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Beyond Newborn Survival Paper 3

Preterm-associated visual impairment and estimates of retinopathy of prematurity at regional and global levels for 2010

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BACKGROUND: Retinopathy of prematurity (ROP) is a leading cause of potentially avoidable childhood blindness worldwide. We estimated ROP burden at the global and regional levels to inform screening and treatment programs, research, and data priorities.
METHODS: Systematic reviews and meta-analyses were undertaken to estimate the risk of ROP and subsequent visual impairment for surviving preterm babies by level of neonatal care, access to ROP screening, and treatment. A compartmental model was used to estimate ROP cases and numbers of visually impaired survivors.
RESULTS: In 2010, an estimated 184,700 (uncertainty range: 169,600–214,500) preterm babies developed any stage of ROP, 20,000 (15,500–27,200) of whom became blind or severely visually impaired from ROP, and a further 12,300 (8,300–18,400) developed mild/moderate visual impairment. Sixty-five percent of those visually impaired from ROP were born in middle-income regions; 6.2% (4.3–8.9%) of all ROP visually impaired infants were born at >32-wk gestation. Visual impairment from other conditions associated with preterm birth will affect larger numbers of survivors.
CONCLUSION: Improved care, including oxygen delivery and monitoring, for preterm babies in all facility settings would reduce the number of babies affected with ROP. Improved data tracking and coverage of locally adapted screening/treatment programs are urgently required.

In 2010, an estimated 19 million children were visually impaired (1), having substantial effects on the individual, family, and society (2). Children born preterm are at greater risk of visual impairment than their term-born peers. Even without manifest neurological complications, e.g., periventricular leukomalacia, intra- or periventricular hemorrhage, or optic atrophy, preterm birth removes the visual system from the nurturing intrauterine environment during a period of rapid maturation and hence increases the risk of reduced visual function (**Table 1** and **Figure 1**) (3).

Retinopathy of prematurity (ROP) is the most widely recognized cause of visual impairment after preterm birth and is defined as a vision-threatening disease associated with abnormal retinal vascular development at the boundary of vascularized and avascular peripheral retina (**Table 2**) (4). Babies who are most preterm or have associated neonatal morbidity, e.g., respiratory distress syndrome, infection, poor weight gain, and hyperglycemia, are at the greatest risk of ROP (5,6). Oxygen plays a critical role in this process, with both hypoxia and hyperoxia affecting levels of growth factors, such as vascular endothelial growth factor, essential for normal retinal vascular development. Hence, rates of ROP are dependent on the quality of care received, including oxygen delivery, with continuous monitoring to maintain safe oxygen saturation levels (7). Most cases of ROP are mild and resolve spontaneously without treatment. A small proportion progress to more severe ROP, which, if untreated, can result in retinal detachment or scarring and distortion of the retina, which are usually associated with irreversible vision loss (8).

ROP was first recognized as an important cause of blindness in high-income countries in the 1940s and 1950s when survival rates of very-low-birth-weight babies "<1,500 g" or approximately <32-wk gestation were improving in association with the widespread use of unrestricted oxygen supplementation. This has been termed the first ROP epidemic, which affected moderately preterm babies in high-income countries. Restricting the use of oxygen reduced blindness from ROP but increased mortality and the risk of cerebral palsy (9). The double-edged sword of supplemental oxygen has, therefore, been known for many years, and oxygen is now known to be associated with other morbidities in preterm infants, including bronchopulmonary dysplasia and periventricular leukomalacia (10).

Since the 1970s, extreme prematurity has been the dominant driving factor of ROP in high-income countries, with most cases being in the most preterm, i.e., gestational age (GA) < 28 wk babies. This is termed the second ROP epidemic. Increasing survival at lower GA has caused this second epidemic to persist, stimulating new developments in methods

Table 1. Long-term visual complications following preterm birth

Structural changes	ROP	ROP is a relatively common complication following very preterm birth. It is associated with long-term adverse visual outcomes and is discussed in detail in this article.
	Refractive errors	Preterm babies are born myopic (near-sighted) due to a shallow anterior chamber, increased corneal curvature, and a spherical lens. They are at increased risk of persistent myopia due to arrested development of the anterior segment, resulting in an eye with low axial length to power ratio, a shallow anterior chamber, and a thick lens, even in the absence of ROP (68,69).
	Strabismus	Babies born preterm are at increased risk of strabismus, with up to 13.5% of those <1,500 g affected (70,71), rising to more than 50% in severe ROP (72). Preterm birth is one of the commonest factors associated with strabismus at a population level (73).
Functional outcomes	Visual acuity	Up to 50% of babies with a birth weight of <1,500 g may suffer from visual dysfunction in late childhood and these range from the subtle to severe, even blindness (68).
	Contrast sensitivity	Reduced contrast sensitivity has been reported in preterm populations with no ROP or other known neurological abnormalities (74). This is important in reading ability and may account for some of the increased school learning impairment in preterm infants.
	Visual field defects	Visual field defects associated with retinal (including treatment for ROP) or visual pathway (including intraventricular hemorrhage) factors have been reported (75).
	Color vision	An increased prevalence of color deficits, especially of the blue–yellow type has been reported (76).
	Perception	Problems with recognition, orientation, depth perception, and perception of movement are common (77).

Babies born preterm are at increased risk of long-term visual problems due to the combination of the removal of the visual system from the nurturing intrauterine environment during a period of rapid maturation and an overall immaturity, leading to localized complications, e.g., ROP, and neurological complications, e.g., cerebral vision impairment due to intracranial complications. This risk is highest in the most preterm babies, but even moderate prematurity of 32–36 wk gestation is associated with an increased risk of visual morbidity (78).
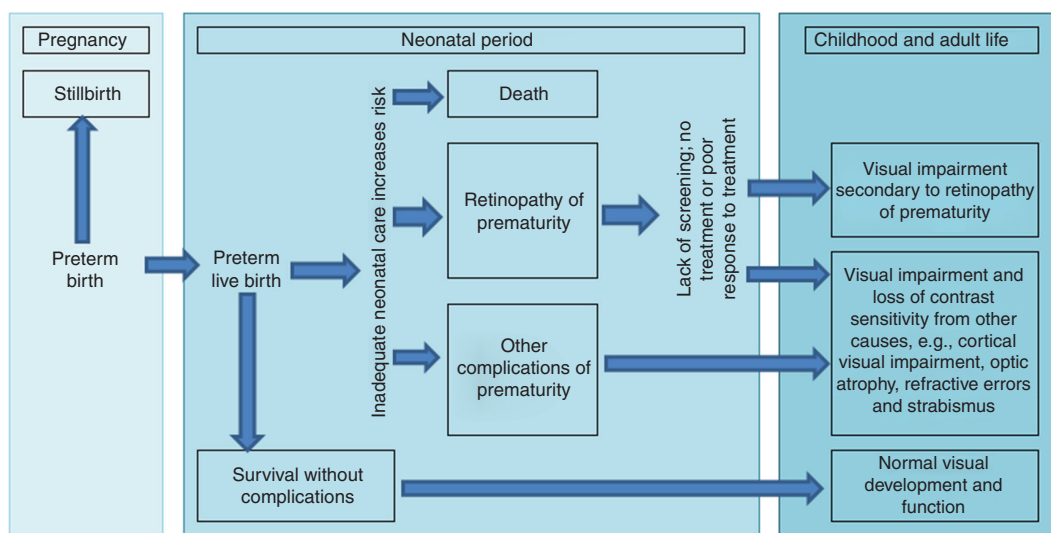
Figure 1. Disease schema for visual impairment after preterm birth.

of detecting potentially blinding ROP and new treatments (**Table 2**). However, even in high-income settings, there is wide variation in the reported rates of ROP between neonatal intensive care units (NICUs), even after adjusting for case mix, which may be explained by differences in the quality of care including varying approaches to oxygen saturation targets and monitoring (11,12). In the early 1990s, an emerging epidemic of blindness in children in low- and middle-income (LMI) countries (LMIC) due to ROP was recognized, initially detected by examining children in schools for the blind in Chile (13). Recent studies suggest that ROP is an increasingly important cause of avoidable blindness in China, Southeast and South Asia, Latin America, and parts of Eastern Europe (14–16).

