Update on Blindness Due to Retinopathy of Prematurity Globally and in India

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Retinopathy of prematurity (ROP), a well-known complication of preterm birth that can result in avoidable blindness and visual impairment, is especially sensitive to the quality of neonatal inpatient care and appropriate, well-monitored oxygen. In 2010, the annual incidence of blindness and visual impairment from ROP was estimated to be 32,200 cases worldwide. The greatest burden is seen in middle-income countries, particularly where coverage of neonatal inpatient care has expanded without due attention to the quality of care provided, and the neonatal nursing skills and training of those providing this care. India accounted for nearly 10% of all estimated worldwide visual impairment following ROP in 2010, with at least 5,000 developing severe disease and 2,900 children surviving with visual impairment related to ROP. Screening all those at risk and providing treatment for those with severe disease will require investment to increase the capacities and competencies of eye-care providers. Scale-up of neonatal services must be coupled with implementation of standards for high quality care, including safe oxygen management, and detection and treatment of ROP. Otherwise the number of children surviving preterm birth with visual impairment secondary to ROP will continue to increase in India and worldwide.

Keywords: *Newborn, Oxygen, Preterm, Visual loss.*

Retinopathy of prematurity (ROP), a vision-threatening disease associated with abnormal retinal vascular development, is a well-known complication of preterm birth [1]. It has increasingly been recognised as an important cause of avoidable blindness and visual impairment in children in Eastern Europe and Latin America, and is becoming a public health concern in many Asian countries, including India, China and Malaysia [2,3]

The Millennium Development goal era has seen unprecedented increases in child survival globally. An estimated 12.7 million children died before their 5th birthday in 2000 [4]; in 2015, the number had reduced to 5.9 million. The progress has been most rapid for children over 1 month of age, and 45% of all child deaths now occur in the first month of life [4]. Direct complications of preterm birth are now the commonest causes of child death, with respiratory distress syndrome the most common complication [5]. This has led to focused efforts to address the challenge of neonatal mortality from the global community, leading to the Every Newborn Action Plan launched in 2014 – a multi-partner movement that aims to end preventable newborn deaths and stillbirths [6,7]. An estimated 15 million babies are born preterm (<37 weeks of completed gestational age) each year [8] and at least 32 million babies are small for gestational age (<10th centile for gestational age) [9]. These babies have higher risks of complications, and requirements for specialised neonatal care to improve their survival. It is estimated that 80% of all neonatal deaths occur in babies that are either preterm, small for gestational age, or both [7].

In response to this, many middle-income countries, including India, are rapidly expanding their neonatal inpatient care services, increasing access to supportive and therapeutic services to address the common complications experienced by preterm babies, including respiratory distress syndrome. This had led to a higher number of preterm babies surviving due to improved respiratory support, including the use of oxygen. ROP is especially sensitive to the quality of neonatal care, including appropriate, well-monitored oxygen. Therefore, unless scale-up of neonatal services are coupled with improvements in implementation of standards for high-quality care and detection and treatment of ROP, the number of children surviving preterm birth with visual impairment secondary to ROP will continue to increase.

This article presents a broad overview of blindness due to ROP globally and in India as part of a special issue dedicated to the specific challenges of ROP in India.

WHAT IS KNOWN?

The introduction of widespread specialized neonatal care

in high-income settings, including unmonitored oxygen, in the 1940s and 1950s led to a large number of moderately preterm babies surviving with visual impairment secondary to ROP (the first epidemic) [10]. In recent decades, sight-threatening ROP has been confined to the most preterm (<28 weeks) in these settings; however, the numbers affected have not decreased due to the increase in survival of extremely preterm babies (the second epidemic). Attention has now shifted to the growing number of affected children in low- and middle-income settings (the third epidemic) [3].

The prevalence of visual impairment secondary to ROP varies substantially by setting and is dependent upon the preterm birthrates, the survival of babies born preterm, the quality of neonatal care and the availability of timely screening and treatment, if required. Survival of babies born preterm is closely linked to the quality of neonatal care and to resource and staffing levels, especially nurses [11]. Facilities with poor practice for monitoring and control of oxygen levels may have reasonable survival levels amongst preterm babies, but high rates of adverse neuro-developmental outcomes, including ROP [10,12,13].

