38
APK, other age groups (>42 m)	17	6	5		28
Total APK	26	23	17		66
LC, 3y (≤42 months)	13	1	13		27
LC, other age groups (>42 m)	176	28	134		338
Total LC	189	29	147		365
Total*	208	49	160	42	459

* One test result per child. 14 children had an APK test as well as a Landolt-C: if they were aged ≤ 42 months the APK result was used, whereas the LC result was used if they were older. 42 of 459 children did not have a result on the APK or LC (no data).

Table 27b. Results Plusoptix test, all children in clinical study

	Plusoptix test				
	Pass	Refer or try again	Refer	No PO measurement	Total
3y (≤42 months)	53	4	14	1	72
3y9m (42–60 m)	126	14	82	15	237
5/6y (≥60 months)	78	14	49	9	150
Total	257	32	145	25	459

Table 28. Results vision charts and Plusoptix children with amblyopia clinical study.

Table 28a. Results of APK and Landolt-C (LC) vision test, children with amblyopia in clinical study

	Vision test				
	Insufficient	Doubtful	Sufficient	No data	Total
APK, 3y (≤42 months)	0	2	0		2
APK, other age groups (>42 m)	3	0	0		3
Total APK	3	2	0		5
LC, 3y (≤42 months)	2	1	0		3
LC, other age groups (>42 m)	30	5	10		45
Total LC	32	6	10		48
Total*	34	8	10	9	61

* One test result per child. 1 child aged 4.3 years had an APK test as well as a Landolt-C: the LC result was used because this test would be performed by the YHC. 9 of 61 children did not have a result on the APK or LC (no data).

Table 28b. Results Plusoptix test, children with amblyopia in clinical study

	Plusoptix test				
	Pass	Refer or try again	Refer	No PO measurement	Total
3y (≤42 months)	4	0	2	0	6
3y9m (42–60 m)	9	1	24	2	36
5/6y (≥60 months)	5	2	10	2	19
Total	18	3	36	4	61

APK. As the APK is meant for children aged 3y in YHC, only children up to 42 months of age should be included in the estimation. Unfortunately, only two children with amblyopia of this age had an APK. This number is too small: sensitivity of the APK test cannot be estimated from the clinical data.
Landolt-C. As the Landolt-C is meant for children aged 3y9m and older in YHC, only children aged 43 months and older should be included in the estimation. Of these, 30 of 45 children with amblyopia had an insufficient Landolt-C. Thus, sensitivity of the Landolt-C is estimated at 67% (95%CI 51-80%).
Plusoptix. The Plusoptix test can be used for all ages. Of 61 children with amblyopia in the clinical study, 4 did not have a measurement with the PO. 36 of the remaining 57 children with amblyopia had a 'refer' on the PO. Thus, sensitivity of the Plusoptix test is estimated at 63% (95%CI 49-75%).

Thus, in the clinical study the estimated sensitivity to detect children with amblyopia of the Landolt-C test is quite similar to the estimate of the Plusoptix.

Sensitivity from clinical study in children with a developmental or language delay. It is hypothesized that children with a developmental or language delay have more difficulties with the vision chart test than with the Plusoptix test. From all 61 children with amblyopia there were 13 children in the clinical study with a developmental or language delay.
These children often lacked a test result on the vision chart tests, but not on the Plusoptix test. At the APK vision chart test, only one child had a test result ('insufficient'). At the Landolt-C test about half of the children (6) did not have a test result. Of the other 7 children, 5 had an 'insufficient' result, 1 scored 'doubtful' and 1 'sufficient', i.e. if the test can be performed the sensitivity is 5/7=71% (95%CI 30-95), which is similar to the value found in all children (67%). For the Plusoptix test, 12 of the 13 children had a test result (2 with a 'pass', 9 'refer', 1 'refer or try again'). The sensitivity of the Plusoptix test in children with a developmental or language delay was 9/12=75% (95%CI 43-93%).

3.9.3 Specificity

The specificity was estimated from the children in the cost-effectiveness study under assumption of a fixed prevalence of 3% for the prevalence of amblyopia. With this prevalence, 64 of the 2,135 children with a Plusoptix result will have amblyopia (number for the cell 'Prev*N' in table 26), and 2,071 will not have amblyopia (cell '(1-prev)*N'). With these column totals, specificity was estimated under two assumptions. The first is that children with a positive test result but an unknown diagnosis of amblyopia have the same probability to have amblyopia as the children with a positive test result who did get a diagnosis. For the Plusoptix (top row in table 26), 23+48*(23/(23+69))=35 children would then have amblyopia and 69+48*(69/(23+69))=105 children would not have amblyopia. In this case, specificity is (2,071-105)/2,071=94.9% (95%CI 93.9-95.8%). The second assumption is that all children with unknown diagnosis do not have amblyopia. For the Plusoptix, 23 children would then have amblyopia, and 140-23=117 would not have amblyopia. Under this assumption, specificity is (2,071-117)/2,071=94.4% (95%CI 93.3-95.3%), i.e. 0.5% less than in the first estimate. These estimates are thus quite robust for this variation in the assumptions. Also, these estimates for the APK and Landolt-C are quite robust: respectively 87.2% (95%CI 84.4-89.5%) and 86.0% (95%CI 83.2-88.5%) for the APK and 88.0% (95%CI 86.1-89.7%) and 86.9% (95%CI 84.9-88.7%) for the Landolt-C. The estimated specificity is also quite independent of the assumption for the prevalence. Varying prevalence between 2% and 5% resulted in estimates of specificity between 94.4% and 94.2% for the Plusoptix, between 86.2% and 85.7% for the APK, and between 87.0% and 86.6% for the Landolt-C (all under the least favorable assumption for the specificity that all children with unknown diagnosis do not have amblyopia).

