DOI: 10.1111/dme.12274

Systematic review or Meta-analysis

Screening intervals for diabetic retinopathy and incidence of visual loss: a systematic review

J. B. Echouffo–Tcheugui[1], M. K. Ali[1], G. Roglic[2], R. A. Hayward[3,4,5] and K. M. Narayan[1]

[1]Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, GA, USA, [2]Department of Chronic Diseases and Health Promotion, World Health Organization, Geneva, Switzerland, [3]Department of Internal Medicine, [4]Department of Health Management and Policy, University of Michigan, and [5]VA Center for Practice Management and Outcomes Research at the University of Michigan, Ann Arbor, MI, USA

Accepted 18 June 2013

Abstract

Screening for diabetic retinopathy can help to prevent this complication, but evidence regarding frequency of screening is uncertain. This paper systematically reviews the published literature on the relationship between screening intervals for diabetic retinopathy and the incidence of visual loss. The PubMed and EMBASE databases were searched until December 2012. Twenty five studies fulfilled the inclusion criteria, as these assessed the incidence/prevalence of sight-threatening diabetic retinopathy in relation to screening frequency. The included studies comprised 15 evaluations of real-world screening programmes, three studies modelling the natural history of diabetic retinopathy and seven cost-effectiveness studies. In evaluations of diabetic retinopathy screening programmes, the appropriate screening interval ranged from one to four years, in people with no retinopathy at baseline. Despite study heterogeneity, the overall tendency observed in these programmes was that 2-year screening intervals among people with no diabetic retinopathy at diagnosis were not associated with high incidence of sight-threatening diabetic retinopathy. The modelling studies (non-economic and economic) assessed a range of screening intervals (1–5 years). The aggregated evidence from both the natural history and cost-effectiveness models favors a screening interval >1 year, but ≤2 years. Such an interval would be appropriate, safe and cost-effective for people with no diabetic retinopathy at diagnosis, while screening intervals ≤1 year would be preferable for people with pre-existing diabetic retinopathy. A 2-year screening interval for people with no sight threatening diabetic retinopathy at diagnosis may be safely adopted. For patients with pre-existing diabetic retinopathy, a shorter interval ≤1 year is warranted.

Diabet. Med. 30, 1272–1292 (2013)

Introduction

Diabetic retinopathy commonly complicates diabetes mellitus [1] and meets the World Health Organization (WHO) criteria of suitability for screening [2]. It is a major cause of vision loss worldwide. Approximately one third of people with diabetes have diabetic retinopathy, and a third of those with diabetic retinopathy may have sight-threatening diabetic retinopathy, defined as clinically significant proliferative retinopathy or macula oedema [1]. The prevalence of diabetic retinopathy is projected to increase in the coming decades. The number of Americans aged 40 years or older, for example, with diabetic retinopathy and sight-threatening diabetic retinopathy is predicted to triple by 2050 [3]. In China, the prevalence of diabetic retinopathy among people with diabetes reaches 43% [1], with up to 9.2 million people in rural areas having diabetic retinopathy, including 1.3 million with sight-threatening diabetic retinopathy [1].

The natural history of diabetic retinopathy is relatively well understood, with recognizable stages. Major risk factors for developing diabetic retinopathy include duration of diabetes [4,5], severity of hyperglycaemia [6–8], hypertension [9] and dyslipidaemia [10]. Once sight-threatening diabetic retinopathy is present, the progression is rapid and complications are unpredictable. Twenty years after diagnosis, almost all people with Type 1 diabetes mellitus and 60% of people with Type 2 diabetes mellitus will have some degree of diabetic retinopathy [4,5].

There are precise, safe and accepted screening tests (ophthalmoscopy and fundus photography) for diabetic retinopathy [11]. Glycaemic and blood pressure control may prevent the progression of diabetic retinopathy [7,9]. Appropriately timed laser photocoagulation therapy and, to a certain extent,

Correspondence to: Justin B. Echouffo-Tcheugui. E-mail: jechouf@emory.edu

anti-vascular endothelial growth factor (VEGF), can dramatically reduce progression of sight-threatening diabetic retinopathy to vision loss [12]. However, large numbers of eligible patients requiring these preventive therapies may not actually be receiving them. In the USA, up to 60% of patients requiring vision-preserving laser surgery may not be receiving optimally timed retinal photocoagulation [13].

Several national agencies recommend annual screening and early treatment for sight-threatening diabetic retinopathy lesions [14–16]. However, given the increasing demand for ophthalmology services and costs associated with ophthalmic care, an optimal screening interval has been debated, with some suggesting the adoption of longer intervals for patients with no background retinopathy, with more frequent surveillance examinations for those at high risk [17–19]. Indeed, there is accumulating evidence that the natural history of diabetic retinopathy is sufficiently slow that 2-yearly retinal screening, or even longer, may be safe for some patients with diabetes [20], especially as information technology underpinning call–recall systems within screening programmes is such that a more effective approach to organizing retinal screening could allow moving towards a biennial retinal screening programme. Consequently, screening low-risk individuals too frequently implies an inefficient use of limited healthcare resources.

Here, we systematically review the evidence regarding the effect of screening intervals for diabetic retinopathy on the incidence of sight-threatening diabetic retinopathy/visual loss, and attempt to synthesize the available data in order to guide the design of appropriate policy recommendations.

Methods

Data sources

We searched the PubMed and EMBASE electronic databases for articles published until December 2012. We used a combination of terms related to screening for diabetic retinopathy (see also Supporting Information, Appendix S1). Titles, abstracts and/or full texts of articles identified through these searches were sequentially screened for inclusion (Fig. 1) and electronic searches were supplemented by scanning the references lists of relevant publications. When published data were unclear, we contacted authors for further information.

Inclusion and exclusion criteria

Studies were included if they:

1. assessed a real-world diabetic retinopathy screening programme and reported the incidence of sight threatening retinopathy or blindness in relation to the screening interval;
2. modelled the effect of varying screening interval for diabetic retinopathy on the costs and/or cost-effectiveness of diabetic retinopathy screening; or
3. modelled the effect of varying screening interval for diabetic retinopathy on the incidence of sight-threatening diabetic retinopathy or blindness.

Data extraction and quality assessment

Two reviewers (JBE-T and MKA) extracted relevant data, including characteristics of the study population, study setting, screening modalities, screening frequency, incidence of sight-threatening diabetic retinopathy or blindness, and measures of efficiency of the screening interval. Disagreements were resolved by a third reviewer (KMN). To our knowledge, there is no commonly agreed-upon unifying framework to evaluate screening programmes and/or studies of the natural history of diabetic retinopathy; we therefore focus on the individual characteristics of each study, giving more credit to well-designed, large, prospective studies with appropriate measures of outcomes. Although not originally designed for use in review articles, the Drummond and Jefferson evaluation scheme [21] for evaluating the quality of economic studies appeared to be a consensual tool that has been previously used [22]; we therefore used it for economic studies (see also Supporting Information, Appendix S2).

Results

Of the 25 studies included in this review (Fig. 1), 15 could be characterized as evaluations of actual screening programmes [17,19,23–34], three as studies modelling the natural history of the disease [35–37], seven were economic modelling studies that explored screening interval (five cost-effectiveness studies [38–42], one a cost-utility study [18] and one combined cost-effectiveness and cost-utility analyses [43]).

Screening studies

Screening programme evaluations examined the relationship between sight-threatening diabetic retinopathy occurrence and the frequency of screening (Table 1), either as a primary [17,27–30,32] or a secondary objective [19,23–26,31,33,34,44]. None of these studies were conducted in regions other than the USA, Europe and Australia. Four studies were hospital-based [23,24,28,30] and the remainder were population-based. Their sample size varied from 185 to 57 199. Six of these studies exclusively recruited Caucasians [19, 23–26, 32] and seven included non-white participants [17,27, 29,31,33,34,44], but had a majority of Caucasians. In two studies, the ethnicity of participants was not clearly reported, but given the setting of these studies it was logical to infer that the vast majority of their participants were Caucasians [28,30]. When clearly reported, the age of participants ranged from 15 to 99 years. One study focused on children and adolescents exclusively [28]. The average duration of