Several attempts to quantify the global burden of ROP have been made. Initial estimates, based on data from schools for the blind together with blindness prevalence estimates suggested that at least 50,000 children aged up to 15 years were blind from ROP worldwide [3]. More recent work suggest that this is likely to be an underestimate with an estimated 32,200 infants becoming blind or visually impaired from ROP in 2010 alone [12]. The latter estimate was derived using data from 66 peer-reviewed publications, meta-analyses, and modelling, using assumptions from the meta-analyses for countries without or with incomplete data. Data from five Indian studies were included. Available data suggests that blindness from ROP may be increasing, especially in middle income settings [14,15]. However, the uncertainty in existing estimates is part of a wider data-gap on the neuro-developmental outcomes of preterm and sick newborns, as well as a lack of accurate data on gestational age and birthweight [16].

Global Update

***Fig.* 1** shows the estimated distribution of the incidence of new cases of visual impairment due to ROP per 100,000 livebirths in 2010. Several patterns are noted. In settings with very high neonatal mortality and low coverage of neonatal inpatient care, few cases of ROP or resulting visual impairment occur, with rates of visual impairment secondary to ROP <10 per 100,000 livebirths.

Two groups of countries have low-moderate incidences of visual impairment secondary to ROP (rates of 10 - <45 per 100,000 livebirths), these include:

(*i*) Low neonatal mortality settings, such as in the United States of America and the United Kingdom, where ROP is predominantly found in the extremely preterm survivors. This is usually detected through screening programmes, but some visual impairment occurs despite treatment. Overall rates in these settings are fairly static; and

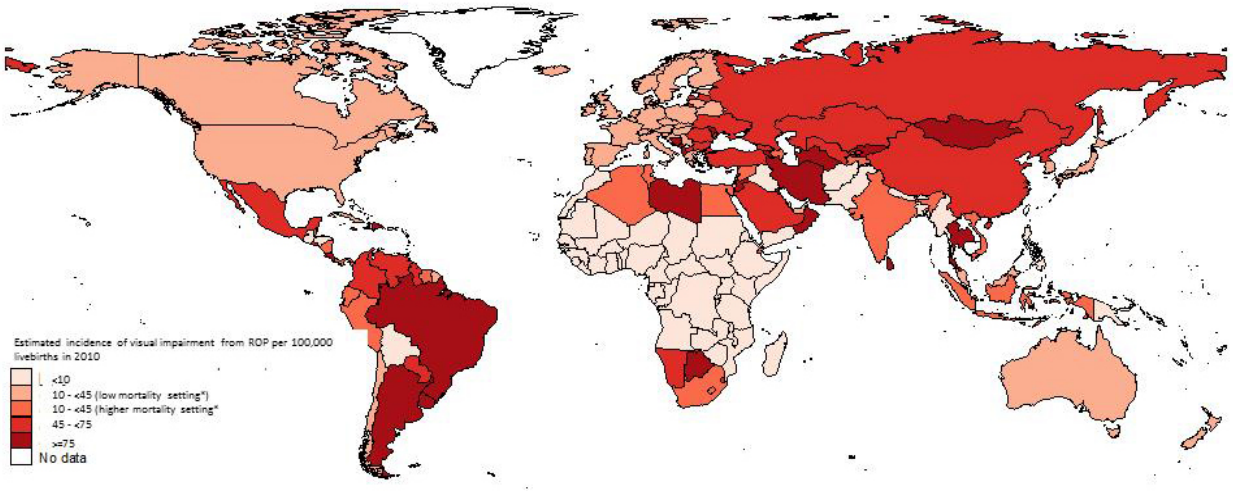
(*ii*) Higher neonatal mortality settings where the survival rates after preterm birth are increasing, but where insufficient priority has been given to quality of neonatal care, or establishment of screening detection and treatment services for ROP, as in India and other middle-income countries. Overall rates in these settings are increasing.

A final group of countries have high rates of ROP (>45 per 100,000 livebirths). These countries are predominantly middle-income particularly where coverage of neonatal inpatient care has expanded without due attention to the quality of care provided, and the neonatal nursing skills and training of those providing this care [12,13].

Two thirds of all cases of visual impairment secondary to ROP in 2010 were estimated to occur in 10 countries – China, India, Brazil, Indonesia, Iran, Russian Federation, USA, Mexico, Thailand and Turkey. These countries also experience the greatest burden of long-term neuro-developmental disability in survivors following preterm birth [13].

