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Costs associated with retinopathy of prematurity: a systematic review and meta-analysis

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ABSTRACT

Objectives To review and analyse evidence regarding costs for retinopathy of prematurity (ROP) screening, lifetime costs and resource use among infants born preterm who develop ROP, and how these costs have developed over time in different regions.

Design Systematic review and meta-analysis

Data sources PubMed and Scopus from inception to 23 June 2021.

Eligibility criteria for selecting studies Included studies presented costs for ROP screening and the lifetime costs (including laser treatment and follow-up costs) and resource use among people who develop ROP. Studies not reporting on cost calculation methods or ROP-specific costs were excluded.

Data extraction and synthesis Two independent reviewers screened for inclusion and extracted data, including items from a published checklist for quality assessment used for bias assessment, summary and random-effects meta-analysis for treatment costs. Included studies were further searched to identify eligible references and citations.

Results In total, 15 studies reported ROP screening costs, and 13 reported lifetime costs (either treatment and/or follow-up costs) for infants with ROP. The range for screening costs (10 studies) was US$5–US$253 per visit, or US$324–US$1072 per screened child (5 studies). Costs for treatment (11 studies) ranged from US$38 to US$6500 per child. Four studies reported healthcare follow-up costs (lifetime costs ranging from US$64 to US$2420, and 10-year costs of US$1695, respectively), and of these, three also reported lifetime costs for blindness (range US$26 686–US$224 295) using secondary cost data. Included papers largely followed the quality assessment checklist items, thus indicating a low risk of bias.

Conclusion The costs of screening for and treating ROP are small compared with the societal costs of resulting blindness. However, little evidence is available for predicting the effects of changes in patient population, screening schedule or ROP treatments.

PROSPERO registration number CRD42020208213.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ PubMed and Scopus were searched systematically.
⇒ Since manual search of reference lists and citations of the identified papers did not identify additional studies, the database search had good coverage of the topic of investigation.
⇒ The main limitations of this work were the exclusion of grey literature and the lack of analyses of publication bias for the meta-analysis.
⇒ Where lack of variance information in included studies hindered meta-analysis, guidance for synthesis in systematic reviews without meta-analyses were followed.

INTRODUCTION

Improvements in neonatal care have resulted in increased survival among children born preterm,[1] but these infants are at risk of developing preterm-related morbidities such as retinopathy of prematurity (ROP). ROP is characterised by abnormal neurovascular development and, in its worst forms, retinal detachment and blindness.[2] Although preventable, ROP is the leading cause of blindness in children worldwide,[3] a ranking associated with the survival of infants with extremely low gestational age and birth weight in some parts of the world, and use of unmonitored treatments with 100% oxygen in other regions.[2]

ROP management and treatment economics are still challenging in many health systems because of screening-associated costs, patient-related costs and medicolegal liability.[4] Thus, there is an urgent need for more concerted efforts to guide healthcare providers in how to use resources efficiently, both in developing economies during a phase of improving survival of preterm infants, such as in many parts of Africa,[5] and in countries like Sweden with major neonatal morbidities still affecting a large proportion of those who survive.[6]

Here, we present an overview of costs associated with ROP screening and treatment, examining the evidence related to costs for ROP screening and lifetime costs (including laser treatment and follow-up costs) and resource use among infants born preterm who

develop ROP. We also examine the trajectories of these costs over time in different regions in a meta-analysis.

METHODS

This work followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (ie, PRISMA),[7] with protocol available in PROSPERO (reference CRD42020208213).[8]

Article search

PubMed and Scopus were searched (online supplemental eTable 1, 23 June 2021) to identify original research on costs for ROP, including full cost or cost increases associated with ROP, without restricting language, publication date or country. Papers were thus included if presenting costs for ROP screening or lifetime costs (including laser treatment and follow-up costs) and resource use among people who develop ROP. Lifetime costs can for example include follow-up healthcare costs but also productivity loss due to blindness or other cost components occurring due to visual impairment later in life. Articles that did not describe the cost calculation method were excluded, as were those not presenting the costs for the group with ROP separately.

Rayyan QCRI was used for handling duplicates and the selection of studies for inclusion. Two independent reviewers (JH and CL or HG) searched the databases, screened articles for eligibility, extracted data using a prespecified data extraction sheet (online supplemental eTable 2), and handsearched included studies (7 July 2021) to identify eligible references and citations. Conflicting views were resolved by discussion with a third reviewer (CL or HG).

The data extraction sheet included items (online supplemental eTable 2) from a published checklist for quality assessment of economic evaluations[9] including a core set of items relevant in assessing the risk of bias in included studies. The 19 checklist items covers design and methods, population and generalisability, as well as ethics and funding, answered as yes or no during the assessment. To aid reading, summary scores indicating the items answered as Yes for each paper were calculated, thus a high summary score indicates that many of the items were covered. Quality of evidence was rated on a scale from 1 to 5 for individual articles, according to: 1=for example, properly powered randomised controlled trials; 2=for example, prospective cohort studies; 3=for example, retrospective cohort studies; 4=case series with or without intervention or cross-sectional study; 5=for example, opinion of respected authorities.[10]

Analysis

Conventional screening (excluding telemedicine costs), laser treatment and long-term follow-up costs were reported, respectively, accounting for ROP severity and differences over time and between countries. Identified costs were adjusted to 2020 US dollars (US$) using annual exchange rates[11] and the Organisation for Economic Co-operation and Development inflation factor.[12] After imputation of missing variance based on the percentage variance in studies presenting such information, treatment costs were summarised in a forest plot, by year and subgroups using the World Bank country classification based on gross national income per capita,[13] as cost levels can be expected to differ.

Patient and public involvement

This project did not include patient or public involvement in developing the research questions, design, conduct, choice of outcome measures or recruitment.

RESULTS

Of the 503 studies screened after duplicates from the databases were removed, 123 were assessed for eligibility based on full text, and 19 studies were included in the synthesis of results (online supplemental eFigure 1). Reasons for exclusion were absence of data on costs associated with ROP, lack of original data or inclusion of data related only to insurance payments or litigation. No additional studies were identified by a hand search of references and a Scopus search of citations of included studies. An overview of all included studies[14–32] is presented in table 1, including references to secondary cost sources.[33–39] In total, 15 studies covered screening costs and 13 reported lifetime costs (treatment and/or follow-up costs) for infants who developed ROP.

Twelve studies were conducted in high-income economies: seven in the USA, two in Canada and one each in the UK, Netherlands and France. Three studies were conducted in upper-middle-income economies: one each in Peru, Thailand and Brazil. Three studies were conducted in lower-middle-income economies: two in India and one in Iran. One study was conducted in both the United States and Mexico (table 1). All studies reported the economic analyses using either US dollars, euros or local currency. The patient populations in all studies were infants at risk for ROP, although the studies used different inclusion criteria based on gestational age at birth and birth weight. In addition, the ROP definition for stages and treatment criteria varied with the timing of the study and international guidelines for classification at that time.

Risk of bias in included studies

The quality assessment indicated a high overall quality of the included studies (online supplemental eTable 3), with 16 of 19 of them fulfilling at least 16 of the assessed criteria. However, eight studies did not fulfil the criteria for discounting future costs and outcomes or for subjecting results to sensitivity analyses to address the effects of assumptions. In addition, 14 studies met criteria regarding the reporting of incremental analysis and potential conflicts of interest. Thus, overall, the assessment suggested a low risk of bias in the included papers,

Table 1 Overview of studies included in this review

#	First author (year)	Country (study period) setting	Study design	ROP definition	Sample size (% of infants with ROP treated)	Inclusion criteria	Mean cost per child with ROP (value year and currency as reported in the original publication)	Cost perspective: cost inclusion
1	Mohammadi (2021)[14]	Iran (2017) Data from Farabi eye hospital	Decision Analytical Model from case series	Threshold ROP	Total: 126 ROP: 126	Randomly selected infants with treatment requiring ROP	Treatment: US$1107/infant	Unclear perspective: out-of-pocket charges*
2	Moitry (2018)[15]	France (2012 and 2014–2015) Data from two hospitals CHSF and Port-Royal	Retrospective, before-and-after study	Type 1 ROP	Not specified	GA <33 weeks or BW <1500 g	Screening: €37/exam	Health system: direct costs
3	Isaac (2018)[16]	Canada (2009–2014) Data from Ontario Ministry of Health and Long-Term Care	Retrospective cohort study (chart review)	Type 1 ROP	Total: 174 ROP: 64 Treated: 3 (5.6%)	BW<1500 g or GA<30 weeks	Screening HSN: C$346/exam (SD: C$306) Screening RVH: C$375/exam (SD: C$300)	Health system: direct costs (excluding equipment and maintenance)
4	Kelkar (2017a)[17]	India (2009–2011) Mobile ROP screening unit	Public health intervention† from case series	ICROP guidelines	Total: 104 ROP: 34 Treated: 5 (15%)	BW<1700 g or GA<34 weeks	Screening: US$240/exam‡ Identifying an infant with ROP: US$735/infant‡ Treatment: US$6500/infant	Health system: direct healthcare costs (including salaries and equipment)
5	Kelkar (2017b)[18]	India (2013–2015) Data from 5 NICUs	Public health intervention† from case series	ICROP guidelines	Total: 102 ROP: 32 Treated: 4 (15%)	BW <1700 g or GA <34 weeks	Screening: US$199/infant§ Identifying an infant with ROP: US$596/infant§ Treatment: US$4137/infant	Health system: direct costs (including salaries and equipment)
6	Rothschild (2016)[19]	Mexico and US (2014) Data from paediatric eye clinics and schools for the blind in Atlanta, Georgia and Mexico City Blindness costs from the literature[33] and other secondary sources.	Decision Analytical Model from case series	ROP caused blindness (WHO)	Total: 95	BW <1500 g	US screening: US$981/infant Mexico screening: US$333/infant US treatment: US$4037/infant Mexico treatment: US$505/infant US follow-up: US$1538/infant Mexico follow-up: US$2214/infant US blindness cost: US$84586/infant Mexico blindness cost: US$24413/infant	Third party payer: charges (including labour and equipment) Societal costs: expenses for raising a blind child
7	van der Akker-van Merle (2015)[20]	Netherlands (2009) Data from NEDROP study and PRN database	Retrospective cohort study	ICROP guidelines	Total: 1380 ROP: 29 Treated: 17 (59%)	GA<32 weeks or BW <1500 g	Screening: €109/exam Treatment: €2755/infant	Health system: direct costs

