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BEST PRACTICE GUIDELINE ARTICLE

Retinopathy of prematurity: A global perspective of the epidemics, population of babies at risk and implications for control

Clare Gilbert *

International Centre for Eye Health, Clinical Research Unit, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT UK

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Retinopathy of prematurity;
Middle income countries;
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Abstract

Globally at least 50,000 children are blind from retinopathy of prematurity (ROP) which is now a significant cause of blindness in many middle income countries in Latin American and Eastern Europe. Retinopathy of prematurity is also being reported from the emerging economies of India and China. The characteristics of babies developing severe disease varies, with babies in middle and low income countries having a much wider range of birth weights and gestational ages than is currently the case in industrialized countries. Rates of disease requiring treatment also tend to be higher in middle and low income countries suggesting that babies are being exposed to risk factors which are, to a large extent, being controlled in industrialised countries. The reasons for this "third epidemic" of ROP are discussed as well as strategies for control, including the need for locally relevant, evidence based criteria which ensure that all babies at risk are examined.

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* Tel.: +44 207 958 8332; fax: +44 207 958 8325.
E-mail address: clare.gilbert@lshtm.ac.uk.

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1. Introduction

1.1. Epidemics of retinopathy of prematurity in industrialized countries and the population of babies at risk

In industrialized countries, two epidemics of retinopathy of prematurity (ROP) have been described. The "first epidemic" (of blindness) occurred in the 1940s and 1950s and principally affected premature babies in the USA and, to a lesser extent, Western Europe. At that time unmonitored supplemental oxygen was the principal risk factor. In the UK the mean birth weight (BW) of affected babies was 1370 g (range 936–1843 g) and 1354 g (range 770–3421 g) [1] in the USA.

A "second epidemic" (of acute ROP) in industrialized countries started in the 1970s, as a consequence of higher survival rates in extremely premature babies—larger, more mature babies were and are surviving usually without developing severe, acute disease. Recent data from Canada, the USA and UK show that the mean BWs of babies needing treatment for threshold disease are 759 g (range 440–1785 g), 763 g (range 415–1255 g) and 737 g (range 450–1260 g) respectively. The gestational ages of the same babies being 25.6 (range 22–32); 25.4 (range 23–29) and 25.3 weeks (range 23–32) respectively [2].

Programs for detecting ROP are well established in most countries in North America, Western Europe, and in the industrialized counties of the Pacific Basin, providing information on the population of babies needing treatment, and how this population is changing over time. This information has, and continues to be used to refine screening criteria, to ensure that programs are as cost effective and efficient as possible [3,4]. However, these are not "screening" programs in the true sense of the word, but are "case detection" initiatives. Screening would entail the use of a simple, safe, non-invasive and valid test which identified babies needing a "gold standard" diagnosis.

1.2. Blindness due to ROP—a global perspective

In 1993 the World Health Organization developed a new system for classifying the causes of blindness in children, which has two components: a descriptive classification (i.e. the site in the visual pathways most affected), and an aetiological classification (i.e. the time of onset of the condition leading to blindness). Over the last 10–15 years this has been used to classify the causes of blindness in almost 9000 children in 38 countries, and data are available from a further 6000 children in 5 other countries. Much of these data come from examining children in special education, as they are a readily accessible "captive audience", but these data are potentially biased. However, in several countries data have been collected concurrently from population based sources as well as schools, and the findings are largely comparable.