3.9.4 Overview of test characteristics

An overview of the estimated test characteristics is presented in table 29. Sensitivity and PPV of a single APK, Landolt-C and Plusoptix test to detect children with amblyopia are comparable, while specificity of the Plusoptix test is higher than specificity of the vision chart tests.

Table 29. Overview of estimated test characteristics to detect children with amblyopia, in %

	PPV best estimate (min-max)	Sensitivity* (95%CI)		Specificity min/max (95%CI) at prevalence of 3%
		Clinical study	Dev./language problems, clin. study	
APK	12.8 (4.8-67.3)	Not estimated	Not estimated	86.0 (83.2-88.5) / 87.2 (84.4-89.5)
LC	17.8 (10.3-52.4)	67 (51-80)	71 (30-95)*	86.9 (84.9-88.7) / 88.0 (86.1-89.7)
PO	25.0 (16.4-50.7)	63 (49-75)	75 (43-93)*	94.4 (93.3-95.3) / 94.9 (93.9-95.8)

LC: Landolt-C, PO: Plusoptix, PPV: positive predictive value

*in children with a test result. Only about half (7 of 13) of the child with a developmental of language problem had a test result on the Landolt-C, whereas 12 of 13 had a result on the Plusoptix.

3.10 Feasibility and acceptability of the current YHC vision screening and screening with the Plusoptix

3.10.1 Learning curve

In the first month of using the Plusoptix test, the number of 'refer or try again' test results was relatively high compared to the months thereafter (figure 4), indicating the need to get experienced. After this first month no further learning curve was visible.

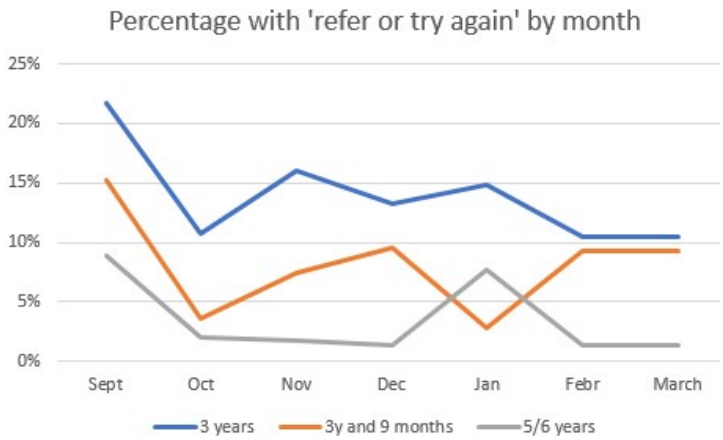


Figure 4. Percentage with 'refer or try again' result for the Plusoptix over time per screening age.

3.10.2 Focus group with YHC assistants

Results from the focus group discussion with YHC assistants show that they are very willing to work with the PO test. Five assistants agreed to participate in a focus group. The assistants had to practice for a while with the Plusoptix device in the beginning. After this period, they enjoyed working with the device. They preferred it over the standard vision screening. They mention more positive aspects of the Plusoptix (such as that it is easy to take a measurement and that it requires very little cooperation from the child). A negative aspect of the Plusoptix was that the touchscreen of some devices did not work well and it was not possible to take a measurement in all children. They mention more negative aspects of the standard vision screening (such as the fact that children need to speak Dutch well). A more extensive report in Dutch is available on request.

3.10.3 Focus group with YHC physicians

Six out of eight invited YHC physicians participated in a Whatsapp focusgroup discussion. Two did not respond. The six participants wrote on average 6.2 messages. The participants find it very important to detect amblyopia. A number of YHC physicians find it most important to detect as many children with amblyopia as possible. They prefer the current vision screening, because in absolute numbers, it detected most children with amblyopia. Other participants also consider the costs and number of false positives as important, because this is frustrating for parents. The YHC physicians mention that the goal of the vision screening is to detect amblyopia, but also refraction error, because this influences the development of children. The YHC physicians are concerned by the low percentage of children who visit the hospital after referral.

In terms of recommendation for the future, the YHC physicians considered a screening alternative with only PO at 3y, and a combination of PO and LC at 3y9m and 5/6y (named scenario 7) as the best option, because children will be screened at the age of three, against low costs. They would like more information on societal cost reduction of detecting children with amblyopia. A more extensive report in Dutch is available on request.

3.10.4 Interviews with parents

Telephone interviews were conducted among fourteen parents of children who were screened using the Plusoptix as well as the chart tests from the current YHC vision screening. Eight out of fourteen parents named positive aspects of the Plusoptix (fast and easy), seven out of fourteen parents named negative aspects of the standard vision screening (takes a long time, child did not like the test). Many parents expected their child not to need glasses before the visit in the hospital. This was a wrong expectation in most of these cases. Eight out of fourteen parents have a preference for the Plusoptix, while two have a preference for the standard vision screening. Three parents do not have a preference and one parent could not remember the tests. From the perspective of most parents, the Plusoptix is acceptable and feasible. A more extensive report in Dutch is available on request.

4. Discussion/Conclusion

In this study, the effectiveness and costs of the current Dutch vision screening was compared to screening with an autorefractive device in a large sample of 2144 children aged 3-6 years visiting the YHC in The Hague, the Netherlands. Two target groups were defined to be detected: children with amblyopia and children with amblyopia or significant refraction error. The first group, i.e. children with amblyopia, certainly need early detection and treatment. However, because YHC physicians mentioned to also find it important to detect significant refraction error at an early age, as they expect that these error also delay normal child development, we gave the results for the target group of children with amblyopia or refraction error in the Appendix. These result did not lead to different conclusions. Therefore, in this discussion, we focus on the main target group of children with amblyopia.
In this study, 35 children with amblyopia were detected in the YHC study group (1.6%). This percentage is lower than was expected based on literature (2-5%) (Lola Solebo, 2015). This can be explained by three reasons: 1) children that are already in care for their eyes/vision were excluded from the study, 2) amblyopia was only assigned if it remained present after a period of refractive adaptation. This rule is not always applied in other studies, which may result in an overestimation of children with amblyopia in literature, and 3) it is possible that not all children with amblyopia were detected during this study.