Previous estimates derived using data from schools for the blind together with blindness prevalence estimates suggested that at least 50,000 children aged up to 15 y are blind from ROP globally, with the highest proportion and numbers being in Latin America (17). The recent Global Burden of Disease estimated that 257,000 (uncertainty range: 154,000–376,000) years lived with disability worldwide in 2010 were associated with visual impairment secondary to ROP, but the methods and inputs are yet to be published (18).

This article presents the first systematic regional and global estimates of the incidence of ROP and visual loss from ROP for 2010. We discuss other adverse visual outcomes associated with preterm birth, and finally, we consider the

Table 2. Classification, screening, and treatment of ROP

Classification	The importance of classification is to predict which babies are most at risk of progression to vision-threatening disease and to intervene in a timely manner. The current classification has several components:
	location or "zone" (1, 2, or 3): three concentric circles centered on the optic disc are used to describe the anteroposterior location of the ROP, which develops at the junction between vascularized and avascular retina. ROP in zone 1, which is the circle nearest the optic disc, carries the worst prognosis. Severity: "stage" classified from 1 (demarcation line only) to 5 (total retinal detachment).
	Presence of "plus disease" indicating dilatation and tortuosity of the retinal vessels (severer disease (79)), or "pre-plus" disease (intermediate severity).
	Extent: clock hours of ROP along the circumference of the junction between vascularized and avascular retina.
	"Aggressive, posterior ROP" denotes a more virulent, rapidly progressing form of ROP. In high-income countries, this is seen only in the extremely preterm. However, it has been reported in bigger babies in other settings, especially where babies receive unblended oxygen (80).
Screening	ROP is a highly predictable condition, with both onset and progression of ROP governed by postmenstrual and not postnatal age (81), with a slight hastening of ROP onset in the most immature infants (82) and compression of its clinical course reported in larger infants of >33 wk GA. Treatment rarely is required before 31-wk PMA (40). Mean age for treatment in high-income settings is 35.2 wk PMA (range: 30.6–42.1 wk) (4). In low-income settings with later case detection, treatment may be required up to 51 wk PMA (40). Screening those most at risk and treating if the ROP progresses to a sight-threatening level is standard care to prevent serious visual disability.
Treatment	The first treatment trial (CRYO-ROP) involved peripheral retinal cryotherapy to eyes with a constellation of clinical signs called "threshold ROP" (i.e., at least five continuous or eight cumulative clock hours of stage 3 ROP in zones 1 or 2, in the presence of "plus" disease—engorgement and tortuosity of the retinal and iris blood vessels), which untreated had a 50% risk of progression to retinal detachment. This trial was highly effective, halving the rate of progression (83). Since then, laser treatment has become the preferred option, giving better results and fewer complications. The current treatment guidelines are based on the findings of a further trial (ETROP) that compared treatment at early stages of disease (called type 1 ROP) with treatment at threshold disease, demonstrating that earlier treatment gives better outcomes in terms of both structure and function. Type 1 ROP is defined as zone 1: stage 3, or stage 1 or 2 with plus disease; or zone 2: stage 2 or 3 with plus disease (4).

PMA, postmenstrual age; ROP, retinopathy of prematurity.

programmatic importance of these findings and how to improve the data.

METHODS

The definitions used in this article are described in **Table 3**. **Table 2** provides details of the system used to classify ROP and the indications for and methods of treatment for ROP, which have changed over time. Many individuals blind from ROP will have other associated neurodevelopmental impairments. In addition to the total burden of ROP, we quantified the estimated number of children blind or severely visually impaired from ROP without neurodevelopmental coimpairment.

Data Searches and Inputs

A systematic literature review was undertaken of the main online literature databases, including Pubmed/Medline, Embase, CAB abstracts, Popline, Web of Science, Cumulative Index to Nursing and Allied Health Literature, Latin American and Caribbean Literature on the Health Science "LILACS," and WHO Regional library databases, applying the general search strategy described in the Methods article of this supplement (19). Search terms included multiple variants of terms covering the following areas "ROP" and "incidence/prevalence" or "screening" or "morbidity" or "visual impairment/blind/myopia". Medical subject heading terms were used when available (see **Supplementary Information** online for full details of search terms, dates, and inclusion criteria). Snowball searching of reference lists was used to identify further studies of interest. Further searches of statistical databases, including EURO-PERISTAT country-based neonatal network reports, were undertaken. Data were abstracted if the study fulfilled the inclusion criteria, regardless of the year of birth of the cohort. In view of the rapid changes and progress in neonatal intensive care in low-mortality settings during the past decades, especially for the preterm baby, only studies with birth cohorts with a median year of 2000 or later were included in the main analysis.

Standard meta-analysis techniques were used to obtain summary estimates of the parameters of interest, including neonatal case fatality risks, risk of ROP (by GA and access to care), and risk of visual impairment in those with ROP (by level of care and access to screening and treatment; **Figure 2**). Heterogeneity across studies was assessed using the I^2 and the χ^2 test. Where evidence of heterogeneity was present ($I^2 > 70\%$ or $P < 0.05$), a random-effects meta-analysis model was used.

Overview of Modeling Approach

A three-step compartmental model was constructed, using the estimated input parameters, to estimate visual impairment attributable to ROP among survivors of preterm birth (**Figure 2**). In step 1, we estimated the prevalence of preterm birth among live births; in step 2, the number of babies born preterm who received neonatal intensive care and survived (postneonatal survivors at risk of ROP) was estimated; and in step 3, we estimated that the number of these survivors who were estimated to have ROP and the number of those affected who are visually impaired, which is screening and treatment dependent. These steps were applied in sequence for the live births in each country with more than 10,000 births for the year 2010 (20). All results are presented at the regional level using the Global Burden of Disease superregional grouping (19).

We calculated a quantitative assessment of the uncertainty surrounding these estimates using a statistical approach based on the compartmental model, taking 1,000 random draws at each step, assuming a normal distribution with mean equal to the point estimate of the parameter and the SD equal to the estimated SE of the parameter. We summed the data for each draw at the worldwide or regional level depending on the data input pooling level and present the 2.5th and 97.5th percentiles of the resulting distributions as the uncertainty range.

RESULTS

The parameters and process of each step are detailed with a short summary of the results. Searches for the prevalence of preterm birth– and gestation-specific case fatality rate yielded 12,828 titles and abstracts, 792 of which were included. For the ROP-specific parameters, including incidence, risk of visual impairment, and neurodevelopmental comorbidity, 3,791 titles and abstracts were reviewed, and 80 studies were included (see **Supplementary Information** online). A summary of the parameter values used is shown in **Table 4** (see also **Supplementary Information** online). A summary of the regional results is given in **Table 5**.

Table 3. Definitions for visual impairment after preterm birth

	Grading	Brief definition/explanation	ICD-10 codes and categories[a]
Retinopathy of prematurity	See text for details	A vision-threatening disease associated with abnormal retinal vascular development in the incompletely vascularized retina of preterm babies.	H35.11–H35.17
Amblyopia		A unilateral or bilateral decrease of visual acuity caused by deprivation of pattern vision (e.g., cataract) or abnormal binocular interaction (e.g., strabismus), for which no cause can be detected and may in some cases be reversed by therapeutic measures (84).	
Strabismus		A misalignment of the eyes, which if uncorrected can lead to failure to develop binocular vision and amblyopia.	H50
Myopia		"Near-sighted." Eyes have too much optical power, or the eye is effectively too long, leading to blurred vision as the image is focused in front of the retina.	H52.1
Hypermetropia		"Far-sighted." Eyes do not have enough optical power, or the eye is effectively too short, leading to blurred vision as the image is focused behind the retina.	H52.0
Visual impairment	Mild	Visual acuity from <6/12 (<20/40) to ≥6/18 (≥20/60)	H54 codes
	Moderate	Visual acuity from <6/18 (<20/60) to ≥6/60 (≥20/200)	
	Severe	Visual acuity from <6/60 (<20/200) to ≥3/60 (≥20/400)	
	Blind	Visual acuity less than <3/60 (<20/400)	