The available data suggest that blindness due ROP varies enormously from country to country [2], and that over 50,000 children are blind from ROP worldwide (Figs. 1 and 2). It is likely that many more will be unilaterally blind, or visually impaired. Data in the figures are presented using World Bank regions because levels of socioeconomic development are such powerful determinants of the prevalence and causes of blindness in children. In Fig. 3 the proportion of blindness due to ROP has been plotted against infant mortality rates (IMRs) for 1999. The plot suggests that there are three distinct groups of countries: those with IMRs above 60/1000 live births do not have a problem of blindness due to ROP. Most of these countries are in sub Saharan Africa, where neonatal intensive care services are either not in place, or premature babies do survive long enough to develop severe ROP [5]. Countries with very low IMRs (i.e. <9/1000) also have low rates of ROP blindness. In these highly industrialized countries low rates of ROP blindness can be attributed to several factors: rates of prematurity are relatively low, neonatal intensive care is good and babies receiving supplemental oxygen are monitored and cared for by well trained neonatal nurses,

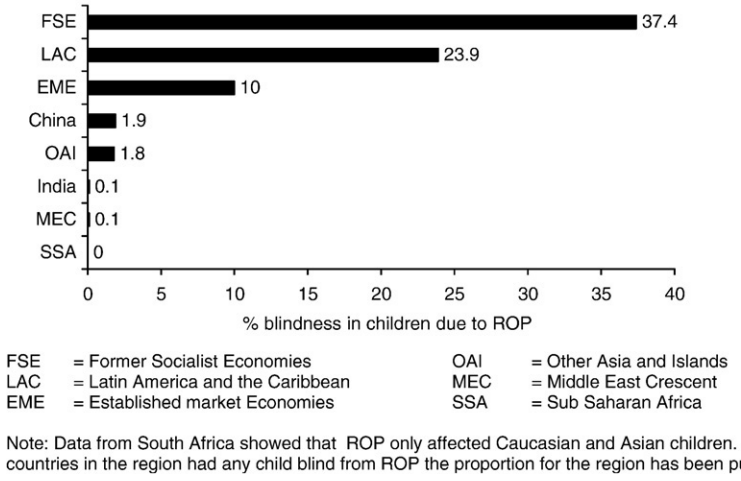

Figure 1 Retinopathy of prematurity as a cause of blindness (%), by World Bank region, using data on >15,000 blind children examined in 43 countries.

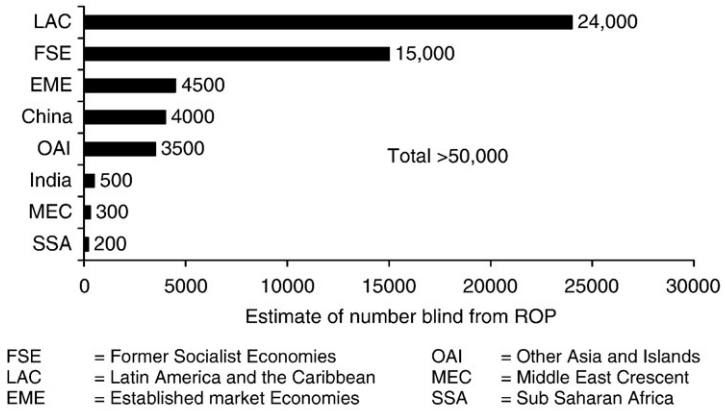

Figure 2 Estimates of the number of children who are blind from retinopathy of prematurity by World Bank region.

and babies needing treatment are being detected and managed well. The last group of countries are those with IMRs in the range 9–60/1000 live births, and it is these countries where ROP is emerging as an important cause of blindness. This has been referred to as the "third epidemic" of ROP [6]. Most of these countries can be classified as middle income, and are mainly in Latin America and the Former Socialist Economies.

1.3. The "third epidemic" of blindness due to ROP

Using IMRs as a proxy, it is possible to predict the risk of blindness due to ROP in countries where data are not currently available (Fig. 4). The map shows that countries in Eastern Europe and Latin America are at greatest risk of ROP blindness, and includes India and China.

As mentioned in the opening paragraph, the first epidemic of ROP principally affected more mature babies than is now the case in industrialized countries. Studies of the BW and GAs of babies developing severe ROP (defined as threshold disease or more advanced) between 2000 and 2004 in countries with low, middle and high levels of development, shows that babies affected in low and middle income countries have a far wider range of BWs and gestational ages than is currently the case in the UK, Canada and the USA (Fig. 5a and b) [2,7–10].