The research questions (referred to with Q and the number, see Introduction) are answered below.

(Q2: What are costs and effectiveness of using Plusoptix in YHC practice as compared to the current Dutch vision screening?)
The current YHC vision screening uses vision chart tests at the ages of three years (3y), 3 years and 9 months (3y9m) and 5/6 years (5/6y), and a VOV test in children with a 'doubtful' result on these test. We found that the costs of this screening are high at the ages of 3y and 3y9m, and can be reduced by using an autorefractive device, in our study the Plusoptix (PO). Details on costs and effectiveness of both ways of screening are presented in table 20.

VOV. In practice, the VOV test is not always performed when indicated, while the VOV is also performed on indication if the vision test has a result other than doubtful (tables 11a-c). This indicates that the VOV test is mostly done upon the professional judgement of its necessity instead of strictly following the guideline. In our study, only one of 2,144 children might have been referred because of the VOV test, and this child had no significant problem. Therefore, the results indicate that the VOV test is of little added value for the screening of children aged 3-6 years, and might be omitted as a structural part of an adapted vision screening guideline.

Other recommendations for vision screening. By using only the current vision screening guideline, in each age group two children of who we know they have amblyopia remained undetected. Thus, by making use of the Plusoptix device six extra children with amblyopia were detected who were missed by the current vision screening guideline. On the other hand, using only PO without vision screening left 12 children of who we know they have amblyopia undetected. This implies that combining both ways of screening may be worthwhile.

For screening at 3y, current vision screening with the APK is not recommended for the detection of children with amblyopia, as total costs for screening this age group are high, resulting in high incremental costs to detect additional children with amblyopia compared to screening with the Plusoptix. In addition, YHC physicians mentioned that the APK in children aged 3 years is often difficult to perform, and they would be pleased if an alternative would be available. Screening with

the PO at 3y should be considered, especially if PO devices are already present at the YHC. If the costs of the PO are already attributed to the screening at age 3y9m, the costs for screening with the PO at the age of 3y and thus detecting already 6 children with amblyopia are €562 per child detected with amblyopia at the early of age of 3 years.

For screening at 3y9m, current vision screening with the Landolt-C is not recommended for the detection of children with amblyopia, again because total costs for screening this age group are high, resulting in high incremental costs compared to screening with the Plusoptix. Screening with the PO at 3y9m detected a similar number of children with amblyopia at much lower costs.
The screening alternative POLC1 seems most attractive for children age 3y9m, as it detects 15 children with amblyopia at costs of €571 per child detected (table 20). In this alternative, all children are screened with the PO, and all children with a 'refer' result are referred to the orthoptist. Only children with a 'refer or try again' result (i.e. no 'pass'or 'refer' on the PO) get a Landolt-C test.

For screening at 5/6y, current vision screening with the Landolt-C is preferable over screening with the PO, as costs are lower and the number of children detected with amblyopia are higher. In this age group, the PO devices were not used efficiently in the study, as only 625 children were screened using four devices, resulting in high costs for the device per child screened (see methods section). However, also with the use of three instead of four PO devices, the preference for a vision chart test over 'only PO' remains.
With the screening alternative LC&PO, in which all children are screened by LC and PO, 2 more children with amblyopia were detected, however this alternative is also about 1.8 times more expensive than the current vision screening, resulting in high incremental costs per extra child with amblyopia detected. Therefore, based on the study results the current vision screening without PO is recommended for the age of 5/6y.

It should be kept in mind that the estimated costs of screening and diagnostics in an age group and the costs per screened child are based on large numbers and thus reliable. However, costs per child detected with amblyopia and incremental costs for detecting additional children with amblyopia while comparing various screening alternatives are less reliable, as the number of children detected with amblyopia is small. In comparing various screening alternatives, especially the total costs per age group or costs per screened child are useful to compare, while it is good to have in mind that the performance of the screening in terms of number of children detected may deviate somewhat from our findings due to coincidence. The number of children to be detected is larger in the target group of children with amblyopia or refraction error. Analyses based on this target group do not give reasons to change the recommendations given above.

Revised YHC guideline for vision screening. The YHC guideline for vision screening is currently under revision. In the concept revised guideline, the APK test and VOV are being omitted. Our data support these changes. However, in the concept revised guideline, no screening is present at all at the age of 3y, and a vision chart test (E-hooks instead of Landolt-C) is recommended for all children aged 3y9m and 5/6y. Whereas our findings support using a vision chart test at the age of 5/6 years, we found alternatives that are cost-effective compared to vision screening for the age group of 3y9m. In the best alternative at 3y9m all children are screened with the PO, and all children with a 'refer' result are referred to the orthoptist to get extensive diagnostic tests on vision. Only children with a 'refer or try again' result get a vision chart test in the YHC setting, thus children with a 'pass' do not get a vision chart test at the age of 3y9m, but all get it at later age (5/6y). We heard hesitations for this recommendation from orthoptists and ophthalmologists, who prefer a functional vision test like the vision chart test for all children at the age of 3y9m as they are afraid that autorefraction tests will miss certain risk factors for amblyopia, like microstrabismus. However, our findings show that with our recommendation similar numbers of children with amblyopia are detected at much lower cost,

and thus are a better alternative. And if part of the children with specific deviations are missed using autorefractive tests, they will get a vision chart test at the age of 5/6 y. We agree that it is better to detect the children at an earlier age, but our findings indicate that not many children will get this delayed detection. Our recommendations are also in accordance with the recommendations of the USPSTF (2011) and AAPOS (2012) to give each child at least one vision screening between the ages of 3 and 5 years, to detect the presence of amblyopia or its risk factors. These institutes indicate that at younger age autorefractive testing might be an alternative to vision charts at the age of 3 through 5 years.