Continued

Table 1 Continued

#	First author (year)	Country (study period) setting	Study design	ROP definition	Sample size (% of infants with ROP treated)	Inclusion criteria	Mean cost per child with ROP (value year and currency as reported in the original publication)	Cost perspective: cost inclusion
8	Wongwai (2015) [21]	Thailand (2013) Hypothetical data and cohort Blindness costs using secondary data on annual government subsidies and utilities from the literature[34]	Decision Analytical Model from prospective cohort study	ET-ROP criteria	Total: 100 ROP: 9		Screening: THB 142/infant Treatment: THB (SE) 1053 (316)/infant Lifetime cost of blindness: THB 146,000 Telemedicine screening: THB 17,397/QALY (3% disc. rate)	Third party payer: charges (including labour and equipment)
9	Black (2015) [22]	US (2001–2010) Medical University of South Carolina	Retrospective cohort study	ROP stage 4	Total: 4292 ROP: 7 Treated: 7 (100%)	GA: 23–37 weeks	Cost increase due to ROP if: GA (23 w): US$19 513 GA (mean, 34.3 w): US$23 121 GA (37 w): US$41 161	Hospital: direct costs
10	Zin (2014) [23]	Brazil (2004–2006) 6 NICUs in Rio de Janeiro	Decision Analytical Model from case series and expert opinion	ICROP criteria	Total: 869 ROP: 70 Treated: 70 (100%)	BW <1500 g	Screening: US$18/infant Treatment: US$398/infant	Health system: direct costs (including labour and equipment)
11	Dave (2012) [24]	Peru (2009) Data from local hospital's NICU and from 2002 study[39] Secondary source for blindness costs[35]	Retrospective cohort study	ROP stage 1–5 with/without plus disease	Total: 1239 ROP: 80		Screening and treatment: US$2496/infant Follow-up (three visits): US$54 ROP caused blindness: US$123,806/infant	Health system: direct costs (including equipment, facility, labour and supplies) Societal costs: expenses for blindness
12	Dunbar (2009) [25]	US (2004–2006) Medicare and Medicaid reimbursement data from California and Louisiana	Microsimulation model from retrospective cohort study	Type 1 ROP	Total: 515 ROP: 58 Treated: 58 (100%)	BW <1500 g or GA<28 weeks	Screening: US$93/exam Screening: US$316/infant Treatment w/o anaesthesia: US$1371/infant Screening and treatment: US$1565/QALY (3% disc. rate)	Third-party payer (Medicare and Medicaid): charges (excluding anaesthesia)
13	Kamholz (2009) [26]	US (2005) Data from ET-ROP study	Decision Analytical Model from randomised trial and expert opinion	Type 1 ROP	ROP: 357	BW<1250 g or GA<32 weeks	Screening: US$189/exam (US$56–$251); treatment w/o anaesthesia: US$2423 (US$638–$3223) Anaesthesia: US$1849 (US$925–$3698)	Third-party payer: charges

Continued

Table 1 Continued

#	First author (year)	Country (study period) setting	Study design	ROP definition	Sample size (% of infants with ROP treated)	Inclusion criteria	Mean cost per child with ROP (value year and currency as reported in the original publication)	Cost perspective: cost inclusion
14	Jackson (2008) [27]	US (2006) Data from CRYO-ROP and ET-ROP studies	Decision Analytical Model from randomised trial	Type 1 ROP	Refer to published data on 4099 infants (65.8% with ROP[36] and 6998 infants (68% with ROP[37]	BW <1251 g	Screening: US$160/exam Screening and treatment: US$4410/QALY (3% disc. rate.)	Third-party payer (Medicare): charges
15	Yanowitch (2006) [28]	US (2001–2004) Data from Dean A. McGee Eye Institute and OUHSC campus	Retrospective cohort study (chart review)	CRYO-ROP and ET-ROP criteria	Total: 259 ROP: 11 Treated: 1 (9%)	BW 1250–1800 g	Screening: US$230/infant Treatment: US$2000/infant	Third-party payer: charges
16	Castillo-Riquelme (2004) [29]	UK (1997–1998) Data from published data[38] and local NICU	Decision Analytical Model from case series and expert opinion	ROP stage 3	ROP: 235	GA<32 or BW<1501 g	Screening: £49/exam Screening: £279/infant Treatment: £540/one eye Treatment: £702/two eyes Follow-up (10 years): £786/infant	Health system: direct costs (including equipment and maintenance)
17	Lee (2001) [30]	Canada (1996–1997) Data from 14 NICU	Retrospective cohort study	Threshold ROP	Total: 16 424	Different criteria at different NICU	Screening: C$236/infant Treatment: C$2655/infant	Health system: direct costs
18	Brown (1999) [31]	US (1998) Database from Pennsylvania	Microsimulation model from randomised trial	Threshold ROP	ROP: 291 Treated: 291 (100%) but only one treated eye per infant	BW<1251 g	Treatment: US$1452/infant Treatment consultation: US$140/exam Treatment: US$678/QALY (3% disc. rate)	Third-party payer: charges
19	Javitt (1993) [32]	US (1989) Medicare reimbursement data	Microsimulation model from retrospective cohort study	Threshold ROP or PNA 24 weeks from CRYO-ROP	Total: 18 220 ROP: 1000 Treated: 1000 (100%)	BW: 500–1249 g	Screening (first visit): US$84/exam Screening (subsequent visit): US$68/exam Screening (weekly): US$6045/QALY Screening (biweekly): US$3623/QALY Screening (monthly): US$2488/QALY	Third-party payer: charges (excluding equipment and personnel training cost)

*Assumption based on methods description indicating cost data collected through survey to parents.
†Studies of the introduction of new screening programmes.
‡Screening costs and costs for identifying an infant with ROP are reduced by 22.6% to account for transport costs (ie, driver and cost of van and fuel to move equipment).
§Screening costs and costs for identifying an infant with ROP are reduced by 0.245% to account for transport costs (ie, fuel to move equipment).
BW, birth wt; GA, gestational age; HSN, Health Sciences North in Sudbury; NICU, neonatal intensive care unit; PNA, postnatal age; QALY, quality-adjusted life-years; ROP, retinopathy of prematurity; RVH, Royal Victoria Hospital in Barrie, Canada.

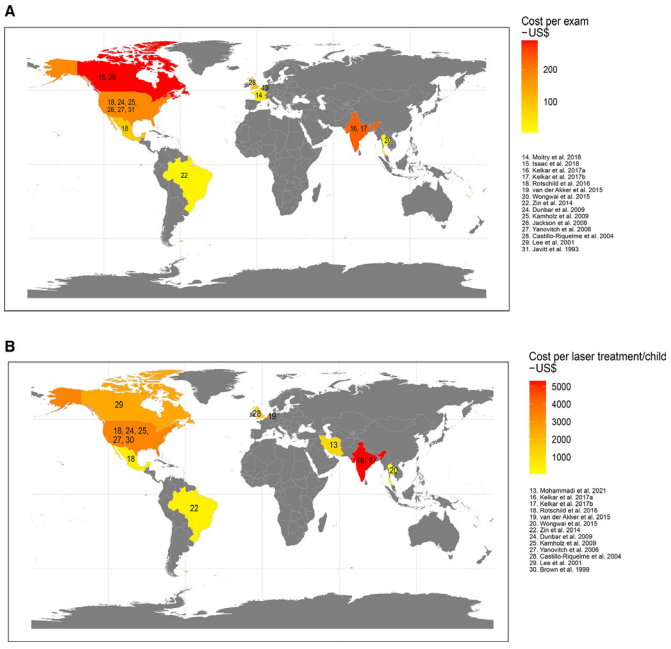

Figure 1 Map of data availability and costs per (A) screening visit and (B) treatment. The map illustrates reported costs or means of reported costs per country for included studies in US$. In studies presenting only total screening cost per infant or by first/follow-up visits,[19 28 32] the cost level per screening was calculated under the assumption of four screening visits per infant. Where only screening cost per eye was reported,[30] it was duplicated to obtain the cost level per screening. In studies reporting only unit cost per treatment,[20 26] the unit cost was assumed to indicate the cost level of treatment per infant. where costs were reported separately for unilateral and bilateral treatment,[29] a weighted mean cost was calculated assuming that 75% of treatments were bilateral.

and also indicated where lack of reporting on potential conflicts of interest was most problematic. Quality of evidence ranged from 1 to 5 for individual articles, with articles most commonly based on data from retrospective cohort studies (evidence rating 3; nine publications).