This "third epidemic" of ROP blindness has several explanations. Firstly, rates of preterm birth tend to be higher in middle income countries than in high income countries, particularly in Latin America where teenage pregnancies are common. Second, in middle income countries the proportion of women who are delivered in health care facilities is high and premature babies are, therefore, likely to be admitted to neonatal intensive care. Third, rates of severe ROP are higher in premature babies in low and middle income countries [7,11,12] even when wider screening criteria have been used, suggesting that babies are being exposed to risk factors which are now largely controlled in industrialized countries. For example, in Latin America neonatal care is provided by a range of service providers, with some units having excellent facilities and high staff: patient ratios. However, many neonatal units in low and middle income countries do not have enough equipment for continuous monitoring of all babies on supplemental oxygen, and nursing shortages mean that one nurse can be responsible for several high dependency babies (S. Varughese and A. Zin, personal communication). Variations in levels of neonatal care means that some babies are cared for in first epidemic environments whereas others are in a second epidemic environments—this is why the third epidemic of ROP affects babies with characteristics of both (Fig. 6). The last, important factor is that screening and treatment programs for ROP are not uniformly in place. The reasons for this vary: in some countries, such as South Africa, there is a real shortage of ophthalmologists in the government sector (C. Cook, personal communication), whereas in other countries there is a shortage of ophthalmologists with the appropriate skills. In many countries there are opportunity costs if ophthalmologists screen in their own time, as government employees need to work in the private sector to supplement their income. Fear of litigation is also emerging as a demotivating factor.

1.4. Control of blindness due to retinopathy of prematurity

To control blindness due to ROP in middle income countries there is an urgent need to increase awareness among the public, health professionals and parents [13]. Given the lifetime of blindness resulting from ROP and the economic and social implications, a powerful case can be made for providing the equipment and staffing levels required to monitor all babies receiving supplemental oxygen. Programs for detecting babies with treatable disease need to be expanded so that all units caring for babies at risk are included. Research is urgently needed to explore and evaluate alternative screening approaches for detecting babies with ROP which warrants evaluation by an ophthalmologist [14] as the current dependence on ophthalmologists is unlikely to meet the need in many parts of the world. Retinopathy of prematurity is being increasingly reported from India and China, home to more than 1/6th of

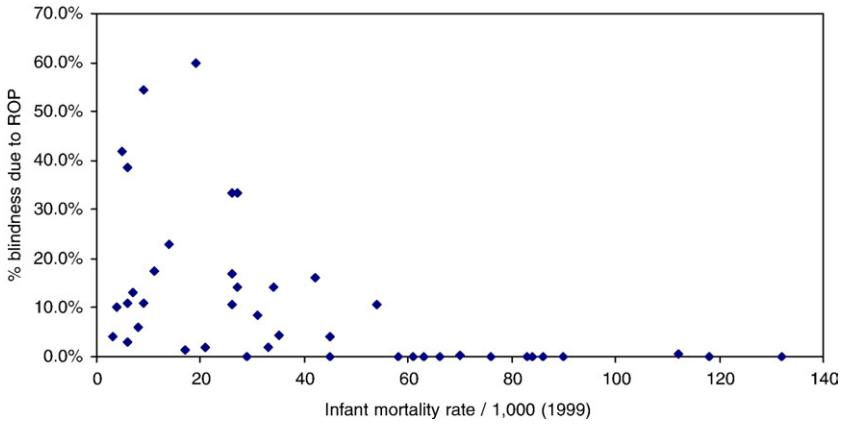

Figure 3 Proportion of blindness due to ROP, by infant mortality rate.

the world's population. As these economies improve neonatal care services are almost certain to expand, with the attendant risk that ROP will soon become a public health issue in these countries unless control activities keep pace with the increased survival of premature babies at risk.