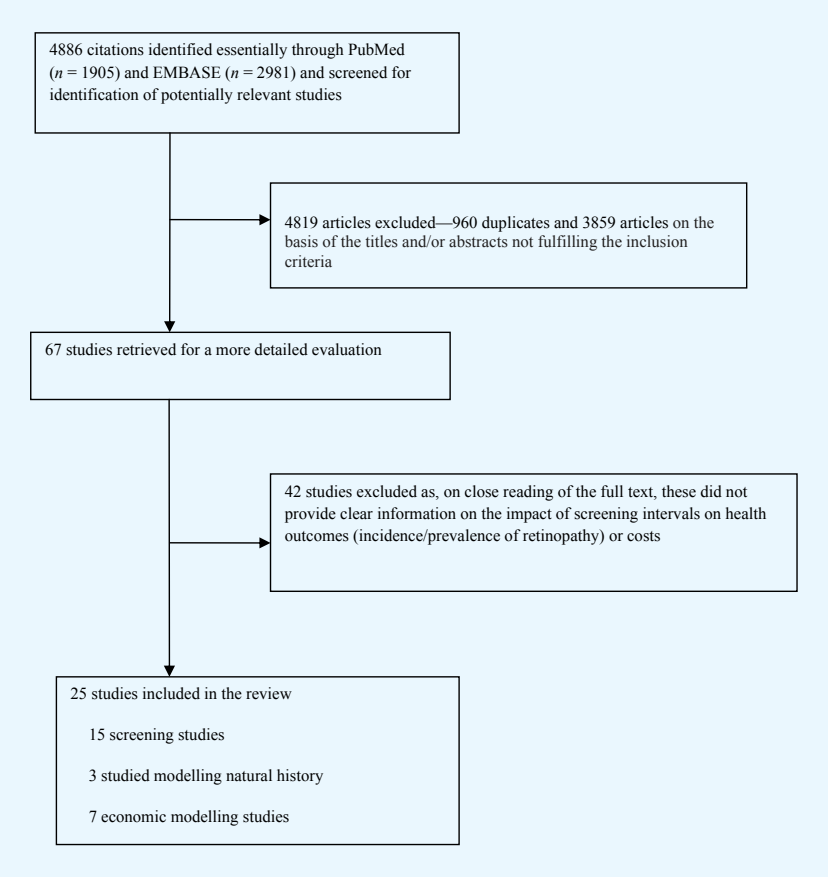

FIGURE 1 Flow of selection of studies for inclusion.

diabetes at first screening varied between 0 and 15 years. Thirteen of the 15 studies were retrospective cohorts and two were prospective cohorts. One study reported using ophthalmoscopy alone to ascertain diabetic retinopathy [23], fundal photography alone was used in nine studies [25,27–30,32–34,44], and a combination of ophthalmoscopy and fundal photography was used in four studies [19,24,26,31].

The vast majority of the 15 screening studies addressed screening for diabetic retinopathy in Type 1 and Type 2 diabetes together [19,23–26,29–31,44]. The screening studies provide unique information based on actual risk among screened individuals, the majority of whom were not receiving ophthalmic care. The appropriate screening interval was variable, ranging from 1 year [44] to 4 years [30] in people with no diabetic retinopathy at baseline. Despite the between-studies variation, the overall tendency observed was that a screening interval > 1 year would be appropriate and safe in people with no diabetic retinopathy at diagnosis, based on the extremely low rate of patients advancing from no diabetic retinopathy to sight-threatening diabetic retinopathy in less than 2–3 years. Twelve of the 15 studies supported a diabetic retinopathy screening interval > 1 year [17,19,24,26–29,31–34,44]. The reported screening compliance rate varied from 21% [27] to 28% [26].

A single study assessed the appropriate surveillance intervals for those with diabetic retinopathy at diagnosis, showing that a 1-year screening interval in the case of background retinopathy and 0.3 of a year for mild proliferative diabetic retinopathy, respectively, would be associated with a 95% probability of remaining free of sight-threatening diabetic retinopathy for patients with Type 2 diabetes [17]. Corresponding figures for Type 1 diabetes were 1.3 of a year for background and 0.4 of a year for pre-proliferative diabetic retinopathy [27]. These were the only studies that assessed the appropriate surveillance intervals for those with diabetic retinopathy at diagnosis [17,27]. Their findings are consistent with current consensus in the medical community that yearly or more frequent screening for people with any sign of diabetic retinopathy should be the norm [12].

Some of the screening studies supporting an interval > 1 year (e.g. a 2-year interval) included large-sample-size, population-based cohorts with extended follow-up and/or were specifically designed to assess the relationship between screening interval and incidence of sight-threatening diabetic retinopathy or blindness [17,27,29,33,34], thus offering more robust evidence on the frequency of screening for diabetic retinopathy. However, other studies putting forward

Table 1 Screening studies assessing the appropriate interval of screening for diabetic retinopathy

Author and year publication	Study design/ period (length of follow-up)	Sample size/ country (ethnicity)	Age at diagnosis or entry in the screening programme	Diabetes type	Setting	Screening modality/ coverage	Screening frequency	Average disease duration at the first screening round	Incidence/ prevalence of sight-threatening diabetic retinopathy	Assessment of screening interval	Authors' conclusion about screening interval
Agardh *et al.*, 1993 [23]	Retrospective cohort/ 5 years	858/Sweden (Caucasian)	Mean age 34.9 years for people with Type 1 diabetes/ 53.8 years for people with Type 2 diabetes	Type 1 diabetes (n = 431) and Type 2 diabetes (n = 367)	Hospital-based	Biomicroscopic indirect ophthalmoscopy with magnifying lens and a slit lamp through dilated pupils/by ophthalmologist	1–2 years if no diabetic retinopathy or minimal diabetic retinopathy	19.8 years for people with Type 1 diabetes/ 9.0 years for people with Type 2 diabetes	5-year incidence of blindness in Type 1 diabetes: 0.5% and 0.6% in Type 2 diabetes 5-year incidence of moderate visual impairment (macular oedema or proliferative diabetic retinopathy): 1.2% in Type 1 diabetes and 1.7% in Type 2 diabetes	No formal testing / implicit	Screening interval 1 to 2 years is appropriate
Kristinsson *et al.*, 1995 [24]	Retrospective cohort/ 2 years	185/Iceland (Caucasian)	≥ 15 years	Type 1 diabetes (n = 87) and Type 2 diabetes (n = 119)	Hospital-based	Dilated biomicroscopic fundoscopy and fundal photography/by ophthalmologist	Yearly	Not reported	2-year incidence of sight-threatening diabetic retinopathy from no retinopathy was 0% 2-year incidence of any retinopathy from no retinopathy was 23% in patients with Type 1 diabetes and 16% in those with Type 2 diabetes	No formal testing/ implicit	2-yearly screening for those with Type 1 diabetes and Type 2 diabetes without retinopathy at diagnosis is safe.
Henricsson *et al.*, 1996 [25]	Retrospective cohort/ 2.9 years	1769/Sweden (Caucasian)	30–60 years	Type 1 diabetes (n = 370) and	Population-based	Colour fundal photography (covered fields 1–3 of the 7	Yearly for people diagnosed between 20 and 30 years of age	18.7 years for those aged < 30 years and 8.3 years for	Incidence of blindness: 1.0 per 1000 person-years	No formal assessment of the relationship	Suggestion that a 1- year screening interval is effective

Table 1 (*Continued*)

Author and year publication	Study design/ period (length of follow-up)	Sample size/ country (ethnicity)	Age at diagnosis or entry in the screening programme	Diabetes type	Setting	Screening modality/ coverage	Screening frequency	Average disease duration at the first screening round	Incidence/ prevalence of sight-threatening diabetic retinopathy	Assessment of screening interval	Authors' conclusion about screening interval
				Type 2 diabetes (n = 1399)		standard fields, with stereopairs of the macula (field 2) in eyes without diabetic retinopathy; if retinopathy, at least two photographs were added of standard fields 4–7)	and after 5 years of diabetes duration 2-yearly if diabetes diagnosed at ≥ 30 years of age and until approximately 75 years of age	those aged ≥ 30 years	(95% CI 0.4–2.1), incidence of visual impairment of 4.6 per 1000 person-years (95% CI 3.0–6.6)	with screening interval / implicit	
Ling *et al.*, 2002 [31]	Retrospective cohort/ 6 years	775/England (mostly Caucasian)	15–99 years	Type 1 diabetes (n = 104) and Type 2 diabetes (n = 671)	Population-based (primary care)	Non-mydriatic fundus single-field photography and indirect ophthalmoscopy	2-yearly	13	2-year incidence of non-proliferative diabetic retinopathy 2.20% at round 2 of screening and 2.25 at round 3 2-year incidence of clinically significant maculopathy 4.79% at round 2 of screening and 5.18% at round 3	Implicit assessment screening interval: incidence of sight-threatening diabetic retinopathy appears to be stable over rounds of screening in a 2-yearly strategy	No reason to believe that a 2-year screening interval would be detrimental
Hansson-Lundblad *et al.*, 2002 [26]	Retrospective cohort/ 8 years	264/Sweden (Caucasian)	≥ 30 years	Type 1 diabetes (n = 39) and Type 2 diabetes (n = 225)	Population-based (primary care)	Mydriaric 3-field fundal photography or biomicroscopy	1–2 years if no or mild diabetic retinopathy	Not reported	8-year rate of blindness in Type 1 diabetes was 0% and 2% for Type 2 diabetes	No formal testing/ implicit	A 2 year screening regimen may be appropriate
Younis *et al.*, 2003 [27]	Retrospective cohort/ 6 years of follow-up	501/England (96.2% Caucasian)	< 30 years	Type 1 diabetes	Population-based (primary care)	Non-stereoscopic 3-field mydriatic photography (and modified Wisconsin grading)	Yearly for patients with non-sight-threatening diabetic retinopathy (no retinopathy or	3.0	Cumulative incidence of sight-threatening diabetic retinopathy in patients without	For a 95% likelihood of remaining free of sight-threatening diabetic	Screening at 2- to 3-year intervals, rather than annually, for patients without