Costs for ROP screening

Studies reporting costs related to screening had different designs: six were retrospective cohort studies using medical chart review or register data,[15 16 20 24 28 30] nine developed economic models[19 21 23 25–27 29 31 32] and two were public intervention studies related to the introduction of ROP screening programmes.[17 18] Although the assessment indicated a low risk of bias, screening costs differed substantially among reporting countries (figure 1A).

Costs for routine ROP screening, excluding transportation costs, are reported in table 2. Ten studies reported a mean unit cost per screening of US$137 (range: 5–253). In addition, five studies reported a mean cost per screened child of US$553 (range: US$324–US$1072). Of these, two studies reported comparably low costs[21 23] for staff and equipment, whereas Rothschild *et al*[19] reported comparably higher costs in the US setting. One study also included transportation costs,[15] and when these costs were removed, screening cost was comparably low. The other studies reported similar costs for screening per child (range: US$324–$602).[25 28 29]

Javitt *et al*[32] reported a mean unit cost of US$183 for a first screening and of US$149 for follow-up screening, whereas Lee *et al*[30] reported a mean unit cost of US$112 for screening one eye. Finally, two studies from India[17 18] reported screening costs of US$1003 and US$630, respectively, for identifying one child with ROP.

In studies comparing alternative screening or treatment options, no common comparator was identified. The incremental cost reported in Black *et al*[22] indicated a savings associated with higher gestational age at birth (table 1). Jackson *et al*[27] used economic modelling to estimate the cost-utility of ROP screening using telemedicine versus conventional ROP screening. Javitt *et al*[32] used modelling to compare weekly, biweekly or monthly screening.

Costs for ROP treatment

In all, 14 studies reported costs related to the laser treatment of ROP (figure 1B). Four studies of treatment costs were retrospective cohort studies,[20 24 28 30] eight were modelling studies[14 19 21 23 25 26 29 31] and two were public intervention studies.[17 18] In addition, two of the included studies[31 32] reported costs for cryotherapy (not included in the analyses below).

Eleven studies reported total treatment costs per child, at a mean US$2442 (range: US$38–US$6500). Castillo-Riquelme *et al*[29] found unilateral treatment costs up to US$1165 and bilateral treatment costs up to US$1514, based partially on secondary data from Brown *et al*.[31] Two studies[20 26] cited unit costs of laser treatment of US$4065 and US$5661, respectively. Laser treatment costs are reported in table 2. Dave *et al*[24] described costs for screening and treatment combined (US$2962) in a cohort of children with blindness.

Accounting for the low assessed risk of bias but large expected variation based on cost-levels of individual countries, the meta-analysis by country classification (figures 2 and 3) estimated the average costs in high-income economies to US$2960 (95% CI US$2003 to US$3917). Corresponding figures were US$329 (95% CI US$9 to US$649) in upper-middle-income economies and US$3692 (95% CI US$670 to US$6715) in lower-middle–income economies, respectively. Most studies did not report variance of results, making publication bias analysis unfeasible. However, model diagnostics (I^2 and Cochrane Q) indicated high heterogeneity between studies within each country classification, which suggests that the results from the meta-analysis should be interpreted with caution.

Follow-up costs and resource use among infants born preterm and developing ROP

Only four studies reported follow-up costs occurring after screening and treatment, and although the risk of bias was assessed as low, the reported results largely differed between studies. Castillo-Riquelme *et al*[29]

Table 2 Costs for screening for ROP among preterm infants (in 2020 values)

#	First author (year)	Screening costs		Treatment costs	Evidence rating	Cost inclusion
		Mean per exam (US$)	Mean per infant (US$)	Mean per infant (US$)		
1	Mohammadi (2021)[14]	–	–	1169	4	Charges
2	Moitry (2018)[15]	44	–	–	3	Direct cost
3	Isaac (2018)[16]	HSN: 342 RVH: 371	–	–	3	Direct cost not including equipment
4	Kelkar (2017a)[17]	253	–	6500	4	Direct cost including equipment and labour
5	Kelkar (2017b)[18]	210	–	4137	4	Direct cost including equipment and labour
6	Rothschild (2016)[19]		US: 1072 Mexico: 362	US: 4413 Mexico: 552	4	Direct cost including equipment and labour
7	van der Akker-van Merle (2015)[20]	160	–	4064*	3	Direct cost
8	Wongwai (2015)[21]	5	–	38	2	Charges including equipment and labour
9	Black (2015)[22]	–	–	–	3	–
10	Zin (2014)[23]	20	–	450	5	Direct cost including equipment and labour
11	Dave (2012)[24]	–	–	–	3	–
12	Dunbar (2009)[25]	119	405	1759	3	Charges
13	Kamholz (2009)[26]	250	–	5661*	5	Charges
14	Jackson (2008)[27]	205	–	–	1	Charges
15	Yanowitch (2006)[28]	–	324	2814	3	Charges
16	Castillo-Riquelme (2004)[29]	106	602	Unilateral: 1165 Bilateral: 1514	5	Direct cost including equipment and maintenance
17	Lee (2001)[30]	Unilateral: 112	–	2507	3	Direct cost
18	Brown (1999)[31]	–	–	2527	1	Charges
19	Javitt (1993)[32]	First: 183 Follow-up: 149	–	–	3	Charges

Evidence rating indicates the quality of evidence rating of included studies: 1=for example, properly powered randomised controlled trials; 2=for example, prospective cohort studies; 3=for example, retrospective cohort studies; 4=case series with or without intervention or cross-sectional study; 5=for example, opinion of respected authorities.
*Unit cost per treatment.
HSN, Health Sciences North in Sudbury; ROP, etinopathy of prematurity; RVH, Royal Victoria Hospital in Barrie.

reported healthcare follow-up costs over 10 years of up to US$1695. Dave *et al*[24] reported a lifetime follow-up visit cost of US$64 and a blindness cost of US$146 952. Rothschild *et al*[19] reported lifetime follow-up healthcare costs of US$1681 (USA) and US$2420 (Mexico), whereas the costs for blindness were estimated to be US$92 460 (USA) and US$26 686 (Mexico). Wongwai *et al*[21] reported the lifetime costs of blindness to be US$224 295. In addition, Black *et al*[22] reported the costs per quality-adjusted life-year (QALY) associated with ROP and other comorbidities associated with being born preterm.

DISCUSSION

The studies we identified could be grouped by whether they reported costs for screening, costs for treatment or costs (and QALYs) during long-term follow-up or even from a lifetime perspective. The cost range per ROP screening was US$5–US$253 per visit, or US$324–US$1072 per screened child. Costs for ROP treatment ranged from US$38–US$6500 per child. In addition, four studies reported healthcare follow-up costs, and three reported lifetime costs using secondary data on costs for blindness. Although quality assessment indicated a low risk of bias,

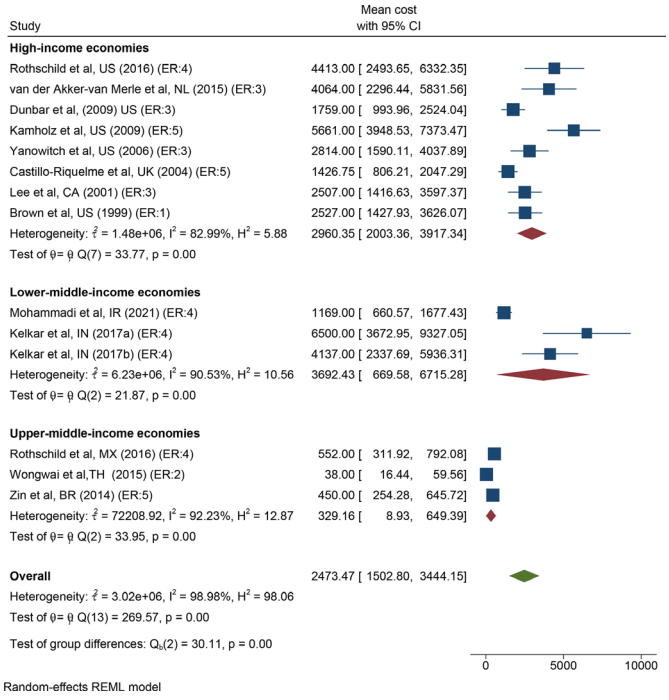

Figure 2 Forest plot of treatment costs, by country categorisation. In parentheses, ER of included studies: 1=for example, properly powered randomised controlled trials; 2=for example, prospective cohort studies; 3=for example, retrospective cohort studies; 4=case series with or without intervention or cross-sectional study; 5=for example, opinion of respected authorities. Country abbreviated according to ISO code. ER, evidence rating; REML, restricted maximum likelihood.