In the concept revised YHC guideline the E-hooks test is recommended instead of the Landolt-C. We are not aware of studies supporting that the performance of the E-hooks test is better than the Landolt-C. Interpretation of our results as outcomes of the concept revised guideline can only be made under the assumption that the performance of the E-hooks test is the same as we measured with the Landolt-C test. At the age of 3y9m the revised YHC guideline has other cut-off values for the E-hooks test than stated in the current guideline for the Landolt-C test: if children score line 0.5 for both eyes, or 0.5 for one eye and 0.63 for the other eye, the conclusion of the test has become 'doubtful' in the revised YHC guideline, whereas it is 'sufficient' in the current guideline. We found that this adaptation increased the number of children with a 'doubtful' result from 13 to 301, i.e. a huge increment. However, we are afraid this cannot be interpreted well, as it may be the case that the YHC professionals stopped testing when the line on the chart that gave a 'sufficient' test result was reached.

Implementation of the recommended screening alternatives at 3y and 3y9m will require investments of the YHC organizations, as they will need to purchase the autorefractive devices. The cost savings are distributed over two parties. The YHC has cost savings as YHC professionals will need less time to perform the vision screening, but also insurance companies will save substantial costs as less children will need a referral to the clinic for diagnostic evaluation. Of the total costs for vision screening per age group, about half is caused by the clinical consultations. Thus, a successful implementation with cost savings is of interest for not only YHC, but also the insurance companies.

Limitations of the study.
Study design. A limitation of our study is that it is a cross-sectional study performed in three age groups, while for the choice of the optimal screening alternative it would be better to follow a cohort of children, to be able to see how the choice of a screening test (or no screening) at a certain age affects the screening outcomes at the next age. It is important to investigate the effect of not screening at all at the age of 3y. It can be expected that part of the children with amblyopia that remain undetected at the age of 3y will be detected at the age of 3y9m, however, with our study design we cannot estimate how many children will remain undetected. Unfortunately, nobody can estimate the effect of omitting a vision screening at the age of 3 years. However, we do know that by using the Plusoptix at this age without the APK, at least part of the children with amblyopia will already be detected at costs which are far less than the current vision screening.
Costs per child detected with amblyopia at the age of 3y9m will likely be less than presented in our study if screening at the age of 3y is omitted, and also if only the Plusoptix test is used at 3y, as the same costs for screening and diagnosis can be distributed among more children with amblyopia that are detected in this age group of 3y9m.
The number of children per age group in our study decreased with age, affecting total costs per age group. This effect was expected, and can be explained because with increasing age more children are already familiar with eye/vision problems and are already in care in the clinic. These children do not need vision screening anymore. Therefore, we did not recalculate the costs to age groups with a fixed number of e.g. 1000 children.

Consecutive test order. Another limitation is that for our study, children aged 5/6y were first screened using the vision chart test, and thereafter the Plusoptix test was done by the same YHC assistant. This order was chosen because we judged the Plusoptix outcome more objective and less dependent on knowledge of the result on the other test. However, if children have become tired of the vision test, it may be harder to obtain a result on the Plusoptix test. Thus, the percentage with 'refer or try again' may be less if this order of testing changes. At the younger ages (3y and 3y9m) the test order was reversed: first the Plusoptix and then – by another YHC professional (blinded for the PO result) - the vision test. The chance that the Plusoptix test negatively affects the vision chart outcomes is also present, but it is likely that the effect is smaller as it takes less time.

Test results. In the analysis, we used the line numbers per eye that the child could still read and the criteria from the YHC vision guideline to draw a conclusion of the standard vision screening per visit, i.e. sufficient, doubtful or insufficient. In 93% this conclusion was in agreement with the conclusion as registered by the YHC professional. However, in some cases this conclusion was not the same. In most cases, the test results were 'insufficient' on one and 'doubtful' on the other conclusion, which is a less relevant difference as follow-up is needed for both of these outcomes. However, in 37 children a sufficient result was registered by the YHC professional, while the line numbers indicated an insufficient or doubtful outcome. In most of these cases this could be explained by misinterpretation of the cut-off values in the vision guideline, i.e. use of the cut-off values for the APK at 5 meter while the APK was at 3 meter. However, the discrepancy might in some cases also have been the result of professional interpretation, e.g. the YHC professional relies on his/her own judgement to draw a conclusion. Based on the frequency and type of discrepancies between the conclusion based on the line numbers per eye and the registration by the YHC professional, we expect that these discrepancies only have a small effect on the results of this study.

Generalizability. Our study was performed by the YHC of The Hague, a large city. A large part of our population was non-Western, which affects the study results (see Q4, Ethnic background). Another issue is the number of Plusoptix devices needed to test the children. This will likely depend on the organization of the YHC. We already saw a large difference between YHC for children aged under 4 years (3y and 3y9m) and YHC for children aged 5/6y. In the latter, 4 devices were used to screen 625 children in half a year (156 children per device), whereas 1,519 children aged 3y and 3y9m were screened in the same period using five devices (304 children per device), i.e. almost twice as much children per device. Obviously, this affects the screening costs. In other areas and other YHC organizations, this likely will also vary. For a successful implementation, it is necessary to investigate per YHC organization how the devices can be optimally used to screen as many children as possible, for instance by transporting the device if YHC locations are only open on one of two days per week. Maybe even other possibilities can be thought off, for instance special sessions in which many children are screened in a short time period.