Table 1 (*Continued*)

Author and year publication	Study design/ period (length of follow-up)	Sample size/ country (ethnicity)	Age at diagnosis or entry in the screening programme	Diabetes type	Setting	Screening modality/ coverage	Screening frequency	Average disease duration at the first screening round	Incidence/ prevalence of sight-threatening diabetic retinopathy	Assessment of screening interval	Authors' conclusion about screening interval
							background retinopathy)		baseline retinopathy was 0.3% (95% CI 0.0–0.9) at1 year and 3.9% (1.4–5.4) at 5 years Rates of progression to sight-threatening diabetic retinopathy in patients with background and mild pre-proliferative diabetic retinopathy at 1 year were 3.6% (0.5–6.6) and 13.5% (4.2–22.7), respectively	retinopathy, mean screening intervals by baseline status were: no retinopathy 5.7 (95% CI 3.5–7.6) years; background retinopathy 1.3 (95% CI 0.4–2.0) years; and mild pre-proliferative diabetic retinopathy 0.4 (95% CI 0–0.8) years	retinopathy at diagnosis
Younis *et al.*, 2003 [17]	Retrospective cohort/ 3.5 years of follow-up	4770 patients/ England (vast majority Caucasian)	> 30 years	Type 2 diabetes	Population-based (primary care)	Non-stereoscopic mydriatic 3-field photography/ graded by trained graders	Yearly for patients with non-sight-threatening diabetic retinopathy (no diabetic retinopathy or background retinopathy)	7.8	Yearly incidence sight-threatening diabetic retinopathy in patients without retinopathy at baseline was 0.3% (95% CI 0.1–0.5) in the first year, rising to 1.8% (95% CI 1.2–2.5) in the fifth year; cumulative 5-year incidence was 3.9% (95% CI 2.8–5.0)	For a 95% probability of remaining free of sight-threatening diabetic retinopathy, mean screening intervals by baseline status were: no retinopathy 5.4 years (95% CI 4.7–6.3), background 1.0 year (95% CI 0.7–1.3)	A 3-year screening interval could be safely adopted for patients with no retinopathy

Table 1 (*Continued*)

Author and year publication	Study design/ period (length of follow-up)	Sample size/ country (ethnicity)	Age at diagnosis or entry in the screening programme	Diabetes type	Setting	Screening modality/ coverage	Screening frequency	Average disease duration at the first screening round	Incidence/ prevalence of sight-threatening diabetic retinopathy	Assessment of screening interval	Authors' conclusion about screening interval
										and mild pre-proliferative diabetic retinopathy 0.3 years (95% CI 0.2–0.5)	
Maguire *et al.*, 2005 [28]	Retrospective cohort/ 12 years	668/Australia (not reported)	Children and adolescents	Type 1 diabetes	Hospital-based	Seven-field stereoscopic mydriatic fundal photography/ graded by an ophthalmologist	Yearly	Not reported	Not reported	Significant increase in retinopathy after 2 years from the first eye examination ($P = 0.03$) in the age group > 11 years, but not until 6 years ($P = 0.01$) in the age group < 11 years	No risk of missing clinically significant, vision-threatening or treatment-requiring retinopathy by extending the screening interval to 2 years
Olafsdottir *et al.*, 2007 [19]	Retrospective cohort/ 10 years	296/Caucasian	16–90 years	Type 1 diabetes ($n = 97$), Type 2 diabetes ($n = 199$)	Population-based	Dilated slit-lamp ophthalmoscopy and colour fundus photo graphy/by an ophthalmologist using. worst eye to define retinopathy level	2-yearly if no retinopathy and yearly once development of retinopathy	18	No patient went from no retinopathy to sight-threatening retinopathy in less than 2 years	No formal testing/implicit	Every 2 years
Misra *et al.*, 2009 [29]	Retrospective cohort/ 17 years	20 788/UK (mainly Caucasian)	Mean age: 68.8 years	Type 1 diabetes ($n = 205$) and Type 2 diabetes ($n = 20\ 583$)	Population-based	Mydriatic 2-field fundus photo graphy/graded by a diabetologist and an opthalmologist	17–19 months	6.8	91% decrease in the prevalence of sight-threatening diabetic retinopathy from the first round of screening (1.7%) to the last round	Compared with intervals of 12–18 months, intervals of 19–24 months were not associated with a higher risk of either referable or sight-	Screening intervals of 18 months–2 years can be safe for patients at low risk

Table 1 (*Continued*)

Author and year publication	Study design/ period (length of follow-up)	Sample size/ country (ethnicity)	Age at diagnosis or entry in the screening programme	Diabetes type	Setting	Screening modality/ coverage	Screening frequency	Average disease duration at the first screening round	Incidence/ prevalence of sight-threatening diabetic retinopathy	Assessment of screening interval	Authors' conclusion about screening interval
									17 years later (0.16%)	threatening diabetic retinopathy (odds ratio 0.93, 95% CI 0.82–1.05), but interval of more than 24 months associated with an increase risk of diabetic retinopathy (odds ratio 1.56, 95% CI 1.14–1.75)	
Arun *et al.*, 2009 [44]	Retrospective cohort study/ 5 years	6430/England (mainly Caucasian)	16–64 years	Type 1 diabetes (n = 5) and Type 2 diabetes (n = 15)	Population-based/ relied on a blindness register	Mydriatic fundus photography/ by trained screeners	Assumed to be 1 year	Not reported	Annual incidence of blindness: 0.22 per 1000, and of partial sightedness 0.43 per 1000	No formal testing of relation to screening interval/implicit	
Soto-Pedre *et al.*, 2009 [30]	Retrospective cohort/ 6 years	430/Spain (mainly Caucasian)	Mean age 52.7 years	Type 1 diabetes (n = 320) and Type 2 diabetes (n = 110)	Hospital-based (tertiary care)	45° non-mydriatic single-field fundus photography (centred on the macula and one photo for each eye)	Not reported	10.1 years for those with no diabetic retinopathy at first screen and 14.9 years for those with diabetic retinopathy at first screening	If no diabetic retinopathy at baseline, the probability of remaining free of sight-threatening diabetic retinopathy was 97% (95% CI 94–99%) at the end of the fourth year. If mild non-proliferative diabetic retinopathy at baseline, the probability of remaining free of	Interval for at least a 95% estimated probability of remaining free of sight-threatening diabetic retinopathy for no baseline diabetic retinopathy was 4 years for those who had Type 1 diabetes and 3 years for those who had	Screening at a 3–4 year interval for patients with diabetes patients of diabetic retinopathy is safe because of their low risk of developing sight-threatening diabetic retinopathy. Patients with mild non-proliferative diabetic retinopathy require screening at a 1-year interval, or at a 2-year

Table 1 (*Continued*)

Author and year publication	Study design/ period (length of follow-up)	Sample size/ country (ethnicity)	Age at diagnosis or entry in the screening programme	Diabetes type	Setting	Screening modality/ coverage	Screening frequency	Average disease duration at the first screening round	Incidence/ prevalence of sight-threatening diabetic retinopathy	Assessment of screening interval	Authors' conclusion about screening interval
									sight-threatening diabetic retinopathy was 99% (95% CI 95–100%) at the end of the first year of follow-up and 94% (95% CI 88–97%) at the end of the second year	Type 2 diabetes. For patients with mild non-proliferative diabetic retinopathy at baseline, the interval for at least a 95% probability of sight-threatening diabetic retinopathy-free survival was 1 year, or in those with a level of glycated haemoglobin ≤ 7.5%.	interval with good metabolic control
Agardh and Tababat-Khani, 2011 [32]	Prospective cohort	1322/Sweden (Caucasian)	Mean age 55 years (SD 12)	Type 2 diabetes	Population-based	Fundal photography (images—1central and 1 nasal fields)	3-year screening interval if no diabetic retinopathy at baseline	6 years	After 3 years, 73% had no diabetic retinopathy, 29% had mild diabetic retinopathy, 0% had severe non-proliferative diabetic retinopathy	73% of patients without retinopathy and 28% with mild or moderate diabetic retinopathy after 3 years	3-year screening intervals is safe in subjects with mild Type 2 diabetes and no diabetic retinopathy
Jones *et al.*, 2012 [33]	Prospective cohort	20 686/ England (mainly Caucasian)	Median 66.7 (interquartile range 58.0–74.5) for those without retinopathy; 68.0 (interquartile range 58.5–75.7) for those with non-proliferative diabetic retinopathy, 66.3 (interquartile range 55.7–66.3) for those with proliferative diabetic retinopathy	Type 2 diabetes	Population-based	Fundal photography (two images of each eye)	Assumed to be 1-year interval (but variable interval, up to 24 months after baseline examination	Not reported (range 0–10 years)	5-year incidence among patients without diabetic retinopathy at baseline was 4.0% for pre-proliferative diabetic retinopathy, 0.59% for sight-threatening maculopathy, 0.68% for proliferative diabetic retinopathy; the respective	No formal testing of the relationship between screening interval and incidence of various stages of diabetic retinopathy/ implicit	Few patients without diabetic retinopathy at first screen developed pre-proliferative diabetic retinopathy, proliferative diabetic retinopathy or sight-threatening maculopathy after 5–10 years