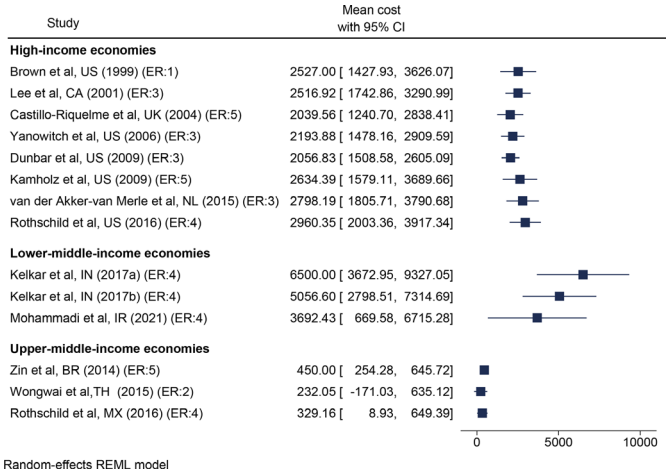

Figure 3 Forest plot of treatment costs, cumulative results by year and country categorisation. in parentheses, ER of included studies: 1=for example, properly powered randomised controlled trials; 2=for example, prospective cohort studies; 3=for example, retrospective cohort studies; 4=case series with or without intervention or cross-sectional study; 5=for example, opinion of respected authorities. Country abbreviated according to ISO code. ER, evidence rating; REML, restricted maximum likelihood.

comparisons between studies were challenging because of the lack of detailed cost and resource use data.

To our knowledge, this is the first systematic review of ROP costs. Included papers largely followed the quality assessment checklist items of a commonly used tool,[40] thus indicating a low risk of bias. However, few of the included articles reported disaggregated cost and resource use data or detailed the included cost components, as is recommended for economic evaluations.[41] The main limitations of this work were the exclusion of grey literature and the lack of analyses of publication bias for the meta-analysis. Guidance for reliability in systematic reviews of retinal disorder interventions[42] was fulfilled, but the standards for systematic reviews of costs and cost-effectiveness studies were not due to the lack of grey literature assessment.[43] Also, since costs were reported purely in a descriptive manner no sensitivity analyses were conducted for alternative categorisations of cost components or country classifications. While not a limitation specific to this analysis but rather of the lack of variance information in the included papers, the findings from the meta-analysis of treatment costs needs to be interpreted with caution after variance was imputed. This lack of variance information also made meta-analysis of screening costs unattainable, since no basis for imputation was available. Moreover, the search strategy and databases are expected to cover largely English-language literature was limited to only two databases, but the reference and citation search yielded no additional studies to include. Thus, we expect our findings to represent a good overview of the available evidence, and that regardless the reservations associated with the meta-analysis to represent current knowledge about costs related to screening and treatment of ROP.

Cost components for ROP screening included staff salaries/time, equipment and maintenance, supplies and staff training. Screening costs for ROP were low compared with other associated costs and, with few exceptions, of the same order of magnitude in the included studies. Exceptions were probably attributable to salary differences.

Screening access and schedules vary between countries.[44] With the possible exception of Javitt *et al*,[32] the included studies provided little evidence for how casemix and alternative screening schedules affect costs for screening. Savings are expected, however, and a modelling study using published cost data calculated an annual cost savings from reduced screening of US$3 million in the USA.[45] However, with low screening costs, the main benefit is reduced discomfort for the infants and reduced travel costs, which can be substantial.[15] The most considerable potential for savings on screening is probably increasing gestational age. US data indicate that ROP frequency increased over time, particularly in infants born very preterm,[46] and infants of lower gestational age usually both require more screening visits and have more severe ROP.[47] Potential savings have been reported from screening using telemedicine (compared with transporting infants to a specialised hospital),[15] or

using bedside screening with mobile equipment instead of moving the infants to a specific screening facility[48]; however, this review did not consider these aspects.

Treatment costs were low compared with the costs for follow-up, with Brazil, Mexico and Peru having substantially lower treatment costs than the other countries. Both Javitt *et al*[32] and Brown *et al*[31] reported low costs for the historically used cryo treatment, at approximately 63% of that for laser treatment. For laser treatment, the cost range was US$2304–$6864 per treated child. None of the studies included the more recent antivascular endothelial growth factor (VEGF) therapy. Moreover, no study reported costs based on ROP stages, age of treated infants, or plus disease status.[49] Thus, studies provide little guidance on how treatment costs will develop over time as more infants of lower gestational age survive.

Variation among studies in whether one or two eyes were treated made comparisons less relevant, which may reflect the unilateral schedule used in the historically influential Cryo-ROP study.[50] However, Swedish registers indicate that bilateral treatment is common (76% of initial treatments and 97% overall)[47] and that retreatment is more frequent among infants with very low gestational age[51] and those treated exclusively with anti-VEGF.[47]

When examining ROP treatment, cost components included staff salaries/time, equipment and maintenance, supplies and staff training. Sometimes anaesthesia costs were reported separately or excluded. Transportation was also a considerable cost component in relation to treatment.[20] Other potential costs that were not measured include those for the added time spent in hospital or intensive care, including parental leave, during treatment. Many studies reported only total charges, which are expected to be higher than costs to the healthcare provider. However, use of charges as opposed to costs was not an obvious cause of variation here. Two studies from India[17 18] reported high costs compared with other studies of both costs and charges, possibly because of some transportation costs remaining as part of additional components. Thus, the apparent decrease in costs over time in the lower-middle-income economies seen in the meta-analysis should be interpreted with caution.

Although ROP results in high costs throughout life, this outcome is primarily based on secondary data for blindness. As the leading cause of preventable childhood blindness[52] and probably the leading cause of childhood blindness in middle-income countries,[53] ROP should be associated with much of the estimated costs of blindness. Moreover, it has been argued that costs for blindness do not differ by cause.[54] Little evidence was available on follow-up after successful, or partially successful, treatment of ROP. Dave *et al*[24] indicated three healthcare visits over the first 7 years of life, whereas Castillo-Riquelme *et al*[29] did not differentiate visits based on treatment or ROP stage. Rothschild *et al* included transportation costs, white canes, Braille equipment and supplies,[19] but disregarded other costs among children retaining sight. Thus, although costs differ by the severity of visual impairment,[55] studies of ROP costs do not tend to report this more detailed level of sight. The current knowledge does not inform potential savings or inform subsidy decisions for ROP treatment developments that can save a little more sight. Taken together, the short follow-up underestimates the total impact of blindness,[56] and not accounting for visual impairment results in underestimating the financial impact of ROP.

There is a need for comprehensive knowledge about the costs of ROP, both during the introduction of new ROP screening programmes and in countries with established programmes that are now redistributing resources to handle the increasing survival of very preterm infants with high disease burden. In addition to relevant cost components of ROP (online supplemental eFigure 2), complementary studies of the benefits of various neonatal preventative strategies, including oxygen delivery, are warranted because evidence of the costs resulting from conditions such as bronchopulmonary dysplasia is also lacking.[57] Such studies should follow state-of-the-art methods for conduct and reporting of health economic studies.

CONCLUSIONS

Although costs of screening and treating ROP are substantial for health systems, they are small compared with the follow-up costs to society of resulting blindness. However, little evidence is available to support predictions about the consequences of changes in the patient population, screening schedule or treatment regimens for ROP.

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Contributors All authors contributed to the design of the study. HG, JH and CL designed the database search and data extraction methods. JH and CL undertook the literature search, assessed studies for eligibility, and extracted data. In case of disagreement, assessments were made in discussion with HG. AH contributed clinical expertise on preterm infants and morbidity. HG, JH, US and CL discussed the data and interpreted the results. HG, JH and CL drafted the manuscript. All authors critically reviewed and approved the final manuscript. HG is the guarantor of the study and thus had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests HG is employed part-time by IQVIA, which is a contract research organisation that performs commissioned pharmacoepidemiological studies. Thus, its employees have been and currently are working in collaboration with several pharmaceutical companies. JH reports no competing interests. AH holds stock/stock options in Premalux AB and has received consulting fees from Takeda Inc. CL holds stocks in Premalux AB.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information. Original data are available in the reviewed publications, which are all cited. Additional data from the data extraction performed are available on reasonable request from the corresponding author, including author template data collection forms, data extracted from included studies, data used for all analyses, analytic code, and any other materials used in the review.