(Q4: Is it possible to improve the current Dutch vision screening in specific subgroups of children (e.g. migrants, lower SES and intellectual disability, various ages) by screening with Plusoptix, with regard to costs and effects?)
Results were also analyzed for subgroups of children to detect if it is possible to improve the current Dutch vision screening in specific subgroups of children (e.g. migrants, lower SES and intellectual disability, various ages) by screening with Plusoptix.

Age. As already discussed above, the effect of age on vision screening results is large, and age-specific recommendations are needed, and provided above.

Ethnic background. We also investigated the results for children with different ethnic backgrounds. It was expected that screening would be improved by the Plusoptix, especially for children with a non-

Western background, of which part may have difficulties with the instructions for the vision chart test due to language problems. Indeed, at the first visit, more Western than non-Western children scored sufficient on the vision test. The non-Western children were more often referred based on the total YHC vision screening (1-3 visits) compared with the Western children. However, similar results were found for the Plusoptix test, where also more Western than non-Western children passed the Plusoptix test. This did not confirm that the Plusoptix would be more helpful in children with a non-Western background.
However, it became clear that the differences resulted in lower costs per screened child for Western children compared to non-Western children. As in our study population about 50% was non-Western, while this is less than 20% for the Netherlands, costs per screened child will likely be less for the total population in the Netherlands, compared to the results presented in this study. This is expected for the vision chart tests as well as for screening with the Plusoptix, although the difference is smaller for the latter test.
We are not aware of differences in prevalence of amblyopia between ethnic groups, but in our study the percentage of children detected with amblyopia in our study was lower in Western (1.3%) than in non-Western children (2.0%). Although this difference is not significant, it might be explained by the possibility that part of the children with amblyopia are not in our study, but were excluded since they were already in care for a vision or eye problem. E.g. in children aged 5/6y none of the children detected with amblyopia were Western, therefore our results indicate that this early detection may occur more often in Western than in non-Western children. Unfortunately, we do not have data to further investigate this, but if this is the case, current vision screening might have contributed to unequal health care effects between these groups. It remains to be seen if the difference becomes smaller after introduction of the autorefractive tests to vision screening.

Language and developmental problems. There was a small group of children identified with language and developmental problems. When we compared the results from the vision test to the results from the Plusoptix, we found that the vision test more often resulted in unnecessary referrals compared with the Plusoptix. Accordingly, we can conclude that in children with language or developmental problems, screening with Plusoptix gives less false-positive test results than the current YHC vision screening.

SES. Indicators for social-economic status are education, income and profession (www.volksgezondheidenzorg.info). Of these, we only have data on education of both parents. For the ages of 3y and 3y9m the percentage of insufficient results at the vision chart test and 'refer' on the Plusoptix, as well as the number of referrals after 1-3 screenings, is higher at a low maternal educational level than with high education. At the age of 5/6y this effect still exists for the Plusoptix, but for the vision chart tests it is disappeared. However, these findings do no give reason to develop a vision screening protocol that is different for children from parents with a low educational level than for children with parents with a high educational level.

(Q5: Is it possible to improve the current referral criteria as defined by the American Association for Pediatric Ophthalmology and Strabismus (AAPOS) to enhance screening performance of the Plusoptix in The Netherlands?)
To investigate the possibility to improve the current referral criteria to enhance screening performance of the Plusoptix in The Netherlands, we investigated the Plusoptix results for children in the target groups that were missed with the Plusoptix test. Many of these children were not referred by Plusoptix because they had a 'refer or try again', i.e. a failed measurement. For ethical reasons, i.e. reducing unwanted referrals to the orthoptist, according to the study protocol no referral was given in these cases. If another choice had been made, these children might have been detected. The other missed children, who did have data from the Plusoptix device, had normal values. No indication was found with for improving the referral criteria in order to detect more children in the target group.

One of the drawbacks of screening with an autorefractive device is that hyperopia may be hard to detect, as the eyes can accommodate which results in lower values for the sphere. In this study, the Plusoptix cut-off value for referral for hyperopia was set at an high value, i.e. ≥ 4.0 D, which may lead to missed cases with hyperopia. The Plusoptix manufacturer advices to use a cut-off value of ≥ 1.0 D for this reason. However, using this value in the YHC population would have led to 726 extra referrals, which is 34% of the children in this cohort, based on the Plusoptix screening result. It is not desirable to send that many children to the orthoptist for clinical consultation.
The reasons for a 'refer' result on the Plusoptix were also investigated. More than half of the 'refer' results in our study were caused by the cut-off value for astigmatism (cylinder≥2 D for children aged 31-47 months and ≥1.5 D for children aged 48 or more months, table 1). In the results with the Plusoptix from Flanders, this cut-off value also caused most refers (49.0% for children age 23-30 months, with a cut-off value of ≥2 D; Kind&Gezin, Cijferrapport oogscreening 2015). After 1 november 2015, Kind&Gezin reduced this cut-off to ≥2.5 D, which resulted in a reduction of over 50% for these refers. However, it was not clear if children belonging to the target group remained undetected by this change. Therefore, unfortunately these data do not help us to get an idea on optimizing the cut-off values for the Plusoptix.

(Q1: What is the validity (sensitivity, specificity, positive predictive value) of the current Dutch vision screening as well as the screening by Plusoptix, in children aged 3y, 3y9m and 5/6y, to detect amblyopia or risk factors for amblyopia requiring treatment?)
The test characteristics of the current Dutch vision screening as well as the screening by Plusoptix were difficult to assess. We used the target group of children with amblyopia to estimate them. An overview of the estimates is given in table 29. In short, sensitivity and positive predictive value of a single APK, Landolt-C and Plusoptix test to detect children with amblyopia are comparable, while specificity of the Plusoptix test is higher than specificity of the vision chart tests.