Table 1 (*Continued*)

Author and year publication	Study design/ period (length of follow-up)	Sample size/ country (ethnicity)	Age at diagnosis or entry in the screening programme	Diabetes type	Setting	Screening modality/ coverage	Screening frequency	Average disease duration at the first screening round	Incidence/ prevalence of sight-threatening diabetic retinopathy	Assessment of screening interval	Authors' conclusion about screening interval
									10-year incidences were 16.4, 1.2 and 1.5%, respectively. Among those with non-proliferative diabetic retinopathy at baseline, after 1 year 23% developed pre-proliferative diabetic retinopathy, 5.2% developed maculopathy and 6.1% developed proliferative diabetic retinopathy; the respective 10-year incidences were 53, 9.6 and 11%, respectively		of follow-up. Screening intervals longer than 1 year may be appropriate for people without diabetic retinopathy at diagnosis
Thomas *et al.*, 2012 [34]	Retrospective cohort	57 199 (with no evidence of diabetic retinopathy at baseline)/ Wales (mainly Caucasian)	≥ 30 years	Type 2 diabetes	Population-based	Fundal photography	≥ 1 year	3.9 years for those with no retinopathy and 5.1 years among those with diabetic retinopathy	4-year incidence of any and referable diabetic retinopathy: 360.27 and 11.64 per 1000, respectively. For those on insulin treatment and with diabetes duration ≥ 10 years, incidence of diabetic retinopathy at 1 and 4 years was 9.61 and 30.99 per 1000, respectively	No formal testing of the relationship between screening interval and incidence of various stages of diabetic retinopathy/ implicit	Extension of the screening interval for people with Type 2 diabetes without diabetic retinopathy beyond 12 months, with the possible exception of those with diabetes duration ≥ 10 years and on insulin

similar recommendations were relatively small in size, [19,23,24,26,28,30,31] or were hospital based [28,30]. Studies supporting annual screening were not always specifically designed to examine the relationship between less frequent screening intervals and incidence of sight-threatening diabetic retinopathy or blindness [25,44]. Furthermore, the largest of these studies used the proportion of blindness attributable to diabetic retinopathy as the main outcome and information about blindness was obtained from a registry [44].

In brief, the vast majority of evaluations of real-world diabetic retinopathy screening programmes supported a screening interval > 1 year.

Modelling studies

Natural history models

Modelling studies of the natural history are shown in Table 2. A brief summary of the key specificities of each of these studies are presented below.

Using a hypothetical population and a range of sensitivities and specificities, to compare annual or biennial screening until background diabetic retinopathy develops and then examination 6 monthly or more frequently, Davies *et al.* found that biennial screening is a safe and efficient strategy, provided that patients' compliance and screening sensitivities are both high [35]. The net benefit of reducing the screening interval for those with no diabetic retinopathy from 2 years to 1 year would range from 0.25–0.42 years of sight saved per person, depending on screening methods used or the screener (ophthalmologist, general practitioner or optometrist).

Two Taiwan-based studies used data from real-world screening programmes to derive the appropriate screening interval for diabetic retinopathy [36,37]. None of these models included the pathway to blindness through maculopathy.

Tung *et al.* advocated annual screening on the basis of the incidence of blindness reduction for various screening regimens: annual 94.4%; biennial 83.9%; 3-year 70.2%; 4-year 57.2%; 5-year 45.6% [36]. The best level of retinopathy in each of the two eyes was used for patients with asymmetric levels of severity; a sensitivity analysis choosing the worst eye was conducted and found that estimates of the efficacy for annual screening, biennial screening and 4-yearly screening regimes were reduced to 40, 37 and 34%, respectively. Although the absolute benefit diminished, the differences in benefits with annual screening and biennial screening against 4-yearly screening were not substantial. The study of Tung *et al.* [36] did not comprehensively describe the screening intervals/strategies and made no clear distinction between screening and surveillance once diabetic retinopathy is detected. Thus, the length of the surveillance once diabetic retinopathy is diagnosed was unclear. Screening was started 6 years after the diagnosis of diabetes; this delay may have led to a higher number of people with advanced stages of retinopathy when first seen. In addition, the average transition time from the mildest form of diabetic retinopathy to proliferative retinopathy in Tung *et al.*'s study was 10.8 years [36]. Thus, a 2-year screening interval in people with no diabetic retinopathy would still be less than one fifth of this interval.

Liu *et al.* advocated biennial screening after finding that annual screening, biennial screening and a 4-yearly screening regime can lead to 54, 51 and 46% reductions in blindness, respectively [37]. They used data from an ophthalmic care centre where patients may have had better care and potentially a lower rate of diabetic retinopathy progression. However, they accounted for the levels of compliance and metabolic control, making their model more close to reality. They chose the best level of retinopathy in each of the two eyes from all patients with asymmetric levels of severity; this may raise concern as to whether this can affect the optimal interval for screening patients with non-proliferative diabetic retinopathy. Nonetheless, a sensitivity analysis choosing the worst eye found that differences in benefits with annual screening and biennial screening against 4-yearly screening were not substantial.

Economic studies

Economic modelling studies evaluated the cost-effectiveness or cost-utility of various screening intervals (Table 3). Two studies addressed screening for diabetic retinopathy in Type 1 and Type 2 diabetes [39,41] and five addressed screening for Type 2 diabetes only [18,38,40,42,43]. As indicated in Table 3 and in the Supporting Information (Appendix S2), economic studies generally followed the key steps of economic modeling, with a good description of the model or simulation, along with source of data, costs and outcome measures. The vast majority of these studies favoured a screening interval > 1 year for people without diabetic retinopathy at baseline. Given the heterogeneity of assumptions used to conduct these studies, we summarize the key aspects of individual studies below.

Dasbach *et al.* [41] examined three cohorts of incident cases of diabetes, using two time horizons (10 and 60 years), and concluded that annual screening would be better than biennial screening. The 60-year net benefit conferred by an annual compared with a biennial programme would be 28–36 years of sight saved for 1000 younger-onset patients, 7–9 years for 1000 older insulin-using patients and 3–4 years for 1000 older patients not using insulin. Over a 10-year time horizon, for the young patient cohort taking insulin, the incremental cost-effectiveness ratio was £2351.38–2554.55 ($3553–3860) per sight year saved for 1-year screening and £2522.78–2624.7 ($3812–3966) for 2-year screening. However, outcomes did not include macular oedema or values for non-discounted sight years, and were unclear as to whether the rates of disease progression

Table 2 Natural history modelling studies assessing the appropriate interval of screening for diabetic retinopathy

Author and year of publication	Study design/ period (length of follow-up)	Sample size/ country (ethnicity)	Age range at diagnosis or entry into the screening programme	Diabetes type	Setting	Screening modality	Screening frequency compared	Assessment of screening interval	Authors' conclusion about screening interval
Davies *et al.*, 1996 [35]	Modelling study	Hypothetical cohort of 1000/UK (mostly Caucasian)	< 35 years	Type 1 diabetes	Population-based (primary care)	Ophthalmoscopy	1 year and 2 years	Net benefit of reducing the screening interval from 2 years to 1 year: 0.25 to 0.42 years of sight saved per person, depending on screening methods used or the screener (ophthalmologist, general practitioner or optometrist)	A 2-year screening regimen may have no detrimental effect compared with yearly screening for people with no or mild retinopathy
Liu *et al.*, 2003 [37]	Modelling study (Markov modelling) based on a date from a real screening programme with 7.4 years of follow-up	Hypothetical population of 80 000/Taiwan (Chinese)	≥ 40	Type 1 diabetes and Type 2 diabetes	Population-based	Ophthalmoscopy	1 year, 2 years and 4 years	Annual screening, biennial screening and a 4-yearly screening regimen can lead to 54% (95% CI 44–62%), 51% (95% CI 41–59%) and 46% (95% CI 36–54%) reductions in blindness, respectively	A screening interval of up to 4 years for patients without diabetic retinopathy may be justified
Tung *et al.*, 2006 [36]	Modelling study based on data from a real screening programme	Hypothetical population 1 000 000/ Taiwan (Chinese)	≥ 30	Type 2 diabetes	Population-based	Mydriatic indirect ophthalmoscopy and mydriatic single-field fundus photography/ interpreted by two ophthalmologists	1 year, 2 years, 3 years and 4 years	Incidence of blindness reduction for various screening regimens: annual 94.4% (95% CI 91.6–96.3%); biennial 83.9% (95% CI 83.6–84.2%); 3-year 70.2% (95% CI 69.8–70.7%); 4-year 57.2% (95% CI 56.7–57.7%); 5-year 45.6% (95% CI 45.0–46.1%)	Annual screening is the most effective for reducing incidence of blindness

and death were derived from the study cohort or not. The major inputs of disease progression and mortality were not varied, which is potentially inadequate.