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REFERENCES

1 Lawn JE, Davidge R, Paul VK, *et al*. Born too soon: care for the preterm baby. *Reprod Health* 2013;10 Suppl 1:S5.
2 Hellström A, Smith LEH, Dammann O. Retinopathy of prematurity. *Lancet* 2013;382:1445–57.
3 Yonekawa Y, Thomas BJ, Thanos A, *et al*. The cutting edge of retinopathy of prematurity care: expanding the boundaries of diagnosis and treatment. *Retina* 2017;37:2208–25.
4 Moshfeghi DM, Capone A. Economic barriers in retinopathy of prematurity management. *Ophthalmol Retina* 2018;2:1177–8.
5 Ademola-Popoola DS, Oluleye TS. Retinopathy of prematurity (ROP) in a developing economy with improving health care. *Curr Ophthalmol Rep* 2017;5:114–8.
6 Norman M, Hallberg B, Abrahamsson T, *et al*. Association between year of birth and 1-year survival among extremely preterm infants in Sweden during 2004-2007 and 2014-2016. *JAMA* 2019;321:1188–99.
7 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
8 NIHR, National INstitute for Health Research. Prospero International prospective register of systematic reviews. Available: https://www.crd.york.ac.uk/prospero/
9 Evers S, Goossens M, de Vet H, *et al*. Criteria list for assessment of methodological quality of economic evaluations: consensus on health economic criteria. *Int J Technol Assess Health Care* 2005;21:240–5.
10 Centre for Evidence-Based Medicine (CEBM), University of Oxford. Oxford centre for evidence-based medicine: levels of evidence (March 2009). Available: https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009 [Accessed 30 Aug 2022].
11 Sveriges Riksbank. Annual average exchange rates (aggregate) Accessed June 8, 2021. Available: https://www.riksbank.se/en-gb/statistics/search-interest--exchange-rates/annual-average-exchange-rates/
12 Organisation for Economic Co-operation and Development, OECD. Prices - Inflation (CPI) - OECD Data. Available: http://data.oecd.org/price/inflation-cpi.htm [Accessed 09 Jun 2021].
13 World Bank Country and Lending Groups. World Bank data help desk. Available: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups [Accessed 13 May 2021].
14 Mohammadi S-F, Rahban A, Darabeigi S, *et al*. Cost-effectiveness analysis of tele-retinopathy of prematurity screening in Iran. *Int J Ophthalmol* 2021;14:560–6.
15 Moitry M, Zarca K, Granier M, *et al*. Effectiveness and efficiency of tele-expertise for improving access to retinopathy screening among 351 neonates in a secondary care center: an observational, controlled before-after study. *PLoS One* 2018;13:e0206375.
16 Isaac M, Isaranuwatchai W, Tehrani N. Cost analysis of remote telemedicine screening for retinopathy of prematurity. *Can J Ophthalmol* 2018;53:162–7.
17 Kelkar J, Agashe S, Kelkar A, *et al*. Mobile unit for retinopathy of prematurity screening and management at urban neonatal intensive care units: outcomes and impact assessment. *Oman J Ophthalmol* 2017;10:13–16.
18 Kelkar J, Kelkar A, Sharma S, *et al*. A mobile team for screening of retinopathy of prematurity in India: Cost - effectiveness, outcomes, and impact assessment. *Taiwan J Ophthalmol* 2017;7:155–9.
19 Rothschild MI, Russ R, Brennan KA, *et al*. The economic model of retinopathy of prematurity (EcROP) screening and treatment: Mexico and the United States. *Am J Ophthalmol* 2016;168:110–21.
20 van den Akker-van Marle ME, van Sorge AJ, Schalij-Delfos NE. Cost and effects of risk factor guided screening strategies for retinopathy of prematurity for different treatment strategies. *Acta Ophthalmol* 2015;93:706–12.
21 Wongwai P, Kingkaew P, Asawaphureekorn S, *et al*. A store-and-forward telemedicine for retinopathy of prematurity screen: is it cost-effective in Thailand? *Asian Biomedicine* 2017;9:665–73.
22 Black L, Hulsey T, Lee K, *et al*. Incremental hospital costs associated with comorbidities of prematurity. *Manag Care* 2015;24:54–60.
23 Zin AA, Magluta C, Pinto MFT, *et al*. Retinopathy of prematurity screening and treatment cost in Brazil. *Rev Panam Salud Publica* 2014;36:37–43.
24 Dave HB, Gordillo L, Yang Z, *et al*. The societal burden of blindness secondary to retinopathy of prematurity in Lima, Peru. *Am J Ophthalmol* 2012;154:750–5.
25 Dunbar JA, Hsu V, Christensen M, *et al*. Cost-Utility analysis of screening and laser treatment of retinopathy of prematurity. *J Aapos* 2009;13:186–90.
26 Kamholz KL, Cole CH, Gray JE, *et al*. Cost-Effectiveness of early treatment for retinopathy of prematurity. *Pediatrics* 2009;123:262–9.
27 Jackson KM, Scott KE, Graff Zivin J, *et al*. Cost-Utility analysis of telemedicine and ophthalmoscopy for retinopathy of prematurity management. *Arch Ophthalmol* 2008;126:493–9.
28 Yanovitch TL, Siatkowski RM, McCaffree M, *et al*. Retinopathy of prematurity in infants with birth weight>or=1250 grams-incidence, severity, and screening guideline cost-analysis. *J Aapos* 2006;10:128–34.
29 Castillo-Riquelme MC, Lord J, Moseley MJ, *et al*. Cost-Effectiveness of digital photographic screening for retinopathy of prematurity in the United Kingdom. *Int J Technol Assess Health Care* 2004;20:201–13.
30 Lee SK, Normand C, McMillan D, *et al*. Evidence for changing guidelines for routine screening for retinopathy of prematurity. *Arch Pediatr Adolesc Med* 2001;155:387–95.
31 Brown GC, Brown MM, Sharma S, *et al*. Cost-Effectiveness of treatment for threshold retinopathy of prematurity. *Pediatrics* 1999;104:e47.
32 Javitt J, Dei Cas R, Chiang YP. Cost-Effectiveness of screening and cryotherapy for threshold retinopathy of prematurity. *Pediatrics* 1993;91:859–66.
33 Frick KD, Foster A. The magnitude and cost of global blindness: an increasing problem that can be alleviated. *Am J Ophthalmol* 2003;135:471–6.
34 Christ SL, Lee DJ, Lam BL, *et al*. Assessment of the effect of visual impairment on mortality through multiple health pathways: structural equation modeling. *Invest Ophthalmol Vis Sci* 2008;49:3318–23.
35 United States, Central Intelligence Agency, United States, Central Intelligence Agency. *The World factbook 2009*. CIA's 2008 Edition. Potomac Books, 2008.
36 Palmer EA, Flynn JT, Hardy RJ, *et al*. Incidence and early course of retinopathy of prematurity. The cryotherapy for retinopathy of prematurity cooperative group. *Ophthalmology* 1991;98:1628–40.
37 Good WV, Hardy RJ, Dobson V, *et al*. The incidence and course of retinopathy of prematurity: findings from the early treatment for retinopathy of prematurity study. *Pediatrics* 2005;116:15–23.
38 Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity: Ophthalmological outcomes at 10 years. *Arch Ophthalmol* 2001;119:1110–8.

39 Resnikoff S, Pascolini D, Etya'ale D, *et al*. Global data on visual impairment in the year 2002. *Bull World Health Organ* 2004;82:844–51.
40 Watts RD, Li IW. Use of checklists in reviews of health economic evaluations, 2010 to 2018. *Value Health* 2019;22:377–82.
41 Husereau D, Drummond M, Petrou S, *et al*. Consolidated health economic evaluation reporting standards (cheers) statement. *Value Health* 2013;16:e1–5.
42 Le JT, Qureshi R, Twose C, *et al*. Evaluation of systematic reviews of interventions for retina and vitreous conditions. *JAMA Ophthalmol* 2019;137:1399–405.
43 Mandrik OL, Severens JLH, Bardach A, *et al*. Critical appraisal of systematic reviews with costs and cost-effectiveness outcomes: an ISPOR good practices Task force report. *Value Health* 2021;24:463–72.
44 Blencowe H, Lawn JE, Vazquez T, *et al*. Preterm-associated visual impairment and estimates of retinopathy of prematurity at regional and global levels for 2010. *Pediatr Res* 2013;74 Suppl 1:35–49.
45 Zupancic JAF, Ying G-S, de Alba Campomanes A, *et al*. Evaluation of the economic impact of modified screening criteria for retinopathy of prematurity from the postnatal growth and ROP (G-ROP) study. *J Perinatol* 2020;40:1100–8.
46 Aly H, Othman HF, Munster C, *et al*. The U.S. national trend for retinopathy of prematurity. *Am J Perinatol* 2022;29:1569–76.
47 Holmström G, Hellström A, Gränse L, *et al*. New modifications of Swedish ROP guidelines based on 10-year data from the SWEDROP register. *Br J Ophthalmol* 2020;104:943–9.
48 Kovács G, Somogyvári Z, Maka E, *et al*. Bedside ROP screening and telemedicine interpretation integrated to a neonatal transport system: economic aspects and return on investment analysis. *Early Hum Dev* 2017;106-107:1–5.
49 Agarwal K, Jalali S. Classification of retinopathy of prematurity: from then till now. *Community Eye Health* 2018;31:S4–7.
50 Nguyen QD, Tawansy K, Hirose T. Recent advances in retinopathy of prematurity. *Int Ophthalmol Clin* 2001;41:129–51.
51 Lundgren P, Jacobson L, Hård A-L, *et al*. High rate and large intercentre variability in retreatment of retinopathy of prematurity in infants born <24 gestational weeks. *BMJ Open Ophthalmol* 2021;6:e000695.
52 Shah PK, Prabhu V, Karandikar SS, *et al*. Retinopathy of prematurity: past, present and future. *World J Clin Pediatr* 2016;5:35–46.
53 World Health Organization. Vision impairment and blindness. Available: https://www.who.int/news-room/fact-sheets/detail/blindness-and-visual-impairment [Accessed 26 Aug 2021].
54 Naguib MM, Soares RR, Anzures R, *et al*. Regionally specific economic impact of screening and treating retinopathy of prematurity in middle-income societies in the Philippines. *J Pediatr Ophthalmol Strabismus* 2019;56:388–96.
55 Köberlein J, Beifus K, Schaffert C, *et al*. The economic burden of visual impairment and blindness: a systematic review. *BMJ Open* 2013;3:e003471.
56 Chakravarthy U, Biundo E, Saka RO, *et al*. The economic impact of blindness in Europe. *Ophthalmic Epidemiol* 2017;24:239–47.
57 Humayun J, Löfqvist C, Ley D, *et al*. Systematic review of the healthcare cost of bronchopulmonary dysplasia. *BMJ Open* 2021;11:e045729.