PPV. A difficulty in the estimation of the positive predictive value (PPV) is that the diagnosis of amblyopia (yes or no) is often unknown. Under two extreme assumptions (all children with unknown diagnosis either do not or do have amblyopia) a minimum and maximum PPV were calculated. Also, a best estimate of the PPV was made by using only data from the children with a positive test who do have a diagnosis. Thus, for the Plusoptix we estimated the PPV at 25.0% (range 16.4-50.7%), for the APK at 12.8% (range 4.8-67.3%) and for the Landolt-C at 17.8% (range 10.3-52.4%).
For the APK and LC these values for a single test are somewhat higher than the estimates of the PPV for the vision screening protocol (guideline, with 1-3 visits with vision screening combined): the PPV to detect amblyopia with a series of APK tests had a best estimated PPV of 11.3%, while for the Landolt-C (1-3 visits) this was 16.2% (text above table 16).

Sensitivity. Sensitivity for detecting children with amblyopia was estimated from the data of the clinical study. The APK, meant for children aged 36-42 months, was performed in only two children with amblyopia of this age. This number is too small: sensitivity of the APK test cannot be estimated from the clinical data. The Landolt-C and Plusoptix were performed in respectively 45 and 57 children with amblyopia in the appropriate age group. With these, sensitivity of the Landolt-C was estimated at 67% (95%CI 51-80%) and sensitivity of the Plusoptix test was estimated at 63% (95%CI 49-75%). Thus, in the clinical study the estimated sensitivity to detect children with amblyopia of the Landolt-C test is quite similar to the estimate of the Plusoptix. However, the number of children with amblyopia was small, giving raise to uncertainty of these estimates. Also, the estimate of the sensitivity of the Landolt-C may be biased upwards, because it is likely that part of the children in the clinical study visited the orthoptist because they scored insufficient on an earlier the Landolt-C test at the YHC vision screening. These children are likely to score 'insufficient' again when the test is repeated.

Besides the upwards bias due to referrals from the same tests, our estimates of sensitivity may also be too low: they become higher if the 'doubtful' score on the vision tests and the 'refer or try again' result of the Plusoptix are not classified as test negative.

Only a small number of children with developmental or language delays belonged to the target group, making the estimate of sensitivity in this group imprecise. However, it is clear that the testability of these children is higher with the Plusoptix than with a vision chart test, as 97% (69 of 71) in the clinical study have a test result on the Plusoptix, whereas this is 72% (51 of 71) for the vision charts (APK or Landolt-C).

Specificity. The specificity was estimated from the children in the cost-effectiveness study under assumptions for prevalence of amblyopia and the fraction of children with a positive test result but an unknown diagnosis of amblyopia that actually have amblyopia. Estimates of specificity were quite independent of these assumption, and are estimated at 86.0-87.2% for the APK, 86.9-88.0% for the Landolt-C, and 94.4-94.9% for the Plusoptix.

Comparison with literature. The USPSTF recently reviewed test accuracy of a divers set of tests used to detect amblyopia or its risk factors (Jonas, 2017).
For the Plusoptix, our sensitivity and specificity were about 0.63 and 0.95. The USPSTF found studies with similar sensitivity and specificity as in our study (their table 4), e.g. a sensitivity of 0.83 and a specificity of 0.95 to detect amblyopia risk factors (Arthur, 2009) or -if criteria for referral are probably less strict - a sensitivity/specificity set of 0.54/0.90 to detect amblyopia risk factors or significant nonamblyogenic refractive error (VIP study group, 2004), and 0.98/0.68 or 0.98/0.88 to detect amblyopia risk factors (Matta, 2008). Only Dahlmann-Noor (2009) had criteria that gave very high specificity: sensitivity/specificity were 0.45/1.0 for decreased visual acuity, strabismus, and ptosis.
For the visual acuity tests (the vision chart tests) no data were reported on the APK and Landolt-C, but sensitivity and specificity of crowded LEA symbols were often similar (e.g. 0.61/0.90 in Schmidt, 2004; ±0.61/±0.91 in VIP study group, 2010) than our results for the Landolt-C (sens/spec 0.67/0.88).

Program validity. While the validity of the chart tests used in the YHC vision screening and the Plusoptix were compared, the validity of the current vision screening as a whole (1-3 visits combined) could not be compared with a screening program of consecutive tests using the Plusoptix because only one PO test was performed. Also, in the clinical study which was used to estimate sensitivity, only one vision chart test and one Plusoptix test were performed, and thus it was not possible to estimate the sensitivity of the combination of more vision chart tests.
The program sensitivity of the current vision screening may be higher than the test sensitivity, as also a 'doubtful' result on two YHC visits will lead to a referral to the clinic, whereas this score was interpreted as 'test negative' in the calculations of test sensitivity. On the other hand, not all children with a test positive result arrive at the clinic for diagnostic testing, which may result in a decrease of the program sensitivity. Especially this last issue may be worthwhile to act upon: if the referral could be optimized this may result in detection of more children in the target group. However, we do not know how many children with amblyopia remain undetected despite a positive test result because they do not arrive at the clinic: possibly professionals or parents make a proper judgement of the child's vision and decide justly that there is no need to visit the clinic despite the positive test result.