Javitt *et al.* [38] found that changing screening frequency from 1 year to 2 years would have no detrimental effects on years of sight saved, while demonstrating positive effects of reducing the costs for patients with no or mild retinopathy. Screening and treatment for diabetic retinopathy saved £164.13 ($248) annually and 53 986 person-years of sight in total. Nevertheless, for those with moderate non-proliferative or more advanced retinopathy, 8960 extra years of sight would be saved by a 1-year programme over the lifetime of the cohort ucode>—equating to 15.6 years per 1000 patients This model did not provide clear information on the exact figures for sight saved by different screening intervals for those with no baseline retinopathy, or include sensitivity analysis for different intervals. Their methods for determining annual and cohort cost and sight savings are not clearly stated and benefits are from treatments for all types of diabetic retinopathy.

Vijan *et al.* [18] showed that annual screening is more effective; however, for most patients, the costs of annual screening are considerable, with little marginal benefit when compared with screening every other or every third year. The marginal cost-effectiveness ratio of 1-year screening vs. 2-year screening was £71150.12 ($107 510/)quality-adjusted life year gained, 2-year screening vs. 3-year was £32931.17 ($49 760/) quality-adjusted life year gained; 3-year screening vs. 5-year screening was £19959.89 ($30 160/) quality-adjusted life year gained. The cost-effectiveness ratio was highest for patients whose onset of Type 2 diabetes occurred at a younger age and whose glycaemic control is poor. Vijan *et al.* addressed the limitations of a single perspective, through an examination of the government or society perspectives in a sensitivity analysis, and recommended a 2-year screening interval, with the option of tailoring the

Table 3 Economic studies assessing the cost-effectiveness or cost-utility of various screening intervals for diabetic retinopathy

Author and year of publication	Population characteristics	Source of cohort of patients	Comparators	Model type	Time horizon	Screening modalities	Source of costs/ discounting	Perspective	Analysis—design	Screening outcomes/ compliance	Economic outcomes	Authors' conclusions
Dasbach *et al.*, 1991[41]	Three hypothetical cohorts of 1000 patients with diabetes—younger onset, older taking insulin or not	The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR)	1. No screening 2. Annual screening 3. Biennial screening	Markov model	10 years and 60 years	Ophthalmoscopy, mydriatic or non-mydriatic camera photography	5% discounting (sight and costs benefits)	Third-party payer	Cost-effectiveness analysis	Treatable proliferative diabetic retinopathy 65% compliance for screening and 79% for surveillance	10-year: for young patients in the insulin-taking cohort, the incremental cost-effectiveness ratio was $3553–3860 per sight year saved for 1-year screening and $3812–3966 for 2-year screening For older patients' using insulin: 1-year screening $0.46–1323; biennial screening $1034–1753. For older non-insulin using patients: annual screening $888–5532; biennial screening $434–2380 60-year: younger patients: annual $3203–$3619, biennial $3549–3751; older insulin-using patients: annual $141–989, biennial $642–1466; older non-insulin-using patients: annual $1435–6603; biennial $10–3109	Results in favour of 1-year screening interval over a 2-year screening interval
Javitt *et al.*, 1994 [38]	Hypothetical cohort of 576 136 Americans with Type 2 diabetes within an age group that develop diabetes within a single year	1988 US population structure	1. Every 1 year if no diabetic retinopathy and 6 months if diabetic retinopathy 2. Every 2 years if no diabetic retinopathy and 6 months if diabetic retinopathy 3. Every 2 years if no diabetic retinopathy and 12 months if diabetic retinopathy 4. Every3 years if no diabetic retinopathy and 6 months if diabetic retinopathy 5. Every 3 years if no diabetic	Combination of Monte Carlo/decision tree and Monte Carlo techniques	Lifetime	Mydriatic ophthalmoscopy by an ophthalmologist (sensitivity of 80% and specificity of 97%)	University of Wisconsin/no discounting	Third party payer (health state agency or some form of national initiative)	Cost-effectiveness analysis	Prolliferative diabetic retinopathy and macular oedema 60% compliance	Screening and treatment for eye disease in Type 2 diabetes saves $248 annually and 53 986 person years of sight in total	1. If no diabetic retinopathy, changing the frequency of screening from 1 year to 2 years has no detrimental effect on years of sight saved while reducing the costs 2. Once a diabetic retinopathy is developed, savings in sight-years are sensitive to screening intervals (a 6-month interval would save 3360 person-years of sight compared with a 12-month interval and 12 320 person-years compared with a 24-month interval

Table 3 (*Continued*)

Author and year of publication	Population characteristics	Source of cohort of patients	Comparators	Model type	Time horizon	Screening modalities	Source of costs/ discounting	Perspective	Analysis—design	Screening outcomes/ compliance	Economic outcomes	Authors' conclusions
			retinopathy and 12 months if diabetic retinopathy 6. Every 3 years if no diabetic retinopathy and 18 months if diabetic retinopathy 7. Every 4 years if no diabetic retinopathy and 6 months if diabetic retinopathy 8. Every 4 years if no diabetic retinopathy and 12 months if diabetic retinopathy 9. Every 4 years if no diabetic retinopathy and 18 months if diabetic retinopathy									
Vijan *et al.*, 2000 [18]	Hypothetical US-based population of 5.3 million people aged > 40 years with Type 2 diabetes	Third US National Health and Nutrition Survey	1. No screening 2. Annual screening 3. Biennial screening 4. 3-year screening	Markov model/ Monte Carlo simulation	Lifetime	Single-field photography by an ophthalmologist	Medicare reimbursement data/3% discounting (costs and years of life)	Third-party payer (government and societal perspectives explored in sensitivity analyses)	Cost-utility analysis	Proliferative diabetic retinopathy and macular oedema/ 100% compliance	Marginal cost-effectiveness of: screening annually vs. every other year costs $107 510 per quality-adjusted life year gained; screening every other year vs. every third year costs $49 760 per quality-adjusted life year gained; screening every 3 years vs. screening every 5 years: $30 160 Marginal cost-effectiveness of screening annually vs. every other year: $40 530 per quality -adjusted life year in high-risk patients [age 45 years, HbA_{1c} 97 mmol/mol; (11%)] group, while the low-risk [age 65 years, HbA_{1c} 53 mmol/ mol (7%)] group cost an additional $211 570 per quality-adjusted life year gained	Annual retinal screening for all patients with Type 2 diabetes without previously detected diabetic retinopathy may not be warranted and tailoring recommendations to individual circumstances may be preferable

Table 3 (*Continued*)

Author and year of publication	Population characteristics	Source of cohort of patients	Comparators	Model type	Time horizon	Screening modalities	Source of costs/ discounting	Perspective	Analysis—design	Screening outcomes/ compliance	Economic outcomes	Authors' conclusions
Davies *et al.*, 2002 [39]	Hypothetical population of 500 000 adults (age not reported)	1991 demographic survey of England and Wales	1. Every 12 months if no diabetic retinopathy and 6 months once diabetic retinopathy 2. Every 12 months if no diabetic retinopathy and 12 months once diabetic retinopathy 3. Every 24 months if no diabetic retinopathy and 6 months once diabetic retinopathy 4. Every 24 months if no diabetic retinopathy and 12 months once diabetic retinopathy 5. Every 24 months if no diabetic retinopathy and 24 months once diabetic retinopathy	Discrete event simulation	25 years	Strategies compared: 1. Optometrist fundoscopy 2. Diabetologist ophthalmoscopy 3. General practitioner ophthalmoscopy 4. 4.Mobile camera (one photograph, reviewed by a diabetologist) 5. Gold standard (mydriatic 7-field photography reported by ophthalmologist	British National Health Service (National Screening Committee)/no discounting	State health insurance	Cost-effectiveness analysis	Proliferative diabetic retinopathy and macular oedema/ 80% compliance for Type 2 diabetes and 90% Type 1 diabetes (82% compliance overall)	Best cost-effectiveness ratio: annual screening and 6-month follow-up after the detection of background retinopathy, with mobile camera, at a cost of £449 200 per year, with £2842 per sight year saved	Screening interval may be extended beyond 1 year, but careful consideration of both screening sensitivity and patient compliance is required beyond 1 year Annual screening with more frequent screening in those with background retinopathy, is robust to realistic fluctuation in compliance and screening sensitivity
Braislford *et al.*, 2007 [40]	Hypothetical population of 100 000 adults aged ≥ 20 years with Type 2 diabetes	General population of England and Wales in 1991 /national census data	Variation of screening interval between 6 and 36 months, in 6-month increments vs. no screening in the comparison of five screening tests or strategies	Ant colony optimization	100 years	Strategies compared: 1. Optometrist fundoscopy 2. Diabetologist ophthalmoscopy 3. General practitioner ophthalmoscopy 4. 4.Mobile camera (one photograph, reviewed by a diabetologist)	British National Health Service (National Screening Committee)/ variable discounting rate	State health insurance	Cost-effectiveness analysis	Proliferative diabetic retinopathy and macular oedema/ compliance not reported	1. Minimum incremental cost per year of sight saved: mobile camera at 30-month intervals between the ages of 30 and 60 years at a cost of £1259 per year of sight saved compared with a no-screening baseline 2. Maximum effectiveness for years of sight saved: screening using gold standard technology in a hospital setting every	If there were no financial constraints on a public healthcare system, deliver a gold standard technology in a hospital setting every 6 months If policymakers want to save the maximum number of sight years per pound expended, use mobile camera for screening at 30-month intervals between the ages of 30 and 60 years