Online-Only Supplements

Costs associated with Retinopathy of prematurity: A Systematic Review and Meta-analysis

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Content

eTable 1. Search strategy[a]

Database	Search string
Pubmed	(((((((Retinopathy) AND Prematur*) OR ((Terry) AND Syndrom*) OR ("ROP"[Title/Abstract]) OR "Retinopathy of Prematurity"[Mesh])) AND (("Economics"[Mesh]) OR ((economic*[Title/Abstract] OR cost[Title/Abstract] OR costs[Title/Abstract] OR costly[Title/Abstract] OR costing[Title/Abstract] OR price[Title/Abstract] OR prices[Title/Abstract] OR pricing[Title/Abstract] OR pharmacoeconomic*[Title/Abstract]))))))
Scopus	(TITLE-ABS-KEY ("Retinopath*") AND TITLE-ABS-KEY ("Prematur*")) OR (TITLE-ABS-KEY ("Retrolental") AND TITLE-ABS-KEY ("Fibroplas*")) OR (TITLE-ABS-KEY ("Terry") AND TITLE-ABS-KEY ("Syndrom*")) AND (TITLE-ABS-KEY (economic* OR cost OR cos OR costly OR costing OR price OR prices OR pricing OR pharmacoeconomic*))

[a] No filters or limitations were used in the searches of databases.

eTable 2. Data extraction sheet

Data extraction

- Reviewer
- Reference (APA)
- Aim/Objective
- Study design
- When was it conducted
- Setting including country and hospital name/database
- How is ROP severity defined
- Total study participants
- Patients with ROP (N)
- Patient group description
- Controls (N)
- Control group description
- Average cost of screening (total per infant/per visit/per eye)
- What costs are measured
- How are the costs measured
- Average Cost for infants with diagnosed sight-threatening ROP
- What costs are measured
- How are the costs measured
- Costs from which year (if adjusted, which year)
- Perspective: cost analysis
- Time horizon of cost analysis
- Funding
- Limitations: Confounders and biases reported
- Conclusions (by author)

Quality assessment (according to instrument developed by Evers et al[1])

1. Is the study population clearly described?
2. Are competing alternatives clearly described?
3. Is a well-defined research question posed in answerable form?
4. Is the economic study design appropriate to the stated objective?
5. Is the chosen time horizon appropriate in order to include relevant costs and consequences?
6. Is the actual perspective chosen appropriate?
7. Are all important and relevant costs for each alternative identified?
8. Are all costs measured appropriately in physical units?
9. Are costs valued appropriately?
10. Are all important and relevant outcomes for each alternative identified?
11. Are all outcomes measured appropriately?
12. Are outcomes valued appropriately?
13. Is an incremental analysis of costs and outcomes of alternatives performed?
14. Are all future costs and outcomes discounted appropriately?
15. Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?
16. Do the conclusions follow from the data reported?
17. Does the study discuss the generalizability of the results to other settings and patient/client groups?
18. Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?
19. Are ethical and distributional issues discussed appropriately

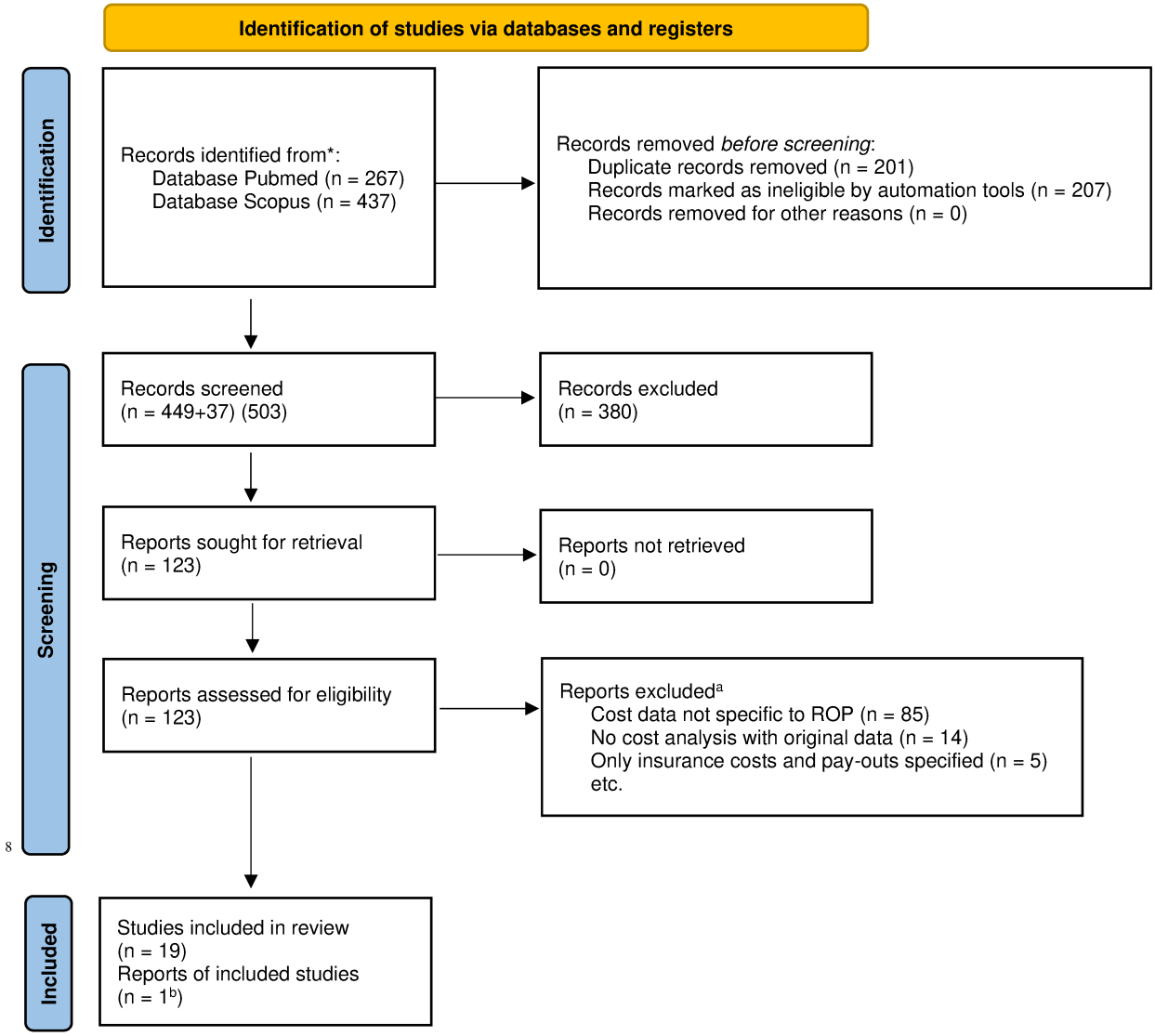
eTable 3. Checklist for the quality appraisal of included papers (from Evers et al[1])

First authors Checklist items[a]	Black[2]	Brown[3]	Castillo-Requilme[4]; Javitt[5]; Lee[6]; Rothchild[7]; Wongwai[8]	Dave[9]	Dunbar[10]	Isaac[11]	Kamholz[12]; Jackson[13]	Kelkar (2017a)[14]; Kelkar (2017b)[15]	Mohammadi[16]	Moitry[17]	Van den Akker-van Merle[18]	Yanowitch[19]	Zin[20]	**Total**
1	+	+	+	+	+	+	-	+	-	+	+	+	+	**16**
2	+	+	+	+	+	+	+	+	+	+	+	+	+	**19**
3	+	+	+	+	+	+	+	+	+	+	+	+	+	**19**
4	+	+	+	+	+	+	+	+	+	+	+	+	+	**19**
5	+	+	+	+	+	+	+	+	+	+	+	+	+	**19**
6	+	+	+	+	+	+	+	+	-	+	+	+	+	**18**
7	+	+	+	+	+	+	+	+	+	+	+	+	+	**19**
8	+	+	+	+	+	+	+	+	+	+	+	+	+	**19**
9	+	+	+	+	+	+	+	+	+	+	+	+	+	**19**
10	+	+	+	+	+	+	+	+	+	+	+	+	+	**18**
11	+	+	+	+	+	+	+	+	+	+	+	+	+	**19**
12	+	+	+	+	+	+	+	+	+	+	+	+	+	**19**
13	+	-	+	+	+	+	+	-	-	-	+	+	+	**14**
14	-	-	+	-	+	-	+	-	-	+	+	+	-	**11**
15	+	-	+	-	-	-	+	-	-	+	-	-	+	**10**
16	+	+	+	+	+	+	+	+	+	+	+	+	+	**19**
17	+	+	+	+	+	+	+	+	+	+	+	+	+	**19**
18	+	+	+	+	-	+	+	-	+	+	-	+	+	**15**

19	+	+	+	+	+	+	+	-	+	+	+	+	+	**17**
Total	**18**	**16**	**19**	**17**	**17**	**17**	**18**	**14**	**14**	**18**	**17**	**17**	**18**	

[a] Item numbering (also in eTable 2): 1. Is the study population clearly described?; 2. Are competing alternatives clearly described?; 3. Is a well-defined research question posed in answerable form?; 4. Is the economic study design appropriate to the stated objective?; 5. Is the chosen time horizon appropriate in order to include relevant costs and consequences?; 6. Is the actual perspective chosen appropriate?; 7. Are all important and relevant costs for each alternative identified?; 8. Are all costs measured appropriately in physical units?; 9. Are costs valued appropriately?; 10. Are all important and relevant outcomes for each alternative identified?; 11. Are all outcomes measured appropriately?; 12. Are outcomes valued appropriately?; 13. Is an incremental analysis of costs and outcomes of alternatives performed?; 14. Are all future costs and outcomes discounted appropriately?; 15. Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?; 16. Do the conclusions follow from the data reported?; 17. Does the study discuss the generalizability of the results to other settings and patient/client groups?; 18. Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?; 19. Are ethical and distributional issues discussed appropriately?

eFigure 1. Flow diagram shows the study selection process, following the PRISMA guidelines.[21]



[a] For detailed reasons for exclusion of studies that might appear to meet the inclusion criteria, but which were excluded, see also eTable 4.