(Q3: What is the feasibility and acceptability of using Plusoptix in YHC practice among professionals and parents, compared to current Dutch vision screening?)
The feasibility and acceptability of using Plusoptix in YHC practice among professionals and parents, compared to current Dutch vision screening, was high. Results from the focus group discussion with

YHC assistants show that they are very willing to work with the PO test. Based on qualitative research methods among YHC professionals and parents, it seems that the Plusoptix is feasible and acceptable in practice. Except for the reason mentioned that the Plusoptix might not be the most effective screening method at all ages, there are no other compelling reasons mentioned against using the Plusoptix in practice. Both parents and YHC professionals comment the Plusoptix for being fast and requiring very little cooperation of the child. All YHC assistants preferred the Plusoptix over the standard vision screening. Some parents and YHC physicians have a preference for the standard vision screening. For parents this was mostly because in their case the Plusoptix was incorrect. For the YHC physicians this was because in absolute numbers, the standard vision screening detected more children with amblyopia.

Conclusion
Our results imply that vision screening in Dutch Youth Health Care (YHC) can be improved by adding the Plusoptix autorefraction test. We recommend the use of autorefractive devices for YHC screening to detect children with amblyopia at the ages of three years and three years and 9 months, and to maintain the current vision screening at the age of 5/6 years.

5. Literature

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Appendix A

A.1 Results for the target group of children detected with amblyopia or significant refraction error

Table A16. Diagnostic results of children needing a referral, for YHC vision screening and screening with Plusoptix.

Diagnostic results	**YHC vision screening**		**Plusoptix**	
	Number	**%**	**Number**	**%**
Number referred (% of total children)	294	13.7	140	6.5
Total arrived (% of children referred)	203	69.0	92	65.7
Number in target group amblyopia or significant refraction error (% of children arrived: PPV)	66	32.0	49	53.3

Table A17. Results on vision screening (1 to 3 visits) and Plusoptix, for children detected with amblyopia or significant refraction error.

	Plusoptix				
Vision test after 1 to 3 visits	Pass	Refer or try again*	*Refer*	Not performed*	Total
Sufficient**	0	0	*11*	0	11
No conclusion**	1	0	*2*	0	3
*Insufficient***	*16*	*13*	*36*	*1*	*66*
Total	17	13	*49*	1	80

* A 'refer or try again' outcome results if measuring circumstances have shortcomings (e.g. the light in the room) or if a complete image of both pupils cannot be made, e.g. because of an obstruction like a cataract or eye lashes, because the eyes are out of focus or because the child does not focus on camera.
Not performed: YHC professional registered in KD+ that the PO-test was not done.
No data: no outcome on the PO test is registered in KD+, and the YHC-ID number was not found back in the data files from the devices.
** Sufficient: 'sufficient' (=voldoende) at least one visit
Insufficient: 'insufficient' (=onvoldoende), or 2x 'doubtful'(=twijfel)/'tried, no result'(=niet gelukt), AND not sufficient
No conclusion: not sufficient or insufficient, e.g. only one doubtful result, or no test result because child did not cooperate

Table A20. Screening performance and costs, for target group amblyopia or significant refraction error, by age group. All study children. In table 3 the screening alternatives are explained.

	Study protocols			Screening alternatives*			
Target group amblyopia or significant refraction error	**Current vision screening^**	**Only PO&**	**Only PO&&**	**POLC1**	**POLC2**	**LCPO**	**LC&PO**
3 years							
Total costs (incl. clinical consultation; €)*	13,718^	5.167					
N with test performed	772	782					
N of children in target group detected	26	15					
N of children in target group missed	5	16					
N of children arrived at the clinic	83	26					
N of children who needed a referral to the clinic	132	49					
Costs per child screened (euro)*	17.77	6.61					
Costs per child in target group detected (€)*	528	344					
3 years 9 months							
Total costs (incl. clinical consultation; €)*	14,704^	5,463	7,257	8,557	18,991	17,451	19,125
N with test performed	721	727		724	710	720	717
N of children in target group detected	28	21		24	31	28	30
N of children in target group missed	3	10		7	0	3	1
N of children arrived at the clinic	92	34		42	101	86	94
N of children who needed a referral to the clinic	122	50		61	186	158	174
Costs per child screened (euro)*	20.39	7.51	9.98	11.82	26.75	24.24	26.67
Costs per child in target group detected (€)*	525	260	558	357	613	623	638
5/6 years							
Total costs (incl. clinical consultation; €)*	4,300^	5,831		6,229	9,244	6,791	7,612
N with test performed	624	620		620	619	624	619
N of children in target group detected	12	13		13	18	12	18
N of children in target group missed	6	5		5	0	6	0
N of children arrived at the clinic	31	32		32	54	27	49
N of children who needed a referral to the clinic	40	44		44	74	41	68
Costs per child screened (euro)*	6.89	9.41		10.05	14.93	10.88	12.30
Costs per child in target group detected (€)*	358	449		479	514	566	423

^Without costs of VOV. As the current vision screening includes VOV tests, we also calculated total costs including costs for VOV for each age group. These were €14,184 for 3y, €15,041 for 3y9m and €4,396 for 5/6y. Costs per child screened including costs for VOV are presented in table 19.

& With costs for the PO devices distributed over the age groups as performed in practice in our study, i.e. 5 devices for age 3y and 3y9m combined, and 4 devices for age 5/6y.

&& The costs for age groups 3y and 3y9m, when the costs of the five PO devices are all attributed to children aged 3y9m only (and not to age 3y). At 3y9m, these costs can be compared to the screening alternatives.

* With costs for the five PO devices for 3y and 3y9m attributed to the age group of 3y9m only. This causes higher costs for the screening alternatives at age 3y9m. When the Plusoptix devices are also used for the 3 year old children, the costs for the devices can be divided over the two groups. Then, the costs for 3y9m become € 5463, 6760, 17177, 14313, and 17313 for 'Only PO', POLC1, POLC2, LCPO and PO&LC respectively. The costs per child screened: € 7.51, 9.34, 24.19, 19.80, and 24.15, and the costs per detected child: € 260, 282, 554, 509, and 577, respectively.