[a]ICD = International Classification of Diseases 10th revision.
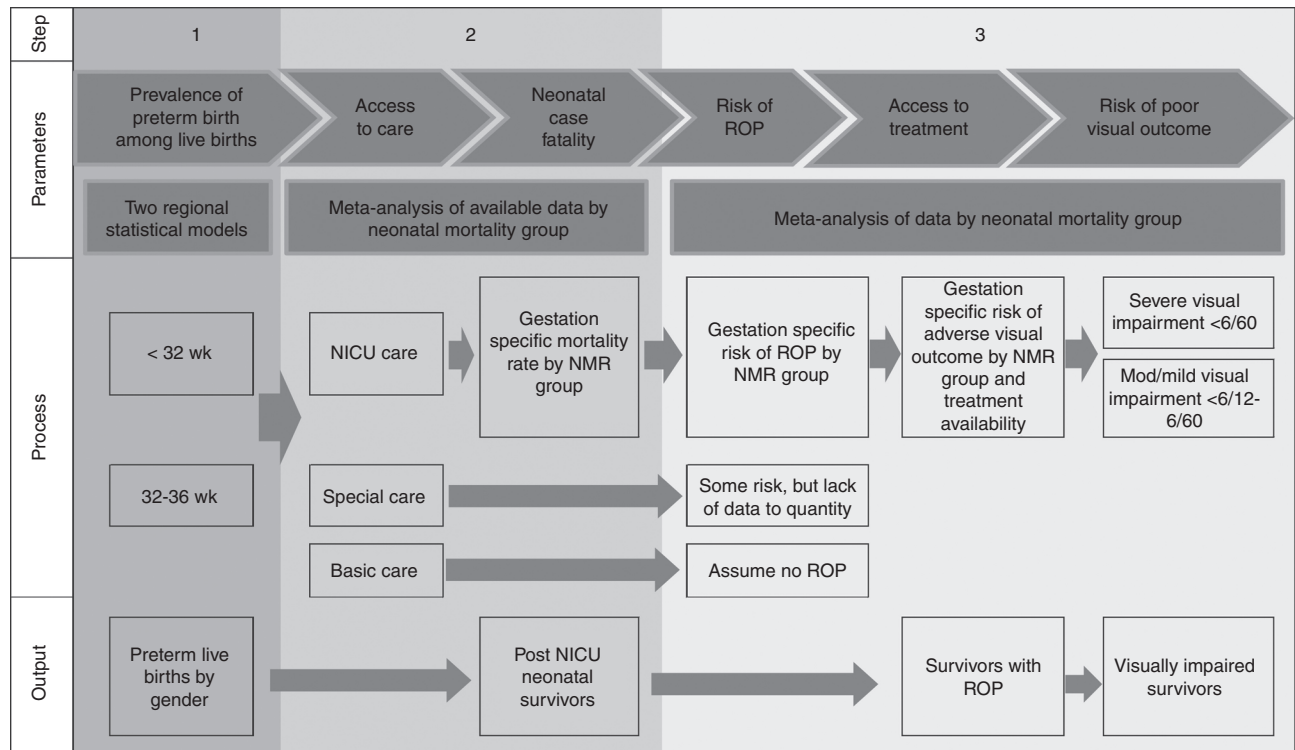
Figure 2. Compartmental model: parameters required and methods for estimation of the global burden of visual impairment due to retinopathy of prematurity.

Step 1: Preterm Live-Birth Prevalence

Preterm live-birth prevalence. National preterm birth rates for 2010 were estimated using two regional multilevel statistical models including data from national registries or statistical offices, Reproductive Health Surveys, unpublished data, and published articles identified through a systematic review. These included 738 reported data inputs from 99 countries; the majority (547/738) of the data available were from high-income countries. Full details of the searches, methodology input data, and results have been published elsewhere,

including the estimates for 2010 for 184 countries and time trends for 65 countries (21).

GA subdivisions. The distribution of preterm births by GA subgroup was based on a meta-analysis of 345 data points (131 million live births (21)). The pooled estimate from these studies shows that of all preterm births, 5.2% (95% confidence interval (CI): 5.1–5.3%) were at less than 28 wk GA, 10.4% (95% CI: 10.3–10.5%) were at 28–31 wk, and 84.3% (95% CI: 84.1–84.5%) were at 32–36 wk. Eighty-five percent of births at 32 wk or more were in the range of 34–36 wk.

Table 4. Countries (184) according to level of neonatal mortality, showing the variation in input data for the estimation of the global burden for visual impairment after retinopathy of prematurity around the year 2010

		Countries according to level of NMR in 2010		
		NMR < 5: level 1	NMR 5 to <15: level 2	NMR ≥ 15: levels 3/4/5
	Number of countries	46	62	76
	Number of live births	13,260,651	40,270,948	81,147,584
STEP 1	Preterm birth (<37 wk) prevalence data (per 100 live births)	30 countries, 415 data sets, N (preterm births) = 10,969,999, data range: 4.1–16.4%, median: 6.8%	28 countries, 187 data sets, N = 5,185,520, data range: 3.1–19.5%, median: 5.9%	41 countries, 136 data sets, N = 1,927,074, data range: 3.5–28.5%, median: 8.5%
STEP 2	Case fatality rate in first 28 d among preterm babies receiving neonatal intensive care unit care (per 100 live births by gestational age group)	21 countries, 36 data sets, N (preterm births) = 388,253. Pooled estimate: <28 wk = 28.3% (95% CI: 25.4–31.2%); 28–31 wk: 5.8% (95% CI: 5.1–6.5%). 32–36 wk, assume no ROP in babies ≥32 wk in 2010 in NMR 1 settings.		12 countries, 17 data sets, N = 5,379. Pooled estimate: <28 wk = 51.7% (95% CI: 43.3 – 69.0%); 28–31 wk: NMR 5 to <15: 15.3% (95% CI: 9.9–20.6%); NMR ≥15: 28.8%) (95% CI: 25.2–32.5%), 32–36 wk = 6.1% (95% CI: 1.4–10.9%)
STEP 3	Incidence of any ROP in survivors after preterm birth	17 countries, 13 data sets. Pooled estimate: all <32 wk = 21.8% (95% CI: 16.6–27.0%). 32–36 wk assume none		23 countries, 42 data sets. Pooled estimate: all <32 wk = 36.5% (95% CI: 31.8–41.1%). 32–36 wk = 7.7% (95% CI: 6.7–8.7%)[a]
	Risk of progression to level at which treatment would be given (prethreshold/type 1 disease)	SWEDROP study (62); <32 wk = 18.1% (95% CI: 14.5–21.8%). 32–36 wk assume none		4 countries, 4 data sets; <32 wk = 36.4% (95% CI: 14.8–58.0%). 2 countries, 2 data sets; 32–36 wk = 10.8% (95% CI: 2.7–18.8)
	Risk of progression to threshold level if not treated[b]	ETROP study (27); <32 wk = 66.4% of those reaching prethreshold and remaining untreate d, i.e., % of 12% all ROP. 32–36 wk assume none		12 countries, 17 data sets; <32 wk =28.2% (95% CI: 20.4–35.9). 4 countries, 5 data sets; 32–36 wk = 10.5% (95% CI: 7.2–13.9)
		All NMR levels		
	Visual impairment in those with severe ROP	Without treatment[c] Mild impairment: 3% (95% CI: 2–6%) Moderate impairment: 10% (95% CI: 7–15%) Severe impairment: 12% (95% CI: 8–17%) Blind: 47% (95% CI: 41–54%)	With treatment[d] Mild visual impairment: 14% (95% CI: 9–40%) Moderate impairment: 26% (95% CI: 22–32%) Severe impairment: 16% (95% CI: 17–25%) Blind: 9% (95% CI: 6–13%)	
	Coimpairment with neurodevelopmental impairment in babies with visual impairment due to ROP	5 countries, 10 data sets, N (visually impaired survivors) = 555. Pooled estimate = 54.9% (95% CI: 38.0–71.7%)		

[a]Single study by Zin *et al*. has screened all neonatal intensive care unit admissions from 32 to <37 wk GA (51). Thirteen studies were very heterogeneous, with large variations in those admitted in this group who were screened. Pooled estimate (13.4% (10.4–16.4%)) (see **Supplementary Information** online). [b]No difference in rates of progression to threshold disease between studies in NMR 2 and 3 countries, so result pooled across these was used. [c]In those reaching threshold and not treated (CRYO-ROP control arm) (8). [d]In those reaching type 1 level (prethreshold; ETROP treatment arm) (4).