Table 3 (*Continued*)

Author and year of publication	Population characteristics	Source of cohort of patients	Comparators	Model type	Time horizon	Screening modalities	Source of costs/ discounting	Perspective	Analysis—design	Screening outcomes/ compliance	Economic outcomes	Authors' conclusions
						5. Gold standard (mydriatic 7-field photography reported by ophthalmologist					6 months at a cost of £5000 per year of sight saved	
Tung *et al.*, 2008 [43]	971 adults aged ≥ 30 years with Type 2 diabetes	Community screening programme in a Taiwanese county	1. No screening 2. Annual screening 3. Biennial screening 4. 3-year screening 5. 4-year screening 6. 5-year screening	Decision tree analysis/ Markov model	10 years	Mydriatic indirect ophthalmoscopy and single-field fundus photography by an ophthalmologist	National Health Insurance/5% discount (costs and benefits) annually	State health insurance	Cost-effectiveness analysis and cost-utility analysis	Proliferative diabetic retinopathy and macular oedema/ compliance not reported	Cost per sight year saved: $NT84 311 for no screening, $NT20 962 for annual screening, $NT24 990 for biennial screening, $NT30 847 for 3-year screening, $NT37 435 for 4-year screening, $NT4449 for 5-year screening $NT61542 for no screening, Cost per quality-adjusted life year: $NT21 924 for annual screening, $NT25 319 for biennial screening, $NT30 098 for 3-year screening, $NT3516 for 4-year, $NT40 037 for 5-year	Annual screening for Type 2 diabetes should be conducted
Rein *et al.*, 2012 [42]	Hypothetical population of 10 million (age: 30–84 years)	2005–2006 Third US National Health and Nutrition Survey	1. No screening 2. Annual screening 3. Biennial screening 4. Annual (digital photography) screening	Monte Carlo simulation	Lifetime	1. Dilated ophthalmoscopy 2. Digital photography	British National Health Service (National Screening Committee)/ 3% discount	Societal perspective	Cost-effectiveness analysis	Proliferative diabetic retinopathy and macular oedema/ 63% annual compliance rate forpatients aged 30–64 years and 74% annual compliance rate for patients aged ≥ 65 years	Compared with no screening, incremental cost-effectiveness ratio for annual telemedicine screening was $US55 000/ quality-adjusted life year gained; incremental cost-effectiveness ratio of biennial evaluation was $US38 000/ quality-adjusted life year gained; and incremental cost-effectiveness ratio of annual evaluation was $US46 000/ quality-adjusted life year gained. incremental cost-effectiveness ratio for biennial screening vs. compared with annual telemedicine was $US8107/quality-adjusted life year. Incremental cost-effectiveness ratio of annual evaluation vs. biennial screening was $US136 170/ quality-adjusted life year	Annual eye evaluations are costly and add little benefit compared with either annual telemedicine screening or biennial screening

screening approach to the individual, so that those with the poorest glycaemic control would be screened more often. An alternate and safer option would be annual screening for all patients, but offering 2- or 3-year screening to those with good glycaemic control and with no retinopathy at baseline was considered appropriate. Vijan *et al.* [18] did not provide a basis for their choice of utility value (0.69) for blindness and lesser levels of visual impairment. The utility value for blindness had the biggest impact on cost-effectiveness in the sensitivity analysis, with annual screening appearing to be cost-effective at 0.48. Other studies defined utility values ranging from 0.60 to 0.86 (depending on severity of vision loss) [22]. Also, the assumed compliance rate in the model was 100%, which is unrealistic. The model overlooked potential variations in retinopathy risk in minority populations in the USA as these groups were not represented in UK Prospective Diabetes Study (UKPDS) (from which the input estimates were derived) [7]. Furthermore, the real-world accuracy for detection is probably lower than that modelled, and the prevalence of diabetic retinopathy was derived from a national US survey that included only a single photograph of each eye (sensitivity for retinopathy, 60%), rather than the criterion standard 7-field photography. Similarly, progression of disease was inferred from clinical trials in which participants are not representative of the overall population [45,46].

Davies *et al.* [39] showed that screening less than once a year would not be cost-effective. The best cost-effectiveness ratio was for annual screening and 6-month follow-up after the detection of background diabetic retinopathy, at a cost of £449 200 per year with £2842 per sight year saved. Screening intervals were found to be a key area of uncertainty, with a trade-off between the intervals, screening sensitivity and compliance. However, they found that increasing surveillance intervals to annual intervals once non-proliferative diabetic retinopathy was detected rendered results on biennial screening (those with no diabetic retinopathy on previous examinations) robust to such real-world fluctuations. A 2-year screening frequency, before the detection of any retinopathy, was associated with a 10% reduction in sight years saved, and an 8% reduction in the cost per sight year saved. Davies *et al.* [39] did not discount for costs and benefits and the non-assessment of patient costs or cost benefits of preventing blindness. They explored the benefits of dividing patients into groups, based on HbA_{1c}, and recalling them at different intervals, but such an approach may not be practical in an actual screening programme. They also combined screening and surveillance intervals, but sensitivity analysis found that biennial screening was cost-effective if surveillance increased to at least annual once any form of diabetic retinopathy was detected on screening.

Using an ethnically mixed population (adjusting for the higher prevalence of diabetes in ethnic minorities), and various sensitivities and specificities of several screening methods conducted by different types of health personnel, Brailsford *et al.* compared the minimum and maximum cost for years of sight saved of various screening policies [47]. They indicated that, without financial constraints on a healthcare system, screening using a gold standard technology in a hospital setting every 6 months (maximum cost-effectiveness ratio: £5000/year of sight saved) can be delivered. In contrast, if saving the maximum number of sight years per pound spent is the objective, screening people aged 30–60 years every 30 months with a mobile camera would be appropriate (minimum cost-effectiveness ratio: £1259/year of sight saved). This suggests that a 30-month screening interval for diabetic retinopathy can be adopted; however, healthcare systems that can afford to pay more to prevent more cases of blindness may well choose not to adopt the described minimum cost-effectiveness scenario. Brailsford *et al.* [47] did not consider compliance, an important variable in relation to screening intervals.

In a Taiwan-based model, using information on disease characteristics and costs data from a real-life community-based screening programme, Tung *et al.* [43] found that efficacy and utility decreased, while cost increased with the length of the screening/surveillance interval. For example, the costs per sight year saved were (in New Taiwan dollars) £1871.17($NT84 311) for no screening, £465.36 ($NT20 962) for 16 annual screening, £554.78 ($NT24 990) for biennial screening, £684.8 ($NT30 847) for 3-year screening, £831.06 ($NT37 435) for 4-year screening and £98.77 ($NT4449) for 5-year screening. The authors concluded that the ideal screening frequency should be annual. By using data from a real-life programme data, Tung *et al.* [43] probably estimated the true benefit of diabetic retinopathy screening more closely than in other modelling studies. However, the programme was relatively small ($n = 725$ patients), thus possibly not representative of patients with Type 2 diabetes. Moreover, the analysis did not consider the sensitivity and specificity of various diabetic retinopathy screening tests, used a single perspective and did not factor in the indirect costs other than those incurred for screening. Duration of diabetes and the HbA_{1c} level were also not examined, which may influence the efficacy of screening at different intervals. Unlike most models, they do not note increasing surveillance intervals once diabetic retinopathy is detected on screening.

In a US-based model, *Rein et al.* [42] compared three screening modalities (annual screening using dilated ophthalmoscopy, annual digital photography screening and biennial ophthalmoscopy screening) and concluded that biennial eye evaluation was the most cost-effective treatment option when the ability to detect other eye conditions (age-related macular degeneration and glaucoma) was included in the model. Telemedicine was most cost-effective when other eye conditions were not considered or when telemedicine was assumed to detect refractive error. Annual eye evaluation recommendation was costly compared with either treatment alternative.