[b] One author[8] was contacted and clarified the currency of reported results. Another author[16] was unsuccessfully contacted to clarify cost perspective.

Abbreviations: ROP = Retinopathy of prematurity.

eTable 4. Excluded articles[a]

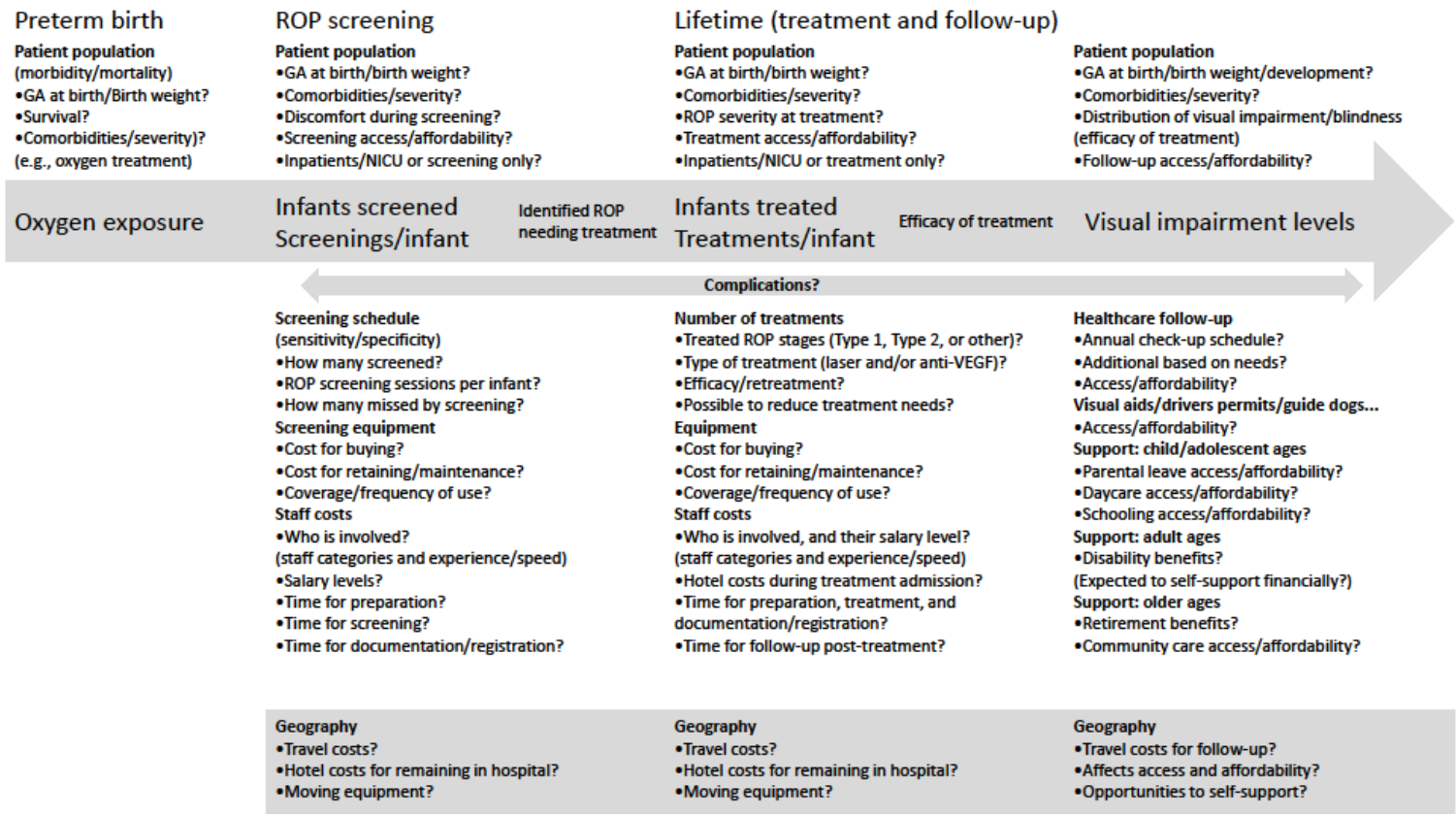
Study	Reason for exclusion
Cross 1973. Cost of preventing retrolental fibroplasia?[22]	No original cost data.
Boncz et al., 2013. [Health-economic analysis of diseases related to disturbed neonatal adaptation: A cost of illness study].[23]	Only insurance payouts.
Yo et al., 2018. Retinopathy of prematurity: the high cost of screening regional and remote infants.[24]	Transport costs but no screening costs.
Scholz and Greiner, 2019. An exclusive human milk diet for very low birth weight newborns-A cost-effectiveness and EVPI study for Germany.[25]	No ROP specific costs.
Zupancic et al., 2020. Evaluation of the economic impact of modified screening criteria for retinopathy of prematurity from the Postnatal Growth and ROP (G-ROP) study.[26]	No original cost data.

[a] In this table are listed studies that might appear to meet the inclusion criteria, but which were excluded, and why they were excluded.

Abbreviations: ROP = Retinopathy of prematurity.

eFigure 2. Cost model

This figure presents our preliminary suggestions for a conceptual model for costs associated with retinopathy of prematurity (ROP), with some additional comments we believe are relevant. Abbreviations: GA=gestational age; ROP=retinopathy of prematurity; VEGF=vascular endothelial growth factor.



Preterm birth

It should be noted that these costs are part of a larger picture of understanding the economic impact of prematurity, which is essential knowledge in predicting the costs and consequences of introducing new interventions that affect gestational age at birth or morbidity and mortality among preterm infants. Thus, the model here is only one part and should be complemented by factors related to, e.g., bronchopulmonary dysplasia and other lung diseases, as well as other neuropsychiatric conditions. The listed items add to the previously published compartmental model of the global burden of ROP,[27] which also accounts for e.g., availability and coverage of screening programs.

ROP screening

Some evidence suggests that screening can be reduced even as infants are still identified with high sensitivity and specificity.[5] Reduced screening can be achieved through either changing the frequency of screening or limiting who is actually screened. Based on register findings in Sweden, infants born after gestational week 30 are no longer routinely screened for ROP.[28] Similarly, a study from the Netherlands found no severe ROP among infants born ≥30 gestational weeks.[29] This pattern differs from the situation in many other parts of the world. However, infants born at lower gestational age are more likely to develop ROP and severe ROP.[30]

Costs for screening in the studies included staff salaries/time, equipment and maintenance, supplies, and staff training. Although the identified studies do not detail the cost components and their associated costs, it can be expected that the reported costs of screening are to some extent underestimated. In time-and-motion studies conducted in our local hospital during a process of developing services (unpublished results), the times spent for preparatory work and documentation of screening results were 7–15 minutes and 7–12 minutes, respectively. This range included the time needed to identify infants who should be screened from those born at the facility, but excluded the time used for the actual screening. The figures can be compared to numbers provided in, e.g., Wongwai et al.,[8] citing 10 minutes used for screening by the ophthalmologist and 60 minutes for the nurse. According to Jackson et al.,[13] an average five examinations were necessary for determining if one infant would require treatment for ROP, which is in line with experiences in our hospital.

Regardless of the setting, there will also be transportation costs associated with screening. In this review, we excluded transportation costs, which are highly specific to each setting. For example, an Australian study reported flights for ROP screening to average 36–75 minutes depending on the healthcare center.[24] Transportation can thus include the time and expenses to the families coming into the hospital (or to visit a telemedicine center), or moving within the hospital if the infant remains hospitalized, but they can also reflect the cost of a specialized physician and assistant nurse or other staff category moving within or between hospitals to conduct screening. In addition to being an important cost component to consider in evaluations, the transportation aspect and hotel costs for staying in the hospital can directly affect screening. Our group has clinical experience of parents selecting not to attend planned screening visits after leaving the hospital, so that travel costs also become an issue related to increasing screening adherence and motivating attendance.

Lifetime (treatment and follow-up)

Treatment costs in individual studies included, e.g., staff salaries/time, equipment and maintenance, supplies, and staff training. Few studies reported detailed data on cost components, but Wongwai et al.,[8] for example, reported post-screening resource use of 60 minutes for an expert ophthalmologist, which we interpret to be the cost for treatment. Although case-mix and survival of extremely preterm infants were not detailed in the included studies, it can be expected that these factors will affect how many infants need treatment for ROP. For example, among infants born ≤30 gestational weeks in Sweden, 32% had any stage ROP and 6% were treated for ROP,[28] but among infants born at <24 gestational weeks, the corresponding figures were 92% and 43%.[31] Moreover, the available treatment options would affect costs, with studies suggesting, e.g., more retreatments with the more recent anti-vascular endothelial growth factor (VEGF) therapy.[28] Surgical intervention, or vitrectomy, could also apply to more severe cases,[32] in particular in countries with low access to screening. Although the costs of vitrectomy itself appear to be low,[33] there are likely other costs associated with these severe ROP cases, such as those linked to follow-up and complications.[34]

The argument regarding transportation costs is highly relevant for the treatment of ROP. The clinical reality of many countries is that patients

must be flown to the treatment site, or undergo multiple relocations by ambulance between local hospitals and specialized units providing the treatment.