Update on Levels of ROP in India

India accounted for nearly 10% of the worldwide estimate of blindness and visual impairment due to ROP in 2010 [12]. In 2010, there were an estimated to be 3,519,100 preterm births in India (uncertainty range: 2,553,100-4,431,900) [8] using the approach previously used to estimate the regional and global burden of neonatal morbidity [12]. If 30% of babies had access to specialised inpatient neonatal care (intensive care or neonatal special care) and gestation-specific survival rates amongst these admitted were similar to reported rates from other low-middle income country settings, 98,077 babies would have survived neonatal care and be at risk of visual impairment from ROP. Among the survivors, an estimated 16,000 would develop any ROP, with 5,000 (uncertainty range: 2,200-8,000) developing severe (type 1) disease requiring treatment. Assuming that 20% of these had access to screening and treatment an estimated 2,900 (uncertainty range: 2,000-4,000) babies would have survived in 2010



Data source: *National level estimates of ROP burden Blencowe, et al. 2013(12); *low mortality setting = neonatal mortality rate <5 per 1,000 livebirths; Higher mortality setting=neonatal mortality rate 5 or more per 1,000 livebirths.*

FIG.1 *Estimated global burden of visual impairment from retinopathy of prematurity in 2010.*

with visual impairment or blindness due to ROP; the majority (2,100) being severely affected [12].

Since 2010, India has continued to make important strides to further improve the coverage of neonatal care, with operationalization of over 500 special newborn care units at district level and nearly 2000 newborn stabilisation units at block level. However, unless adequate attention is given to the quality of care and screening, detection and treatment of ROP, these numbers are likely to continue to increase.

IMPLICATIONS FOR SERVICE DELIVERY

The estimate of 98,077 survivors represents the minimum number of infants who require screening for ROP, as it does not include sick, more mature infants who also need to be screened. Using the figure of almost 100,000, and if each infant requires an average of three retinal examinations before they require treatment or can safely be discharged from further follow up, this would entail approximately 300,000 examination sessions a year. If both eyes of all 5000 infants estimated to develop severe ROP were to be treated with peripheral retinal laser, and each eye requires an hour of an ophthalmologists time, this represents 2,500 working days of highly skilled ophthalmologists' time.

Another paper in this special issue presents the findings of a situation analysis of services provided for ROP by 30 tertiary-level eyecare training institutions in 11 major cities in India. Twenty-four provided a service for ROP, 15 of whom screened in only one neonatal unit. The mean number of infants treated annually for ROP was 39 (range 1-200).

ROP prevention, detection and treatment globally: Increasing attention and research funding has been directed to preterm birth prevention over the past five years [17-19]. However, to date, limited progress has been made, in part, due to the complexity of the preterm birth syndrome, coupled with a limited understanding of the mechanisms controlling normal birth timing in humans. Attention to the quality of maternity and neonatal care has also increased, with recognition that it will be essential to end preventable deaths and reduce morbidities such as ROP [20]. Standardised guidelines, for example the new WHO preterm guidelines and Neonatal Networks can play an important role in achieving this [21,22].

Close attention to the development of adequate screening and treatment of ROP programs as countries such as India, introduce and scale-up access to specialised inpatient neonatal care will be imperative to monitor and mitigate the potential effects of this ROP epidemic. Scaling up screening and treatment to reach all babies at risk in a given population will require innovative approaches. Screening by members of the neonatal team using new imaging systems is now on the horizon [23].

CONCLUSION

The burden of visual impairment following ROP globally is large and increasing, especially in low- and middle-income settings, including India. India has played a trail-blazing role in the efforts to scale-up inpatient care for preterm newborns, backed by a comprehensive India Newborn Action Plan and exemplary data monitoring systems. The scale-up of specialized neonatal care is

welcomed, in India and other low and middle-income countries, but there is a need to minimize the potentially negative impact of preterm birth on these vulnerable survivors. This requires careful attention to the quality of inpatient care, backed by comprehensive policies and guidelines, including safe oxygen monitoring and delivery mechanisms. High quality inpatient care cannot be achieved in India without specialized training for neonatal staff, especially neonatal nurses. As ROP is largely preventable, rates of ROP are an important indicator of the quality of inpatient care available for preterm babies. Rates of ROP are also an important indicator of a system's ability to provide ongoing neuro-developmental care into early childhood. To avoid an increasing epidemic of visual impairment secondary to ROP, India's health system must include ROP screening and detection as part of their comprehensive child health programs.