Discussion

Our review provides a comprehensive synthesis of the available evidence on the appropriate screening interval for diabetic retinopathy. Although the evidence reviewed is heterogeneous in nature, the general trend suggests that a screening interval > 1 year, but no longer than 2 years, would be effective (associated with reduction in the incidence of sight-threatening diabetic retinopathy/blindness), safe and cost-effective for people without diabetic retinopathy at diagnosis. However, in high-risk patients with no diabetic retinopathy at diagnosis with poor control of glycaemia or blood pressure, more frequent screening may be warranted. Also, a surveillance interval of 1 year or less would be preferable in people with any diabetic retinopathy on a previous examination. These findings somewhat contrast with the currently recommended 1-year screening interval for diabetic retinopathy in most Western countries, which is based on observations from early population-based cohort studies [4,8,48,49]. However, these cohort studies mainly reported progression to proliferative diabetic retinopathy, clinically significant macular oedema or photocoagulation, rather than on progression to sight-threatening diabetic retinopathy. The idea of a 2-year screening interval among people without diabetic retinopathy is gaining ground in Western countries and professional organizations such as the Scottish Intercollegiate Guidelines Network have advocated such an interval [50].

To our knowledge, this review is the first attempt to assess the full range of studies addressing the issue of an 'optimal' screening interval for diabetic retinopathy. A previous review examined this question, but only focused on economic studies [22]. Studies evaluating real-world screening programmes provide an additional basis for the derivation of appropriate screening intervals. By combining information from these programmes and modelling studies, this review presents information about screening interval in accordance with the natural history of diabetic retinopathy and indications about the economic implications of various intervals. However, it is important to understand the limitations of studies included in this review.

Screening programmes were mainly evaluated using a retrospective cohort design, which somewhat limits their validity. However, in a context where no randomized controlled trial of diabetic retinopathy screening exists, and given the challenges of conducting one, decision-making can reasonably rely on the best available observational evidence, preferably from prospective studies. Ideally, decision on appropriate screening intervals would be based on a randomized controlled trial that randomly allocates people to differing frequencies of screening. Nonetheless, it is very difficult to afford such an allocation in a single study; as this would require an incredibly high number of participants to detect the true impact of any one screening interval. Alternatively, parallel trials can assess the efficacy of the same screening modality employed at different intervals. However, such an approach may be intrinsically confounded; it would be difficult to know if any observed difference is related to differences in screening frequency, or rather to variations in the nature of programmes, the early treatment for the condition across settings or the population characteristics that bear on the ability of screening to reduce outcomes rates.

The methods used in evaluations of screening programmes (sample size, setting, lack of control for important potential confounders, definition and classification of sight-threatening diabetic retinopathy/blindness, ascertainment of the presence of retinopathy, timing of measurements and average diabetes duration at diagnosis) were variable, rendering comparisons difficult; hence, the variations noted in recommended screening intervals for patients without baseline retinopathy. There was a potential for underestimation of sight-threatening diabetic retinopathy/blindness incidence in some, if not all, screening studies. For example, the definition of macular oedema used in some studies did not meet the standard of clinically significant macular oedema [30]. Although ophthalmic imaging was the most commonly used screening tool [17,19,24–32,44], none of the screening programmes actually performed the gold standard test for diabetic retinopathy screening (mydriatic stereoscopic 7-field retinal photography). Thus, sight-threatening diabetic retinopathy or blindness frequency may have been biased, although this would be expected to affect mild diabetic retinopathy much more than detection of vision-threatening diabetic retinopathy. However, the potential for bias is limited, given that the sensitivity of screening tools used is in the range of 70–90% [11]. Furthermore, using mydriatic 7-field retinal photography in population-based screening programmes may be logistically challenging.

Some of the screening studies were relatively small in size [19,23,24,26,28,30,31], or were hospital based [28,30], with a potential for selection bias that could limit the generalizability of their findings. Furthermore, the use of the proportion of blindness (obtained from a registry) attributable to diabetic retinopathy as the main outcome of a screening evaluation may limit the findings, given that a blindness registry may not adequately capture all people with diabetic retinopathy, thus raising the question of the completeness of information on the data on blindness and other states of lower vision [44].

In screening programmes, non-response was reasonably common [26,27]. If non-attenders had worse glycaemic control, and therefore a higher rate of progression than those who comply, the incidence of sight-threatening diabetic retinopathy may have been biased, as estimates are limited to those who attended follow-up screening sessions.

The head-to-head comparison of modelling studies (both non-economic and economic) is difficult, as these originated from different countries, used different currencies and

costing methodologies and are based on different clinical practices. The limitations of economic studies mainly relates to their various assumptions. Some of the models did not include the pathway to blindness through maculopathy [36,37,41], potentially underestimating the incidence of sight-threatening diabetic retinopathy. Other potential sources of bias from the models include not varying the major inputs of disease progression and mortality [41], not considering the sensitivity and specificity of various diabetic retinopathy screening tests [41], using a single perspective without any sensitivity analysis including other perspectives [38–41,43], not factoring in the indirect costs other than those incurred for screening (with a potential bias toward the effectiveness of the programme) [43], not discounting costs and/or consequences associated with differential timing [38,39], not specifying how costs were measured [38,43], not measuring all the consequences [38], not accounting for the duration of diabetes and the HbA_{1c} level (may influence the efficacy of screening at different intervals) [38,41,43] and not accounting for the screening compliance rate [40,43].

The vast majority of studies examined in this review were conducted in populations of predominantly European descent. Furthermore, some of the modelling studies including a mixed population overlooked potential variations in retinopathy risk in all the subgroups included [7], raising the issue of the generalizability of the findings. The susceptibility to diabetic retinopathy and rate of progression may be higher in other ethnic groups (people of African, Hispanic or Native American descent), given the frequency of diabetic retinopathy in these groups [1] and their genetic susceptibility [12,51]. It may therefore be difficult to extrapolate the results presented here to these groups. In addition, the screening programmes were conducted in high-income countries, where the systems are generally better suited to influence progression of diabetes, than in low- and middle-income countries.

Strengths and limitations of the review

The strengths of this review include the appraisal of the totality of the evidence on screening interval for diabetic retinopathy, especially that from real-world screening programmes, and thus its potential utility in helping to choose the most appropriate screening interval in guidelines. However, any policy modification or adoption should be followed by an extensive evaluation, especially in low- and middle-income countries, as the vast majority of existing studies have been conducted in the Western world. The review is limited by the partial reliance on modelling studies with their many assumptions, rather than real-life data. Also, we ranked the quality of economic studies using a scoring system; such a rating is not completely without subjectivity. Finally, our ability to assess publication bias was limited.

Conclusions

This review of evidence suggests that a 2-year screening interval for people with diabetes and no diabetic retinopathy at diagnosis may be safely adopted. However, this is contingent upon the availability of facilities to conduct appropriate eye examinations and deliver appropriate care to people detected. Available data, especially from real-life screening programmes, was mainly retrospective and originated from studies in Caucasians; additional prospective data from non-Caucasian populations, especially in low- and middle-income countries, are therefore needed. Such data may confirm whether the suggested 2-year screening interval is safe and sustainable in any population and/or any health system. The choice of a screening interval should account for the context; consideration should be given to capacity of the health system to perform screening at the indicated frequency and to provide appropriate treatment.

Funding sources

This work was supported by the World Health Organization. The views expressed within this paper are those of the authors and not necessarily those of the World Health Organization.

Competing interests

None declared.

References

1 Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T *et al*. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care* 2012; **35**: 556–564.
2 Wilson JGM, Jungner G. *Principles and Practice of Screening for Disease*. Geneva: World Health Organization, 1968.
3 Saaddine JB, Honeycutt AA, Narayan KM, Zhang X, Klein R, Boyle JP. Projection of diabetic retinopathy and other major eye diseases among people with diabetes mellitus: USA, 2005–2050. *Arch Ophthalmol* 2008; **126**: 1740–1747.
4 Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. IX. Four-year incidence and progression of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol* 1989; **107**: 237–243.
5 Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Arch Ophthalmol* 1984; **102**: 527–532.
6 Diabetes Control and Complications Trial Research Group. Progression of retinopathy with intensive versus conventional treatment in the Diabetes Control and Complications Trial. *Ophthalmology* 1995; **102**: 647–661.
7 UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; **352**: 837–853.
8 Stratton IM, Kohner EM, Aldington SJ, Turner RC, Holman RR, Manley SE *et al*. UKPDS 50: risk factors for incidence and