ROP, retinopathy of prematurity.

Prevalence estimates. We previously estimated that globally 14.9 million babies (uncertainty range: 12.3–18.1 million) were born preterm in 2010 (**Table 5**). Approximately 0.8 million (0.7–0.9 million) were of GA <28 wk, 1.6 million (1.5–1.7 million) were 28–31 wk, and 12.6 million (12.3–14.0 million) were 32–36 wk (21).

Table 5. Estimated number of preterm births at risk of ROP, severity of ROP, and visually impaired survivors by region in 2010

	High income	Eastern Europe/Central Asia	Latin America and Caribbean	East and Southeast Asia and Pacific	North Africa and Middle East	South Asia	Sub-Saharan Africa	Total
Number of live births	11.7 million	5.4 million	9.9 million	29.0 million	9.7 million	37.1 million	32.1 million	135 million
% of worldwide total	9%	4%	7%	22%	7%	28%	24%	100%
Number of preterm births (uncertainty range)	1,064,000 *(1,047,000–1,124,000)*	413,000 *(333,000–517,000)*	851,000 *(680,000–1,222,000)*	2,808,000 *(2,057,000–3,560,000)*	911,000 *(665,000–1,214,000)*	4,954,000 *(3,724,000–6,256,000)*	3,935,000 *(3,038,000–5,064,000)*	14,900,000 *(12,300,000–18,200,000)*
% of worldwide total	7%	3%	6%	19%	6%	33%	26%	100%
Number of preterm babies receiving neonatal intensive care unit care at risk of ROP surviving the neonatal period[a] (uncertainty range)	149,900 *(148,900–156,400)*	79,100 *(77,200–94,500)*	133,300 *(127,600–160,000)*	292,500 *(268,000–326,000)*	82,800 *(78,000–95,000)*	79,600 *(68,300–89,400)*	31,200 *(30,100–40,000)*	848,300 *(838,400–924,700)*
Number of preterm babies developing any ROP (uncertainty range)	32,700 *(26,200–40,700)*	17,200 *(15,900–21,800)*	29,300 *(26,500–37,000)*	64,000 *(55,600–75,100)*	18,100 *(16,000–21,800)*	16,800 *(13,800–19,700)*	6,700 *(6,400–9,000)*	184,700 *(169,600–214,500)*
Number of babies progressing to severe (type 1) disease requiring treatment (uncertainty range)	6,300 *(4,700–8,300)*	5,200 *(2,600–9,000)*	9,300 *(4,400–15,900)*	19,900 *(9,500–31,700)*	5,700 *(2,600–9,400)*	5,300 *(2,300–8,500)*	2,100 *(1,000–3,900)*	53,800 *(28,800–85,000)*
Number of babies receiving treatment (uncertainty range)	5,500 *(4,000–7,400)*	1,900 *(1,100–3,200)*	3,700 *(1,700–6,200)*	7,800 *(3,900–12,300)*	2,200 *(1,000–3,600)*	1,100 *(500–1,700)*	500 *(300–1,100)*	22,700 *(13,800–33,700)*
Number of survivors with severe impairment or blindness (uncertainty range)	1,700 *(1,300–2,300)*	2,000 *(1,500–2,900)*	3,500 *(2,600–5,200)*	7,500 *(5,500–10,300)*	2,200 *(1,600–3,100)*	2,200 *(1,500–3,000)*	900 *(700–1,300)*	20,000 *(15,500–27,200)*
Number of survivors with mild/moderate visual impairment (uncertainty range)	2,300 *(1,700–3,200)*	1,100 *(800–1,800)*	2,000 *(1,200–3,400)*	4,400 *(2,600–6,700)*	1,200 *(800–2,000)*	900 *(500–1,300)*	400 *(300–700)*	12,300 *(8,300–18,400)*

[a]Admissions <32 wk GA in all countries and those 32–36 wk GA in countries with NMR ≥ 5.

ROP, retinopathy of prematurity.

Step 2: Calculation of the Number of Postneonatal Survivors at Risk of ROP

Coverage and quality of care. Data were not available to estimate every parameter individually for each country. To overcome this, we used neonatal mortality rate (NMR) as a proxy for the proportion of neonatal units with an ROP program and the quality of newborn care, classifying countries into three categories (**Table 4**) (19).

Defining the population at risk of ROP. For the purpose of these estimates, we assumed that only babies with access to NICU would be at risk of ROP, with high-intensity neonatal care defined as a minimum of the following: availability of ventilatory support, ability to deliver and monitor oxygen saturations, and high nurse-to-patient ratios). However, babies cared for in lower-level facilities, e.g., special care baby units in low-resource settings, may also be at risk, especially if receiving unmonitored oxygen; however, insufficient data are available to quantify this risk. To be consistent with previous work on coverage of care around the time of birth, we used coverage assumptions based on facility birth coverage as in the Lives Saved Tool (22). We undertook a literature- and Web-based search to identify LMICs with data on the number of neonatal intensive care cots to inform these assumptions, assuming a requirement of approximately one NICU cot per 1,000 live births (19).

In high-income countries, with good- to high-quality NICU care, ROP is currently only seen in babies with GA < 32 wk at birth (23). We therefore assumed that no baby of more than 32-wk gestation would be at risk in these settings. In LMI settings, substantial variation in the quality of NICU care exists, especially in terms of ventilatory support and oxygen-monitoring practices. Maturer preterm babies born at 32–36 wk are also at risk of ROP in these settings (24,25). Hence, the population at risk was defined as babies surviving NICU care with GA < 32 wk in all settings and babies surviving NICU care with GA 32–36 wk in countries with an NMR of >5 per 1,000 live births.

Gestation-specific case fatality rate by NMR group among those admitted to NICU care. For low-mortality countries (NMR < 5), GA-specific neonatal mortality data were abstracted from cohort studies identified from searches, predominantly from NICUs, which included the great majority of live-born babies less than 32-wk GA in these countries. Further searches of statistical databases, including EURO-PERISTAT and country-based neonatal networks were used to provide population-based data from countries with more advanced data-reporting systems. Case fatality risks were estimated as 28.3% (95% CI: 25.4–31.2%) for those <28 wk GA and 5.8% (95% CI: 51.0–65.0%) for 28–31 wk (**Table 4**).

For higher-mortality countries (NMR ≥ 5), 17 studies of mortality in babies <28 wk with access to NICU were identified. No strong evidence of a difference in mortality for babies <28 wk was found between NMR 5 to <15 and NMR ≥ 15 countries (*P* < 0.05), and the pooled estimate of 51.7% (95% CI: 43.3–60.0%) was used for all babies with access to NICU in countries with NMR ≥ 5. For babies 28–31 wk with

access to NICU care, the pooled estimated mortality was 15.3% (95% CI: 9.9–20.6%; 10 studies) in NMR 5 to <15 and 28.8% (95% CI: 25.2–32.5%; 5 studies) in NMR ≥ 15 countries. For babies 32–36 wk GA admitted to NICU, only one study reporting neonatal mortality was available. This study from Nepal (NMR ≥ 15) suggested a mortality of 6.1% (95% CI: 1.4–10.9%) in this group (26).

Estimates of the number of deaths and postneonatal survivors at risk of ROP. A total of 666,600 (28.5% (uncertainty range: 662,900–719,600)) of those born preterm at <32 wk are estimated to have received NICU care, 168,000 (153,900–193,500) of whom died during the first month of life. Moreover, 498,600 (487,200–547,700) are estimated to have survived the neonatal period, being at risk of ROP. In addition, an estimated 372,500 (329,400–397,100) babies born at 32 to <37 wk in LMICs received NICU care, 349,800 (329,400–397,100) of whom survived the first month of life. A total of 848,300 (838.400–924,700) surviving babies are estimated to have been at risk of ROP-associated visual impairment in 2010 (**Table 5**).