2. Key guidelines

- The available evidence suggest that the population of premature babies at risk of ROP needing treatment varies, with larger, more mature babies developing treatable disease in low and middle income countries than in industrialised countries. Programs for detecting babies needing treatment in low and middle income countries should take account of this variation and include larger, more mature babies. Neonatal care also needs to be improved.

3. Research directions

- More data are needed on the causes of blindness in children, including that due to ROP, in countries where these data are not yet available. The World Health Organization's classification system should be used, to allow comparisons to be made [15]
- More data are needed on the population of babies at risk of ROP in low and middle income countries, so that locally relevant, evidence based guidelines can be developed for case detection initiatives
- Operational research is needed to explore reasons for the high rate of ROP needing treatment in low and middle income countries, with evaluation of appropriate interventions
- Operational research is needed to explore alternative approaches to screening which are feasible, safe, cost effective and which have high levels of sensitivity and

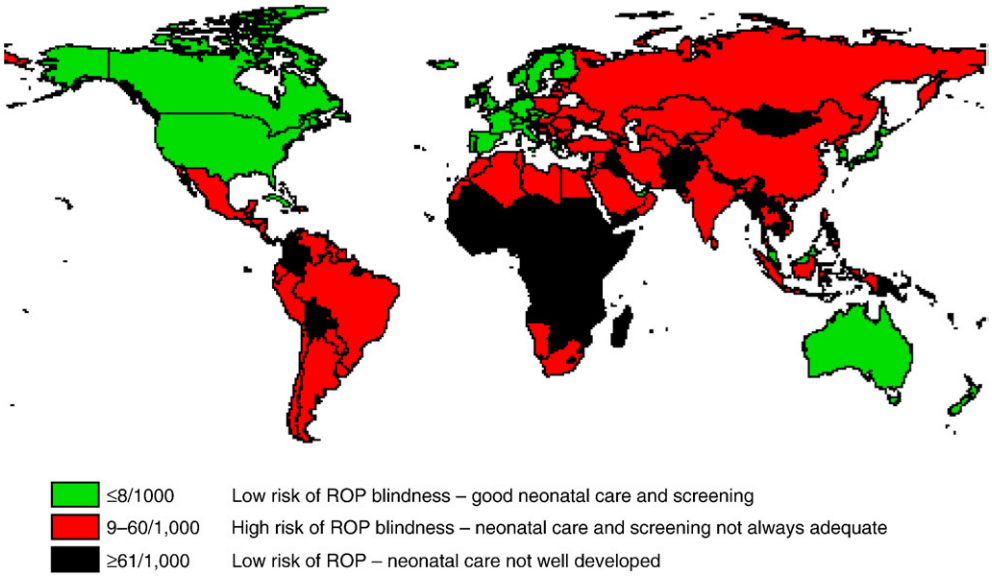

Figure 4 Likely distribution of blindness in children due to retinopathy of prematurity as a public health problem, using infant mortality rates as an indicator. [Reproduced with permission from Eye 2007 21: 1338–43].