progression of retinopathy in Type II diabetes over 6 years from diagnosis. *Diabetologia* 2001; **44**: 156–163.
9 UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *Br Med J* 1998; **317**: 703–713.
10 Klein R, Sharrett AR, Klein BE, Moss SE, Folsom AR, Wong TY *et al*. The association of atherosclerosis, vascular risk factors, and retinopathy in adults with diabetes: the Atherosclerosis Risk in Communities Study. *Ophthalmology* 2002; **109**: 1225–1234.
11 Hutchinson A, McIntosh A, Peters J, O'Keeffe C, Khunti K, Baker R *et al*. Effectiveness of screening and monitoring tests for diabetic retinopathy—a systematic review. *Diabet Med* 2000; **17**: 495–506.
12 Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. *Lancet* 2010; **376**: 124–136.
13 Ferris FL 3rd, Davis MD, Aiello LM. Treatment of diabetic retinopathy. *N Engl J Med* 1999; **341**: 667–678.
14 American Diabetes Association. Diabetic retinopathy. *Diabetes Care* 2002; **25**: s90–s93.
15 National Screening Committee. *The UK NSC policy on Diabetic Retinopathy Screening*. National Health Service: Gloucester, 2005.
16 Spurling G, Askew D, Jackson C. Retinopathy—screening recommendations. *Aust Fam Physician* 2009; **38**:780–783.
17 Younis N, Broadbent DM, Vora JP, Harding SP. Incidence of sight-threatening retinopathy in patients with type 2 diabetes in the Liverpool Diabetic Eye Study: a cohort study. *Lancet* 2003a; **361**: 195–200.
18 Vijan S, Hofer TP, Hayward RA. Cost-utility analysis of screening intervals for diabetic retinopathy in patients with type 2 diabetes mellitus. *J Am Med Assoc* 2000; **283**: 889–896.
19 Olafsdottir E, Stefansson E. Biennial eye screening in patients with diabetes without retinopathy: 10-year experience. *Br J Ophthalmol* 2007; **91**: 1599–1601.
20 Leese GP. Should diabetes retinal screening intervals change? *Diabet Med* 2013; **30**: 43–45.
21 Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *Br Med J* 1996; **313**: 275–283.
22 Jones S, Edwards RT. Diabetic retinopathy screening: a systematic review of the economic evidence. *Diabet Med* 2010; **27**: 249–256.
23 Agardh E, Agardh CD, Hansson-Lundblad C. The 5-year incidence of blindness after introducing a screening programme for early detection of treatable diabetic retinopathy. *Diabet Med* 1993; **10**: 555–559.
24 Kristinsson JK, Gudmundsson JR, Stefansson E, Jonasson F, Gislason I, Thorsson AV. Screening for diabetic retinopathy. Initiation and frequency. *Acta Ophthalmol Scand* 1995; **73**: 525–528.
25 Henricsson M, Tyrberg M, Heijl A, Janzon L. Incidence of blindness and visual impairment in diabetic patients participating in an ophthalmological control and screening programme. *Acta Ophthalmol Scand* 1996; **74**: 533–538.
26 Hansson-Lundblad C, Holm K, Agardh CD, Agardh E. A small number of older type 2 diabetic patients end up visually impaired despite regular photographic screening and laser treatment for diabetic retinopathy. *Acta Ophthalmol Scand* 2002; **80**: 310–315.
27 Younis N, Broadbent DM, Harding SP, Vora JP. Incidence of sight-threatening retinopathy in Type 1 diabetes in a systematic screening programme. *Diabet Med* 2003b; **20**: 758–765.
28 Maguire A, Chan A, Cusumano J, Hing S, Craig M, Silink M *et al*. The case for biennial retinopathy screening in children and adolescents. *Diabetes Care* 2005; **28**: 509–513.
29 Misra A, Bachmann MO, Greenwood RH, Jenkins C, Shaw A, Barakat O *et al*. Trends in yield and effects of screening intervals during 17 years of a large UK community-based diabetic retinopathy screening programme. *Diabet Med* 2009; **26**: 1040–1047.
30 Soto-Pedre E, Hernaez-Ortega MC, Vazquez JA. Six-year retrospective follow-up study of safe screening intervals for sight-threatening retinopathy in patients with diabetes mellitus. *J Diabetes Sci Technol* 2009; **3**: 812–818.
31 Ling R, Ramsewak V, Taylor D, Jacob J. Longitudinal study of a cohort of people with diabetes screened by the Exeter Diabetic Retinopathy Screening Programme. *Eye (Lond)* 2002; **16**: 140–145.
32 Agardh E, Tababat-Khani P. Adopting 3-year screening intervals for sight-threatening retinal vascular lesions in type 2 diabetic subjects without retinopathy. *Diabetes Care* 2011; **34**: 1318–1319.
33 Jones CD, Greenwood RH, Misra A, Bachmann MO. Incidence and progression of diabetic retinopathy during 17 years of a population-based screening program in England. *Diabetes Care* 2012; **35**: 592–596.
34 Thomas RL, Dunstan F, Luzio SD, Roy Chowdury S, Hale SL, North RV *et al*. Incidence of diabetic retinopathy in people with type 2 diabetes mellitus attending the Diabetic Retinopathy Screening Service for Wales: retrospective analysis. *Br Med J* 2012; **344**: e874.
35 Davies R, Sullivan P, Canning C. Simulation of diabetic eye disease to compare screening policies. *Br J Ophthalmol* 1996; **80**: 945–950.
36 Tung TH, Chen SJ, Shih HC, Chou P, Li AF, Shyong MP *et al*. Assessing the natural course of diabetic retinopathy: a population-based study in Kinmen, Taiwan. *Ophthalmic Epidemiol* 2006; **13**: 327–333.
37 Liu WJ, Lee LT, Yen MF, Tung TH, Williams R, Duffy SW *et al*. Assessing progression and efficacy of treatment for diabetic retinopathy following the proliferative pathway to blindness: implication for diabetic retinopathy screening in Taiwan. *Diabet Med* 2003; **20**: 727–733.
38 Javitt JC, Aiello LP, Chiang Y, Ferris FL 3rd, Canner JK, Greenfield S. Preventive eye care in people with diabetes is cost-saving to the federal government. Implications for healthcare reform. *Diabetes Care* 1994; **17**: 909–917.
39 Davies R, Roderick P, Canning C, Brailsford S. The evaluation of screening policies for diabetic retinopathy using simulation. *Diabet Med* 2002; **19**: 762–770.
40 Brailsford S, Rauner M, Gutjahr W, Zeppelzauer W. Combined discrete-event simulation and ant colony optimisation approach for selecting optimal screening policies for diabetic retinopathy. *Comput Manage Sci* 2007; **4**: 59–83.
41 Dasbach EJ, Fryback DG, Newcomb PA, Klein R, Klein BE. Cost-effectiveness of strategies for detecting diabetic retinopathy. *Med Care* 1991; **29**: 20–39.
42 Rein DB, Wittenborn JS, Zhang X, Allaire BA, Song MS, Klein R *et al*. The cost-effectiveness of three screening alternatives for people with diabetes with no or early diabetic retinopathy. *Health Serv Res* 2011; **46**: 1534–1561.
43 Tung TH, Shih HC, Chen SJ, Chou P, Liu CM, Liu JH. Economic evaluation of screening for diabetic retinopathy among Chinese type 2 diabetics: a community-based study in Kinmen, Taiwan. *J Epidemiol* 2008; **18**: 225–233.
44 Arun CS, Al-Bermani A, Stannard K, Taylor R. Long-term impact of retinal screening on significant diabetes-related visual impairment in the working age population. *Diabet Med* 2009; **26**: 489–492.
45 Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. *Ophthalmology* 1991; **98**: 766–785.
46 The Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy. Clinical application of Diabetic Retinopathy Study (DRS) findings, DRS report number 8. *Ophthalmology* 1981; **88**: 583–600.

47 Brailsford SC, Davies R, Canning C, Roderick PJ. Evaluating screening policies for the early detection of retinopathy in patients with non-insulin dependent diabetes. *Health Care Manag Sci* 1998; **1**: 115–124.
48 Kohner EM, Stratton IM, Aldington SJ, Holman RR, Matthews DR. Relationship between the severity of retinopathy and progression to photocoagulation in patients with Type 2 diabetes mellitus in the UKPDS (UKPDS 52). *Diabet Med* 2001; **18**: 178–184.
49 Henricsson M, Sellman A, Tyrberg M, Groop L. Progression to proliferative retinopathy and macular oedema requiring treatment. Assessment of the alternative classification of the Wisconsin Study. *Acta Ophthalmol Scand* 1999; **77**: 218–223.
50 Scottish Intercollegiate Guidelines Network (SIGN). Management of diabetes. A national clinical guideline. In: Brown K, Cant B, Twaddle S eds. *National Health Service Quality Improvement Scotland*. Edinburgh: Scottish Intercollegiate Guidelines Network, 2010: 97–99.
51 Abhary S, Hewitt AW, Burdon KP, Craig JE. A systematic meta-analysis of genetic association studies for diabetic retinopathy. *Diabetes* 2009; **58**: 2137–2147.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Search terms and strategies.
Appendix S2. Scoring the quality of economic studies.