Step 3: Calculation of the Number of Babies With ROP and With Associated Visual Impairment

The precise risk was determined by GA and quality of care received using pooled risk from studies across the same NMR banding as a proxy of quality of neonatal intensive care.

Gestation-specific risk of any ROP by NMR group. The pooled estimate from studies reporting population-based incidence of ROP from 2000 to 2010 suggested that 21.8% (95% CI: 16.6–27.0%; 13 studies) of all survivors <32-wk GA in countries with NMR < 5, and 36.5% (95% CI: 31.8–41.4%; 42 studies) in countries with NMR ≥ 5 developed some degree of ROP (**Figures 3** and **4**).

Coverage of screening. The visual outcome after ROP is dependent on the severity of ROP and access to screening and treatment. Screening detects stages of ROP that have a high risk of progression to the blinding stages so that treatment can be given to reduce the risk of lifelong visual impairment. Limited data were available on coverage of screening in all settings. In countries with NMR < 5, it was assumed that coverage of screening would be near universal and that 95% of those <32 wk GA would be screened. In NMR 5 to <15 countries, coverage of screening was more variable, and it was assumed that 40% of those at risk in NMR 5 to <15 countries and 20% of those in countries with NMR ≥ 15 would be screened based on expert opinion.

Risk of progression to type 1 disease and requiring treatment in those with ROP. We assumed that 18.1% (95% CI: 14.5–21.8%) of those with any ROP would progress to type 1 prethreshold disease requiring treatment in NMR < 5 settings based on one large population-based study from Sweden (23). For settings with NMR ≥ 5, we used a pooled estimate from four studies suggesting that 36.4% (95% CI: 14.8–58.0%) of those <32 wk
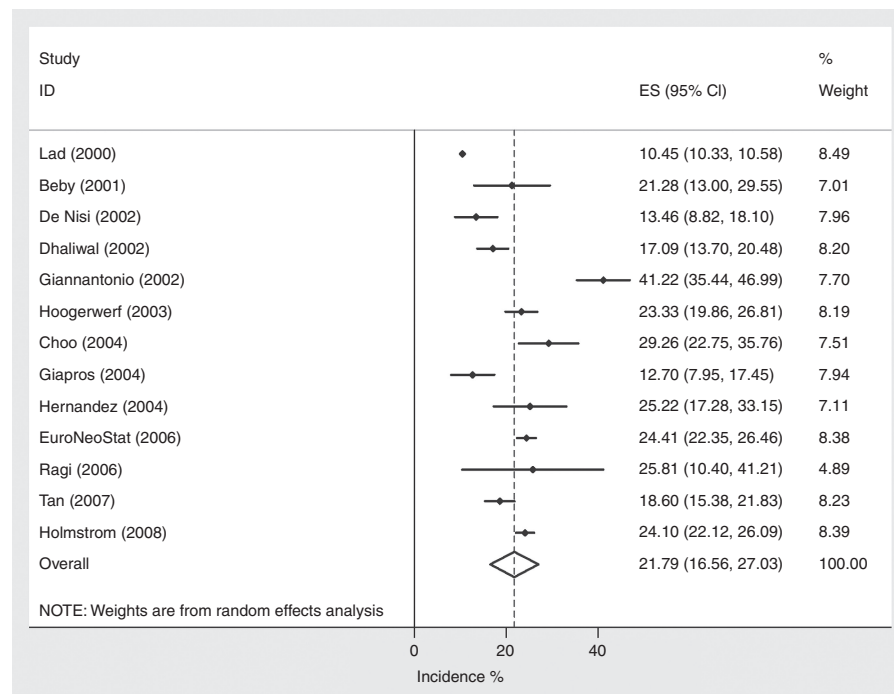
Figure 3. Meta-analysis of 13 studies in 2000–2010 reporting incidence of any retinopathy of prematurity in babies <32-wk GA in countries with neonatal mortality rate < 5. See **Supplementary Information** online for full details of the included studies.

with ROP and 10.8% (95% CI: 2.7–18.8%) of those ≥32 wk would progress to type 1 disease (**Table 4**).

Risk of visual impairment in those receiving treatment for type 1 disease. With treatment, it was assumed that 25% (95% CI: 23–28%) of children would be blind or have severe visual impairment in all settings, with an additional 40% (95% CI: 31–72%) having milder visual impairment based on the outcome data from the intervention arm in the ETROP trial (27).

Risk of developing threshold disease in those with untreated type 1 disease. Natural history information on visual outcome in those with ROP and no access to treatment was only available from studies reporting outcomes of those with "threshold" and not "type 1" disease. Therefore, the proportion of those with type 1 disease who progress to threshold level if untreated was required. Based on the ETROP trial, 66.4% of those with type 1 disease and no treatment in NMR < 5 countries would develop "threshold disease" (4). The risk is likely to be greater in countries with NMR ≥ 5 with more variable quality of neonatal care. A pooled estimate suggested that 28.2% (95% CI: 20.4–35.9%) of those <32 and 10.5% (95% CI: 7.2–13.9%) of those 32–36 wk GA with any ROP would develop threshold disease.
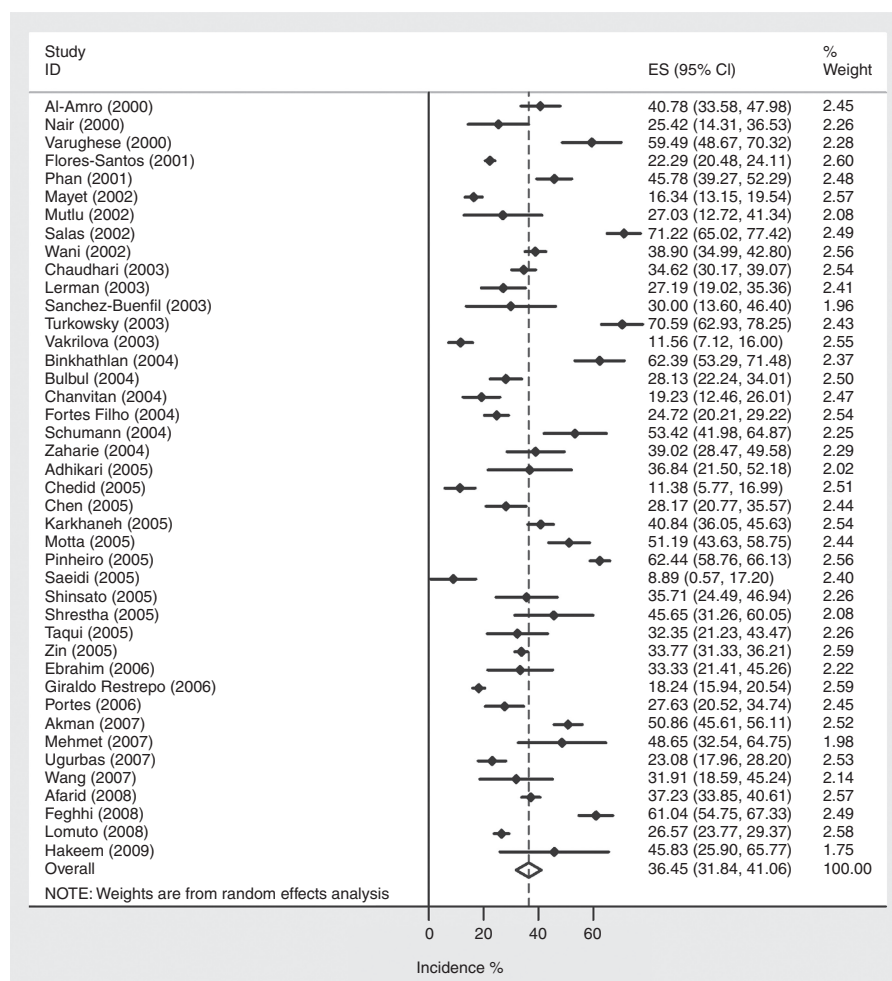
Risk of visual impairment in those with untreated threshold disease. Using data on rates of visual impairment following untreated threshold disease from the control arm of the CRYO-ROP trial, we assumed that 59% (95% CI: 49–71%) of those not receiving treatment would have a severe adverse outcome, with an additional 13% (95% CI: 9–21%) having milder

visual impairment (**Table 4**) (28). These are similar to other natural history data findings (6,29).