Table A21. Children with amblyopia or significant refraction error who were not identified by the Plusoptix device*.

Age group	Sphere OD	Sphere OS	Cylinder OD	Cylinder OS	Gaze asymmetry	Refraction error HMC
3y	0.87	1.07	-0.65	-0.66	2.39	Hyperopia
3y	2.04	1.18	-0.93	-0.69	0.66	Hyperopia
3y	0.42	0.60	-0.21	-0.60	1.33	Hyperopia
3y9m	1.06	0.87	-0.37	-0.62	1.33	Hyperopia
3y	0.48	0.62	-0.76	-0.73	3.32	Hyperopia
5/6y	0.84	1.04	-0.87	-0.64	0.94	Hyperopia
3y9m	0.23	0.92	-0.36	-0.92	1.48	Hyperopia
3y	0.51	1.70	-0.44	-0.69	1.48	Hyperopia
3y9m	0.82	1.68	-1.00	-1.72	3.32	Astigmatism
3y9m	0.98	1.21	-1.73	-1.98	2.97	Astigmatism
3y9m	0.26	-0.09	-0.76	-0.35	1.99	Hyperopia
3y9m	1.20	1.78	-0.75	-0.26	1.48	Hyperopia

*14 children are left out of this table because the result was 'refer or try again' and thus failed, and 5 children are left out because they are already in table 21 'Children with amblyopia who were not identified by the Plusoptix device'.

Table A25. Diagnostic results of children needing a referral, for YHC vision screening and screening with Plusoptix for Western children and for non-Western children.

	YHC vision screening		Plusoptix	
Western children (N=818)	**Number**	**%**	**Number**	**%**
Number referred (% of total children)	80	9.8	35	4.3
Total arrived (% of children referred)	55	68.8	22	62.9
Number in target group amblyopia or significant refraction error (% of children arrived: PPV)	19	34.5	14	63.6
Non-Western children (N=951)				
Number referred (% of total children)	166	17.5	86	9.0
Total arrived (% of children referred)	118	71.1	59	68.6
Number in target group amblyopia or significant refraction error (% of children arrived: PPV)	37	31.6	28	47.5

Table A26. Estimation of test characteristics based on data from cost-effectiveness study.

All children, Plusoptix		**Target group amblyopia or refraction error**				**PPV**		
		+ (yes)	-(no)	*unknown*	*Total*	PPV_{min}	PPV_{max}	PPV_{best}
PO	+ (refer)	49	43	48	140	35.0	69.3	53.3
	- (pass)	17	166	1606	1789			
	? (refer or try again)	13	19	174	206			
		Prev*N	(1-prev)*N		N*: 2135			
3y, APK		**Target group amblyopia or refraction error**						
		+ (yes)	-(no)	*unknown*	*Total*			
APK	+ (insuff)	13	26	65	104	12.5	74.0	33.3
	- (suff)	2	14	393	409			
	? (doubt/tried, but no result)	14	47	157	218			
		Prev*N	(1-prev)*N		N*: 731			
					788			
3y9m & 5/6y combined, LC		**Target group amblyopia or refraction error**						
		+ (yes)	-(no)	*unknown*	*Total*			
Landolt-C	+ (insuff)	37	70	78	185	20.0	62.2	34.6
	- (suff)	8	39	998	1045			
	? (doubt/tried, but no result)	3	22	52	77			
		Prev*N	(1-prev)*N		N*: 1307			
					1356			

*N with a test result: 9 children did not have a PO result, 57 did not have an APK result and 49 did not have a landolt-C result.

Table A28a. Results of APK and Landolt-C (LC) vision test, children with amblyopia or significant refraction error in clinical study

	Vision test				
	Insufficient	Doubtful	Sufficient	No data	Total
APK, 3y (≤42 months)	4	7	5		16
APK, other age groups (>42 m)	11	3	1		15
Total APK	15	10	6		31
LC, 3y (≤42 months)	8	1	2		11
LC, other age groups (>42 m)	107	11	29		147
Total LC	115	12	31		158
Total*	124	20	36	13	193

* One test result per child. 9 children had an APK test as well as a Landolt-C: the APK result was used for children age ≤42 months, the Landolt-C was used for children age >42 m. 13 of 193 children did not have a result on the APK or LC (no data).

Table A28b. Results Plusoptix test, children with amblyopia or significant refraction error in clinical study

	Plusoptix test				
	Pass	Refer or try again	Refer	No PO measurement	Total
3y (≤42 months)	13	2	11	0	26
3y9m (42–60 m)	31	9	53	6	99
5/6y (≥60 months)	14	10	41	3	68
Total	58	21	105	9	193

Table A29. Overview of estimated test characteristics to detect children with amblyopia or significant refraction error, in %

	PPV best estimate (min-max)	Sensitivity* (95%CI)		Specificity min/max (95%CI) at prevalence of 8%
		Clinical study	Dev./language problems, clin. study^	
APK	33.3 (12.5-74.0)	25 (8-53)	Not estimated	86.5 (83.6-88.9) /89.6 (87.0-91.8)
LC	34.6 (20.0-62.2)	73 (65-80)	75 (47-92)*	87.7 (85.7-89.5) /89.9 (88.0-91.6)
PO	53.3 (35.0-69.3)	57 (50-64)	67 (45-84)*	95.4 (94.3-96.2) /96.7 (95.8-97.4)

LC: Landolt-C, PO: Plusoptix, CE: cost-effectiveness

^71 of the 459 children in the clinical study had a developmental of language problem. 25 of them were in the target group of children with amblyopia or significant refraction error.

*in children with a test result. 16 of 23 (70%) of 3y9m and 5/6y of the children with a developmental of language problem in the target group had a test result on the Landolt-C, whereas 24 of 25 had a result on the Plusoptix.