At least in countries with high access to healthcare, it can be expected that children with ROP, and particularly those with severe forms requiring treatment, will have multiple follow-ups during childhood, adolescence, and possibly into adulthood. The low number of healthcare visits for follow-up indicated in the included articles differs considerably from the national guidelines in Sweden, recommending annual follow-up of ROP until adulthood and, after that, according to need. In a recent publication reporting on a model for predicting visual outcomes after ROP treatment,[35] follow-up every 6 months was even indicated for some patient groups.

Although costs for blindness can be expected to be similar regardless of the cause of blindness, data are available on approximate cost levels for different levels of visual impairment.[36] Thus, tapping into models for measuring costs of visual impairment can add to understanding of the long-term consequences of ROP.

References

1. Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. *Int J Technol Assess Health Care*. 2005;21(2):240-245.

2. Black L, Hulsey T, Lee K, Parks DC, Ebeling MD. Incremental Hospital Costs Associated With Comorbidities of Prematurity. *Manag Care*. 2015;24(12):54-60.

3. Brown GC, Brown MM, Sharma S, Tasman W, Brown HC. Cost-effectiveness of treatment for threshold retinopathy of prematurity. *Pediatrics*. 1999;104(4):e47.

4. Castillo-Riquelme MC, Lord J, Moseley MJ, Fielder AR, Haines L. Cost-effectiveness of digital photographic screening for retinopathy of prematurity in the United Kingdom. *Int J Technol Assess Health Care*. 2004;20(2):201-213.

5. Javitt J, Cas RD, Chiang YP. Cost-effectiveness of screening and cryotherapy for threshold retinopathy of prematurity. *Pediatrics*. 1993;91(5):859-866.

6. Lee SK, Norm, C., et al. Evidence for changing guidelines for routine screening for retinopathy of prematurity. *Arch Pediatr Adolesc Med*. 2001;155(3):387-395.

7. Rothschild MI, Russ R, Brennan KA, et al. The Economic Model of Retinopathy of Prematurity (EcROP) Screening and Treatment: Mexico and the United States. *Am J Ophthalmol*. 2016;168:110-121.

8. Wongwai P, Kingkaew P, Asawaphureekorn S, Kolatat T. A store-and-forward telemedicine for retinopathy of prematurity screen: Is it cost-effective in Thailand? *Asian Biomedicine*. 2015;9(5):665-673.

9. Dave HB, Gordillo L, Yang Z, Zhang MS, Hubbard GB 3rd, Olsen TW. The societal burden of blindness secondary to retinopathy of prematurity in Lima, Peru. *Am J Ophthalmol*. 2012;154(4):750-755.

10. Dunbar JA, Hsu V, Christensen M, Black B, Williams P, Beauchamp G. Cost-utility analysis of screening and laser treatment of retinopathy of prematurity. *Journal of AAPOS*. 2009;13(2):186-190.

11. Isaac M, Isaranuwatchai W, Tehrani N. Cost analysis of remote telemedicine screening for retinopathy of prematurity. *Can J Ophthalmol*. 2018;53(2):162-167.

12. Kamholz KL, Cole CH, Gray JE, Zupancic JA. Cost-effectiveness of early treatment for retinopathy of prematurity. *Pediatrics*. 2009;123(1):262-269.

13. Jackson KM, Scott KE, Graff Zivin J, et al. Cost-utility analysis of telemedicine and ophthalmoscopy for retinopathy of prematurity management. *Arch Ophthalmol*. 2008;126(4):493-499.

14. Kelkar J, Agashe S, Kelkar A, Kh, ekar R. Mobile unit for retinopathy of prematurity screening and management at urban Neonatal Intensive Care Units: Outcomes and impact assessment. *Oman J Ophthalmol*. 2017;10(1):13-16.

15. Kelkar J, Kelkar A, Sharma S, Dewani J. A mobile team for screening of retinopathy of prematurity in India: Cost - effectiveness, outcomes, and impact assessment. *Taiwan J Ophthalmol*. 2017;7(3):155-159.

16. Mohammadi S-F, Rahban A, Darabeigi S, et al. Cost-effectiveness analysis of tele-retinopathy of prematurity screening in Iran. *Int J Ophthalmol*. 2021;14(4):560-566. doi:10.18240/ijo.2021.04.13

17. Moitry M, Zarca K, Granier M, et al. Effectiveness and efficiency of tele-expertise for improving access to retinopathy screening among 351 neonates in a secondary care center: An observational, controlled before-after study. *PLoS One*. 2018;13(10):e0206375.

18. van den Akker-van Marle ME, van Sorge AJ, Schalij-Delfos NE. Cost and effects of risk factor guided screening strategies for retinopathy of prematurity for different treatment strategies. *Acta Ophthalmol*. 2015;93(8):706-712.

19. Yanovitch TL, Siatkowski RM, McCaffree M, Corff KE. Retinopathy of prematurity in infants with birth weight>or=1250 grams-incidence, severity, and screening guideline cost-analysis. *J aapos*. 2006;10(2):128-134.

20. Zin AA, Magluta C, Pinto MF, et al. Retinopathy of prematurity screening and treatment cost in Brazil. *Rev Panam Salud Publica*. 2014;36(1):37-43.

21. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71

22. Cross KW. Cost of preventing retrolental fibroplasia? *Lancet*. 1973;2(7835):954-956. doi:10.1016/s0140-6736(73)92610-x

23. Boncz I, Kovács LG, Ertl T, Ágoston I, Molics B, Bódis J. Health-economic analysis of diseases related to disturbed neonatal adaptation: A cost of illness study. *Lege Artis Medicinae*. 2013;23(3-4):193-197.

24. Yu T-Y, Donovan T, Armfield N, Gole GA. Retinopathy of prematurity: the high cost of screening regional and remote infants. *Clin Exp Ophthalmol*. 2018;46(6):645-651. doi:10.1111/ceo.13160

25. Scholz SM, Greiner W. An exclusive human milk diet for very low birth weight newborns-A cost-effectiveness and EVPI study for Germany. *PLoS One*. 2019;14(12):e0226496. doi:10.1371/journal.pone.0226496

26. Zupancic JAF, Ying G-S, de Alba Campomanes A, Tomlinson LA, Binenbaum G, G-ROP Study Group. Evaluation of the economic impact of modified screening criteria for retinopathy of prematurity from the Postnatal Growth and ROP (G-ROP) study. *J Perinatol*. 2020;40(7):1100-1108. doi:10.1038/s41372-020-0605-5

27. Blencowe H, Lawn JE, Vazquez T, Fielder A, Gilbert C. Preterm-associated visual impairment and estimates of retinopathy of prematurity at regional and global levels for 2010. *Pediatr Res*. 2013;74(Suppl 1):35-49. doi:10.1038/pr.2013.205

28. Holmström G, Hellström A, Gränse L, et al. New modifications of Swedish ROP guidelines based on 10-year data from the SWEDROP register. *Br J Ophthalmol*. 2020;104(7):943-949. doi:10.1136/bjophthalmol-2019-314874

29. Trzcionkowska K, Groenendaal F, Andriessen P, et al. Risk Factors for Retinopathy of Prematurity in the Netherlands: A Comparison of Two Cohorts. *Neonatology*. 2021;118(4):462-469. doi:10.1159/000517247

30. Isaza G, Arora S. Incidence and severity of retinopathy of prematurity in extremely premature infants. *Canadian Journal of Ophthalmology*. 2012;47(3):296-300. doi:10.1016/j.jcjo.2012.03.027

31. Lundgren P, Jacobson L, Hård A-L, et al. High rate and large intercentre variability in retreatment of retinopathy of prematurity in infants born <24 gestational weeks. *BMJ Open Ophthalmol*. 2021;6(1):e000695. doi:10.1136/bmjophth-2020-000695

32. Rajan RP, Kannan NB, Sen S, et al. Clinico-demographic profile and outcomes of 25-gauge vitrectomy in advanced stage 5 retinopathy of prematurity. *Graefe's Archive for Clinical and Experimental Ophthalmology*. 2021;259(7):1695-1701. doi:10.1007/s00417-020-05063-2

33. Nicod E, Jackson TL, Grimaccia F, et al. Direct cost of pars plana vitrectomy for the treatment of macular hole, epiretinal membrane and vitreomacular traction: a bottom-up approach. *European Journal of Health Economics*. 2016;17(8):991-999. doi:10.1007/s10198-015-0741-6

34. Zhao D-Y, Zhang Y-J, He Z-J, et al. Clinical analysis of apnea after operation for retinopathy of prematurity. *Journal of Shanghai Jiaotong University (Medical Science)*. 2010;30(2):132-134.

35. Huang C-Y, Kuo R-J, Li C-H, et al. Prediction of visual outcomes by an artificial neural network following intravitreal injection and laser therapy for retinopathy of prematurity. *British Journal of Ophthalmology*. 2020;104(9):1277-1282. doi:10.1136/bjophthalmol-2019-314860

36. Köberlein J, Beifus K, Schaffert C, Finger RP. The economic burden of visual impairment and blindness: a systematic review. *BMJ Open*. 2013;3(11):e003471. doi:10.1136/bmjopen-2013-003471