Associated neurodevelopmental comorbidity. Ten studies were identified quantifying the risk of associated neurodevelopmental impairment in ROP-affected visually impaired survivors of preterm birth. These suggested that 54.9% (95% CI: 38.0–71.7%) of visually impaired survivors with ROP had associated neurodevelopmental impairment. We have applied this rate to survivors in all regions; however, all 10 studies were undertaken in high-income settings where the majority of these babies would be extremely preterm and hence at high risk of neurodevelopmental impairment. In settings where survival rates among extremely preterm babies are low, and ROP occurs in relatively more mature babies, rates of associated neurodevelopmental impairment may be lower.

Estimates of the number of impaired survivors. We estimate that 184,700 (uncertainty range: 169,600–214,500) preterm babies worldwide developed some degree of ROP in 2010, 26,900 (23,700–32,400) of whom were born at 32–36 wk GA. 53,800 (28,800–85,000) of these babies developed potentially vision-impairing severe disease, requiring treatment, but only 22,700 (42%; (13,800–33,700)) of these babies received treatment.

An estimated 32,300 (24,800–44,500) preterm survivors in 2010 suffered from long-term visual impairment secondary to ROP: 20,000 (15,500–27,200) with severe visual impairment or blindness and a further 12,300 (8,300–18,400) with mild or moderate visual impairment. Worldwide, only 6.2% (2,000 (1,400–2,900)) of those with visual impairment were born at

Study ID		ES (95% CI)	% Weight
Al-Amro (2000)		40.78 (33.58, 47.98)	2.45
Nair (2000)		25.42 (14.31, 36.53)	2.26
Varughese (2000)		59.49 (48.67, 70.32)	2.28
Flores-Santos (2001)		22.29 (20.48, 24.11)	2.60
Phan (2001)		45.78 (39.27, 52.29)	2.48
Mayet (2002)		16.34 (13.15, 19.54)	2.57
Mutlu (2002)		27.03 (12.72, 41.34)	2.08
Salas (2002)		71.22 (65.02, 77.42)	2.49
Wani (2002)		38.90 (34.99, 42.80)	2.56
Chaudhari (2003)		34.62 (30.17, 39.07)	2.54
Lerman (2003)		27.19 (19.02, 35.36)	2.41
Sanchez-Buenfil (2003)		30.00 (13.60, 46.40)	1.96
Turkowsky (2003)		70.59 (62.93, 78.25)	2.43
Vakrilova (2003)		11.56 (7.12, 16.00)	2.55
Binkhathlan (2004)		62.39 (53.29, 71.48)	2.37
Bulbul (2004)		28.13 (22.24, 34.01)	2.50
Chanvitan (2004)		19.23 (12.46, 26.01)	2.47
Fortes Filho (2004)		24.72 (20.21, 29.22)	2.54
Schumann (2004)		53.42 (41.98, 64.87)	2.25
Zaharie (2004)		39.02 (28.47, 49.58)	2.29
Adhikari (2005)		36.84 (21.50, 52.18)	2.02
Chedid (2005)		11.38 (5.77, 16.99)	2.51
Chen (2005)		28.17 (20.77, 35.57)	2.44
Karkhaneh (2005)		40.84 (36.05, 45.63)	2.54
Motta (2005)		51.19 (43.63, 58.75)	2.44
Pinheiro (2005)		62.44 (58.76, 66.13)	2.56
Saeidi (2005)		8.89 (0.57, 17.20)	2.40
Shinsato (2005)		35.71 (24.49, 46.94)	2.26
Shrestha (2005)		45.65 (31.26, 60.05)	2.08
Taqui (2005)		32.35 (21.23, 43.47)	2.26
Zin (2005)		33.77 (31.33, 36.21)	2.59
Ebrahim (2006)		33.33 (21.41, 45.26)	2.22
Giraldo Restrepo (2006)		18.24 (15.94, 20.54)	2.59
Portes (2006)		27.63 (20.52, 34.74)	2.45
Akman (2007)		50.86 (45.61, 56.11)	2.52
Mehmet (2007)		48.65 (32.54, 64.75)	1.98
Ugurbas (2007)		23.08 (17.96, 28.20)	2.53
Wang (2007)		31.91 (18.59, 45.24)	2.14
Afarid (2008)		37.23 (33.85, 40.61)	2.57
Feghhi (2008)		61.04 (54.75, 67.33)	2.49
Lomuto (2008)		26.57 (23.77, 29.37)	2.58
Hakeem (2009)		45.83 (25.90, 65.77)	1.75
Overall		36.45 (31.84, 41.06)	100.00

NOTE: Weights are from random effects analysis

Incidence %

Figure 4. Meta-analysis of 42 studies in 2000–2010 reporting incidence of any retinopathy of prematurity in babies <32 wk admitted to neonatal intensive care units in countries with neonatal mortality rate ≥ 5. See **Supplementary Information** online for full details of the included studies.

32–36 wk GA. An estimated 55% of those with visual impairment will have other associated neurodevelopmental impairment (**Table 5**; **Figures 5** and **6**).

These global figures mask big regional differences: 36% of worldwide live births, 31% of preterm births, 39% of cases of neurodevelopmental impairment, 60% of ROP cases, and 65% of visually impaired survivors in 2010 were estimated to occur in the predominantly middle-income regions of Latin America, East Asia/Pacific, and North Africa/Middle East (**Figure 4**). Worldwide, in 2010, 16% of survivors born at <32-wk GA are estimated to have some degree of ROP, with 3% having associated visual impairment (**Figure 6**).

DISCUSSION

In 2010, 13.0 million (12.7–14.3 million) babies of the 15 million born preterm are estimated to have survived the neonatal period (30). At least 184,700 (169,600–214,500) have some degree of ROP, with 53,800 progressing to potentially vision-impairing disease. The risk is greatest for the most premature survivors in every setting, who also have the highest risk of associated neurodevelopmental impairment (30). In high-income countries, both ROP and associated adverse

neurodevelopmental outcomes are most common in babies of <26 wk gestation (23,31). However, in LMICs, these adverse outcomes are still common in relatively maturer preterm survivors at 28- to 31-wk gestation and above (25,31,32).

These estimates of visually impaired preterm survivors are likely to be conservative for a number of reasons. In the estimates of ROP, we only included babies who were cared for in NICUs, which may result in a substantial underestimation of the total burden because it does not include sick babies in special care baby units, with no access to NICU, but who may have received unblended, unmonitored supplemental oxygen. In addition, these estimates do not include causes of visual impairment secondary to preterm birth that are not associated with ROP, including cerebral vision impairment.