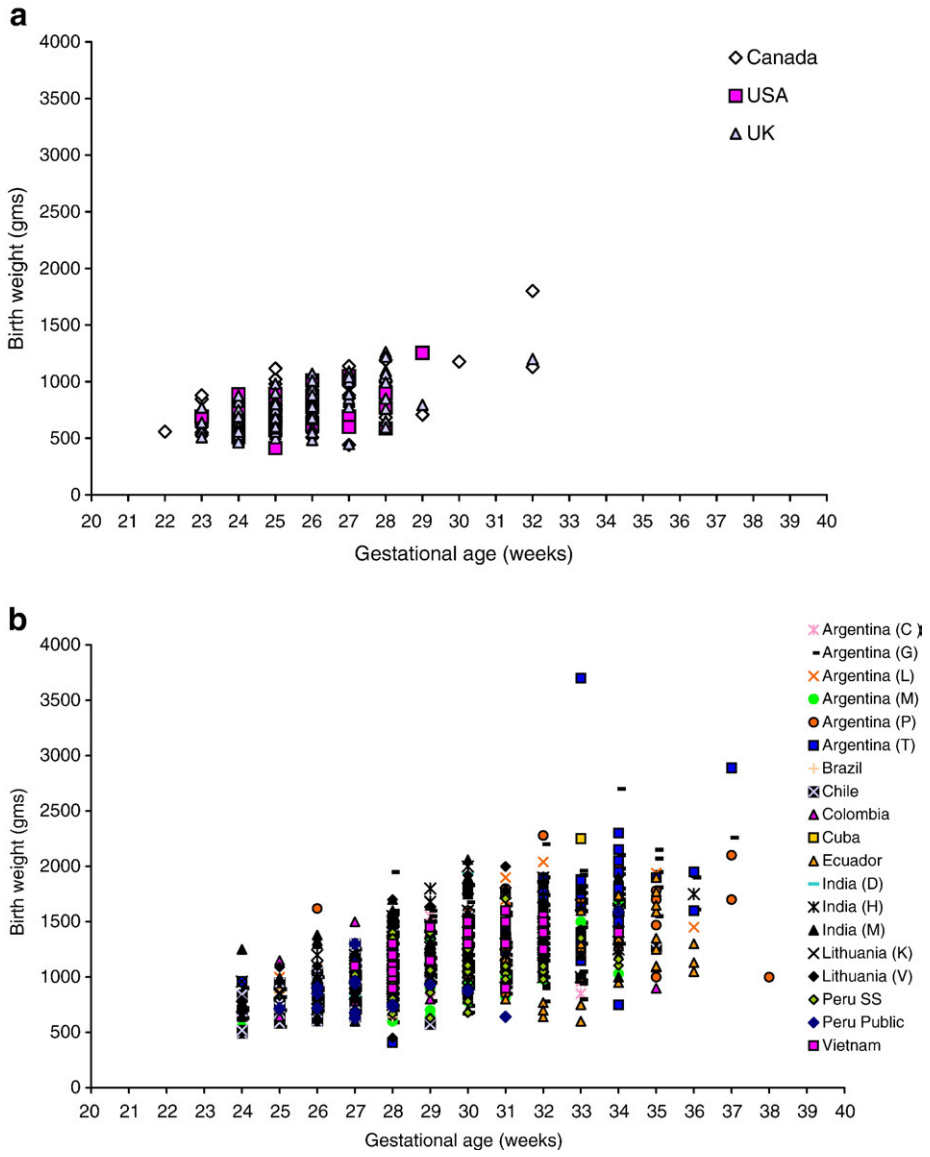

Figure 5 a. Birth weights and gestational ages of babies treated for threshold ROP in Canada, the USA and UK (2000 to 2004). b. Birth weights and gestational ages of babies with severe retinopathy of prematurity in low and middle income countries between 2000 and 2004. [Reproduced with permission from Pediatrics 115: 518–525 2005 by the American Academy of Pediatrics].

	Historical perspective		
	1940-50s	**1960-70s**	**1980-2000s**
Risk factors for ROP: - prematurity - low birth weight - high oxygen - sickness	 + + ++++ +	 ++ ++ +++ +	 ++++ ++++ + +/-
BW: <1,000 gms	High mortality No ROP	Mod mortality ROP +	Low mortality ROP +++
BW: 1,000-1,500 gms	Survive ROP +++	Survive ROP ++	Very low mortality No ROP
	Poor	**Moderate**	**Excellent**
	Current level of neonatal care provided		

Figure 6 Historical and current risk factors for retinopathy of prematurity, and the population of babies at risk.

specificity for identifying babies with ROP severe enough to warrant the expert opinion of an ophthalmologist.

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