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REFERENCES

1. Fielder A, Blencowe H, O'Connor A, Gilbert C. Impact of retinopathy of prematurity on ocular structures and visual functions. Arch Dis Child Fetal Neonatal Ed. 2015;100:F179-84.
2. Courtright P, Hutchinson AK, Lewallen S. Visual impairment in children in middle- and lower-income countries. Arch Dis Child. 2011;96:1129-34.
3. Gilbert C. Retinopathy of prematurity: A global perspective of the epidemics, population of babies at risk and implications for control. Early Hum Dev. 2008;84:77-82.
4. UN Inter-agency Group for Child Mortality Estimation (UN-IGME). Levels and Trends in Child Mortality. Available from: *http://wwwwhoint/maternal_child_adolescent/documents/levels_trends_child_mortality_2015/en/*. Accessed November 28, 2015.
5. Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, *et al*. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: An updated systematic analysis. Lancet. 2015;385:430-40.
6. UNICEF, The World Health Organization. Every Newborn: An action plan to end preventable newborn deaths. Available from: *www.everynewborn.org*. Accessed April 15, 2014.
7. Lawn JE, Blencowe H, Oza S, You D, Lee AC, Waiswa P, *et al*. Every Newborn: progress, priorities, and potential beyond survival. Lancet. 2014;384:189-205.
8. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, *et al*. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: A systematic analysis and implications. Lancet. 2012;379:2162-72.
9. Lee AC, Katz J, Blencowe H, Cousens S, Kozuki N, Vogel JP, *et al*. National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010. Lancet Glob Health. 2013;1:e26-36.
10. Cross KW. Cost of preventing retrolental fibroplasia? Lancet. 1973;2:954-6.
11. Hamilton KE, Redshaw ME, Tarnow-Mordi W. Nurse staffing in relation to risk-adjusted mortality in neonatal care. Arch Dis Child Fetal Neonatal Ed. 2007;92:F99-f103.
12. 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;74:35-49.
13. Blencowe H, Lee AC, Cousens S, Bahalim A, Narwal R, Zhong N, *et al*. Preterm birth-associated neuro-developmental impairment estimates at regional and global levels for 2010. Pediatr Res. 2013;74:17-34.
14. Al Alawi EK, Al Omran MS, Al Bahrana EH. Incidence of Retinopathy of Prematurity in Bahrain, 2002-2011. Middle East African journal of ophthalmology. 2015;22:335-9.
15. Chang KM, Patel DK, Tajunisah I, Subrayan V. The trend of retinopathy of prematurity in Malaysia from 1992 to 2001 based on a nationwide blind schools study. Asia-Pacific journal of public health / Asia-Pacific Academic Consortium for Public Health. 2015;27:217-24.
16. Moxon SG, Lawn JE, Dickson KE, Simen-Kapeu A, Gupta G, Deorari A, *et al*. Inpatient care of small and sick newborns: A multi-country analysis of health system bottlenecks and potential solutions. BMC Pregnancy Childbirth. 2015;15:S7.
17. Rubens CE, Sadovsky Y, Muglia L, Gravett MG, Lackritz E, Gravett C. Prevention of preterm birth: Harnessing science to address the global epidemic. Sci Transl Med. 2014;6:262sr5.
18. Villar J, Papageorghiou AT, Knight HE, Gravett MG, Iams J, Waller SA, *et al*. The preterm birth syndrome: a prototype phenotypic classification. Am J Obstet Gynecol. 2012;206:119-23.
19. Avraham S, Azem F, Seidman D. Preterm birth prevention: How well are we really doing? A review of the latest literature. Journal of obstetrics and gynaecology of India. 2014;64:158-64.
20. Tuncalp, Were WM, MacLennan C, Oladapo OT, Gulmezoglu AM, Bahl R, *et al*. Quality of care for pregnant women and newborns-the WHO vision. Bjog. 2015;122:1045-9.
21. Profit J, Soll RF. Neonatal networks: clinical research and quality improvement. Semin Fetal Neonatal Med. 2015.
22. World Health Organization. WHO recommendations on interventions to improve preterm birth outcomes. Available at: *http://wwwwhoint/reproductivehealth/publications/maternal_perinatal_health/preterm-birth-guideline/en/*. Acessed November 25, 2015.
23. Gilbert C, Wormald R, Fielder A, Deorari A, Zepeda-Romero LC, Quinn G, *et al*. Potential for a paradigm change in the detection of retinopathy of prematurity requiring treatment. Arch Dis Child Fetal Neonatal Ed. 2016;101:6-9.