Following the identification of unmonitored supplemental oxygen as a causal factor in the development of ROP in the 1950s, it was anticipated that improvements in neonatal care and oxygen management would prevent visual loss from ROP. However, although this reduced the disease in those moderately preterm in high-income countries, blindness from ROP persisted, albeit at a low rate, especially among the increasing number of extremely preterm (<28 wk) survivors (33).
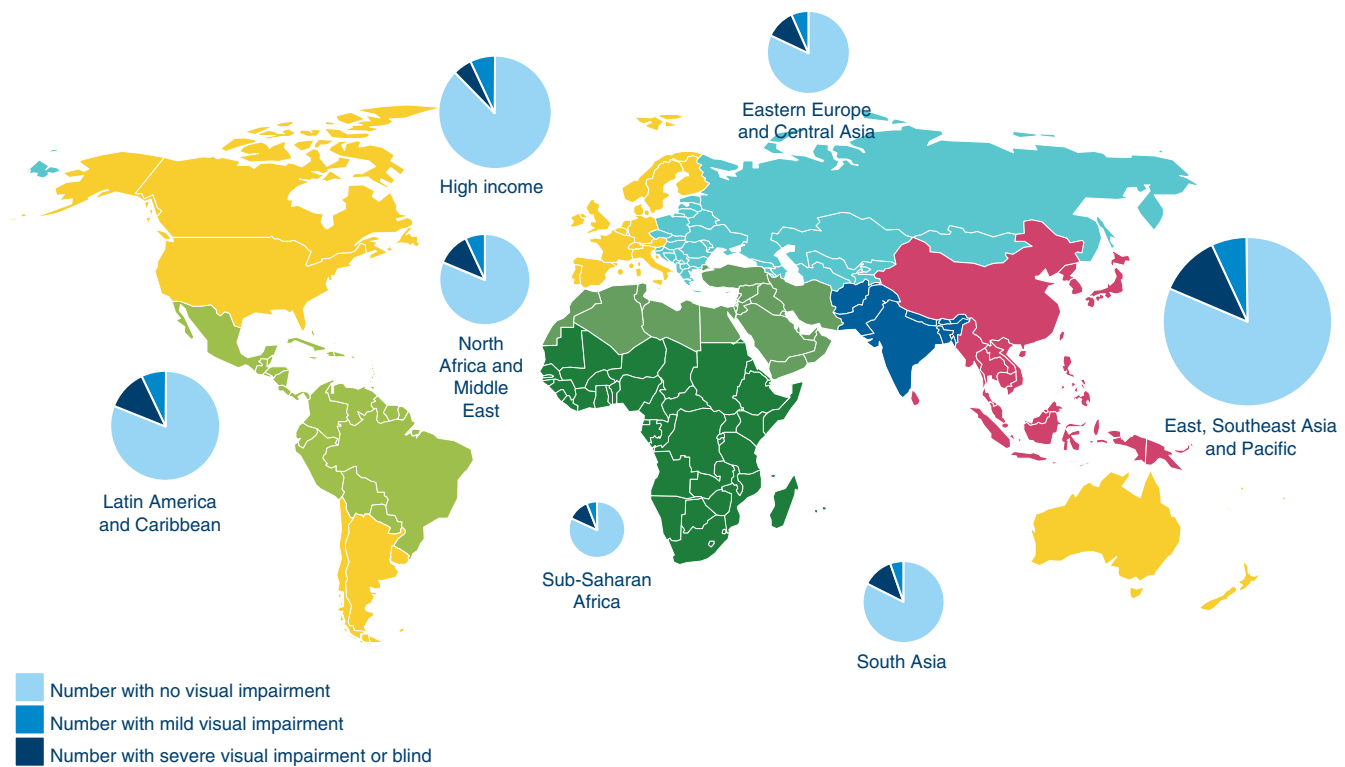
Figure 5. Regional burden of visual impairment from retinopathy of prematurity among preterm babies born in 2010 and surviving the neonatal period.

Widespread introduction and refinement of screening protocols to include those most at risk of visually impairing disease and timely treatment has further reduced the burden in high-income countries, despite the increasing number of extremely preterm survivors. However, even in urban settings in LMICs with increasing provision of NICUs, awareness of ROP as a possible vision-impairing disease is frequently lacking among those providing neonatal care (34). State-of-the-art ophthalmological and modern NICU equipments are increasingly available, especially in private facilities, but standards of neonatal care often remain low, and systematic programs to detect and treat babies with severe ROP are not yet in place in all NICUs. Consequently, many infants are becoming blind, having never been screened or examined by an ophthalmologist.
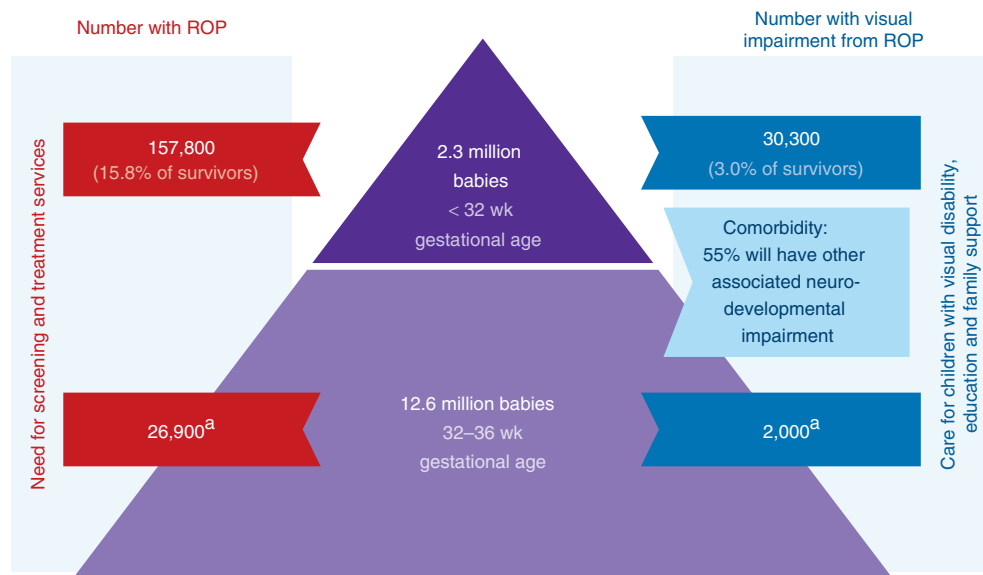
[a]<1% of survivors after preterm birth at 32–36 wk GA.

Figure 6. Summary of retinopathy of prematurity and associated visual impairment outcomes for survivors of 15 million preterm births worldwide in 2010.

Table 6. Research in context regarding the burden of ROP

Data findings	Retinopathy of prematurity presents an important burden worldwide, with an estimated 185,000 babies affected in 2010 and 43,000 visually impaired survivors. The proportion of affected babies is low in the lowest-income regions, notably sub-Saharan Africa, because of the excess mortality for preterm babies. The proportion is higher in middle-income regions because of increasing access to neonatal intensive care, with challenges in the quality of care. In high-income, low-mortality settings, the proportion of visually impaired babies is lower, probably related to improved quality of care (prevention) and systematic approaches to ophthalmological management and follow-up.
Data gaps and improvements	Major gaps were found in the quantity and the quality of data including geographic gaps, especially for low- and middle-income countries. Data on visual impairment need immediate prioritization for settings where neonatal intensive care is being scaled up. Challenges of data comparability over time with changes in classifications used to report ROP; reporting using birth weight versus gestational age criteria or eyes versus children; and in some cases, unclear population denominators.
	Actions/possible solutions: Ministries of Health to document which neonatal intensive care units have high-quality ROP programs; ophthalmologists to report findings of screening, treatment, and follow-up using standard formats and definitions; inclusion of ROP in routinely collected statistics, e.g., neonatal surveillance standard data set for all at-risk babies.
Data for action	Key program priorities include the following: prevention of ROP; strategically addressing methods for the prevention of preterm birth and scaling up the use of antenatal corticosteroids in all settings, coupled with improving the quality of neonatal care, including infection prevention, and crucially ensuring optimal use of oxygen and making oxygen monitoring a standard of care in all facilities caring for preterm babies. Prevention of visual impairment: screening for all babies at risk of developing visual impairment from severe ROP, using locally validated screening criteria. Access to timely treatment, if required, to prevent adverse visual outcomes. Identification and care of survivors at risk of disability: routine follow-up of all with severe ROP. Correction of severe refractive errors or strabismus to prevent amblyopia and ensure optimal visual development. Early identification of blindness and severe visual impairment along with facilitation of educational and family support, including for those with associated neurodevelopmental disability.

ROP, retinopathy of prematurity.

Many of these babies are relatively more mature (GA > 30 wk), as in the first epidemic in high-income countries, and much severe ROP should be both preventable and treatable in these settings (25,35). Some countries with improving human development index ratings may have reversed this trend during the past decade, e.g., Poland (36).

Data Limitations
We were not able to quantify the risk of ROP in preterm babies outside of NICU settings, and this may include large numbers of cases. In many special care baby units in LMICs, oxygen is available and is given by different devices, some of which will expose the babies to unblended high-flow oxygen, placing them at even higher risk of ROP. Historically, blindness due to retrolental fibroplasia, as end-stage ROP was described at that time, principally affected infants with birth weights in the range 1,000–2,000 g who had received high levels of unmonitored supplemental oxygen.

Many included studies were reports by ophthalmologists of babies they had examined, with few details on the total preterm population from which the cases arose. Data limitations, especially from LMI settings, required a simplistic model, grouping babies into two GA groups, <32 wk and 32–36 wk. However, this led to the exclusion of useful resources of incidence data from high-income countries, e.g., neonatal network reports, where screening policies for babies born at 30 and 31 wk gestation are variable. An increasing number of studies from LMIC recommend wider screening criteria than those used in high-income countries, but these criteria are often not evidence based. It is likely that severe ROP in maturer, less-sick babies is still being missed because they are not included in screening programs.

The recommendation to lower the treatment level for ROP to type 1 prethreshold from threshold was changed after the findings of the Early Treatment for Retinopathy of Prematurity (ETROP) study in 2003 (37). In view of this recent recommendation, few data were available on the risk of long-term visual outcomes in those treated for type 1 ROP. We therefore used the ETROP study to estimate the risk of long-term visual outcomes. This may overestimate the risk because the trial included a high proportion of babies with the severest type of ROP, "zone 1 disease," who would be expected to have the poorest visual outcomes. Some very small recent studies have suggested that the risk in general NICU populations may be lower (38,39), and even with very severe aggressive posterior ROP, that complete regression of the disease is possible in the majority of eyes with aggressive laser treatment (142/169) (40).

We have not adjusted for ethnicity in our model. Several studies have reported a lower risk of severe ROP in those from black African descent compared with the risk in other ethnic groups and a higher risk in Hispanics and those of south Asian descent (6,41–44).

Programmatic Implications and Future Developments
Prevention of ROP
Interventions before preterm birth. Much can be done to prevent ROP, starting before preterm birth (**Table 6**). There is evidence that antenatal corticosteroids given within 48 h of preterm delivery promote lung maturation and reduce the risk of respiratory distress syndrome. This is likely to reduce these babies' requirement for oxygen and hence reduce the risk of ROP due to the use of poorly controlled oxygen therapy (45). However, this simple inexpensive intervention has low coverage in LMI settings.

Improving quality of neonatal care. Care provided immediately after birth, including prevention of hypothermia, consideration of delayed cord clamping, minimizing lung damage by avoiding initial 100% oxygen, and early use of nasal continuous positive airway pressure can have a major impact

on subsequent morbidity, including ongoing need for oxygen support (46). Optimal oxygen levels are required for preterm babies to maximize survival and minimize ROP, pulmonary morbidity, and disability (10). However, these optimal levels have not yet been determined. Two recent oxygen regulation trials have supported the benefit of targeting tight control of oxygen saturations in the range of 91–95%, with an increased risk of death with an 85–89% target (47,48); however, a third trial found no difference in death or disability at 18 mo between these two groups (49). A collaborative study group is currently conducting a meta-analysis of the full risks and benefits of these different oxygen targets (50). Until further evidence is available, the general conclusion is not to target levels less than 90% (50), but because higher oxygen saturations in the range 91–95% will increase the risks of ROP compared with lower targets of 85–89%, it is important to ensure that oxygen saturations do not exceed the upper limit of 95%, especially in very preterm babies. Oxygen monitoring is routine in high-income countries, but variable in other settings, especially in units that are overcrowded and that lack both equipment and trained nursing staff in adequate numbers (51,52). A preliminary study from Peru suggests that severe ROP has declined since workshops were held for neonatal staff on how to improve the delivery and monitoring of oxygen (53). Infection increases the risk of ROP and should be minimized by strict adherence to infection control measures. Improving the quality of all aspects of neonatal care is required, with adequately equipped and staffed NICUs required to achieve this.

Prevention of Visual Impairment in Those Developing ROP
Screening for ROP. Implementation of locally adapted screening and treatment guidelines, alongside improvements in the quality of neonatal care, including optimal use and monitoring of oxygen, has minimized ROP-related blindness in high-income countries (54). However, even in well-resourced settings with clear guidelines, actual practice and rates of ROP may vary substantially (55). Screening guidelines need to include a clear definition of the population at risk of visually impairing ROP, which will be location specific, but the reduced evidence base available from a specific location should be used only to broaden and not to narrow inclusion criteria. Some middle-income countries have developed local screening criteria guidelines (56).

The screening examination is associated with pain and stress for the babies, and unnecessary examinations have substantial workload implications (57). Recent work in high-income countries has therefore focused on refining the screening protocols, e.g., using scores to detect those most at risk, to minimize the number of examinations of babies at very low risk of visually impairing ROP (58).

Screening requires significant infrastructure investment, coordination, planning, skilled ophthalmologists, and teamwork (59). Standard screening examination by indirect ophthalmoscopy, a highly specialized procedure, is challenging in all settings, either due to a lack of specialist expertise or

because it is not seen as an efficient use of ophthalmologists' time because 39–55 examinations are required to detect a single case needing treatment (60).

Digital imaging of the neonatal retina is used increasingly in ROP screening. Studies have shown that digital imaging has high accuracy and reliability and that it may be superior to indirect ophthalmoscopy in some situations and is less painful to the infant (61,62). Retinal findings can be viewed by the neonatal team and infant's family, promoting greater understanding of the condition. Digital imaging has also provided the platform for telemedicine, which permits retinal images to be captured by either a trained technician, physician, or neonatal nurse and transmitted to an expert who may be a few miles or another country away, with successful telemedicine networks in the United States, Germany, India, and New Zealand (54). Experience to date has shown that severe disease is not missed by digital imaging and is identified 1–2 wk earlier than by indirect ophthalmoscopy (54). A challenge in the use of telemedicine is that severe ROP needs to be treated within 48 h of detection, and many babies still need to be examined after discharge from the NICU (63). Mothers need to know at the time of examination/image capture whether their babies need treatment, whether they should come back for another examination, or whether they can be discharged.

The diagnosis of ROP is entirely visual, qualitative, and prone to error. Another anticipated development arising from digital imaging is the measurement and semiautomated analysis of the vascular changes associated with ROP, i.e., plus disease. Several software systems have been developed, including Retinal Image multiScale Analysis, Computer-aided image analysis of the retina, and the ROP tool (54). To date, unfortunately, all methods are slow, but they can detect plus disease and are better at measuring tortuosity than vessel width. However, it has been shown that vessel tortuosity close to the optic disc correlates well with ROP in the periphery (64).

Management of potentially vision-impairing ROP. Laser photocoagulation, sometimes augmented by cryotherapy, is the current standard of care for severe ROP (**Table 3**). The treatment destroys the hypoxic peripheral avascular retinal tissue, which produces the vascular growth factors that stimulate ROP. Despite treatment, visual acuity remains suboptimal in up to 60% of children (27). Newer treatments, e.g., anti–vascular endothelial growth factor agents bevacizumab or ranibizumab, for the severest disease may be promising, but there are concerns over their long-term systemic and ocular safety, and so, currently cannot be recommended for first-line treatment (65). Centralized treatment services, if multiple small NICUs are in close proximity, may increase access to laser treatment and ophthalmologists skilled in the treatment of ROP, so improving the quality of treatment (60).

Identification and Care of Visually Impaired Survivors
In view of the risk of visual impairment from a range of conditions, including ROP, there has been debate in some countries

whether preterm babies should be routinely screened for visual impairment during childhood, even if they were not affected by ROP (7). Routine screening is not currently carried out in many settings, and increasing awareness among parents and teachers of the increased risk—and encouraging vision testing if they have concerns—is important in all settings. Prompt treatment of strabismus and high refractive errors is required to prevent amblyopia and to promote normal development. Spectacles present a simple and affordable method of treating refractive errors associated with preterm birth but require fitting and long-term follow-up so that the prescription can be changed as the child grows; moreover, repairing or replacing broken or lost spectacles also is essential (66). As blindness is associated with poor educational achievement, social isolation, and poverty, particularly in LMICs (67), children with profound vision loss will also require assessment in low vision services, access to assistive devices, and appropriate placement and support in school to improve their independence and quality of life, and ensure a productive adulthood (66).

Conclusion

More than 30,000 preterm babies worldwide in 2010 are estimated to be visually impaired due to ROP. Much of this burden is preventable with improved quality of neonatal care, notably oxygen monitoring, and with screening and treatment of vision-threatening ROP. Urgent action is required to improve awareness of ROP among all involved in the care of preterm babies, coupled with commitments to improve neonatal care, and to develop and implement national guidelines for the prevention, detection, and treatment of ROP.

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