Retinopathy of prematurity (ROP) is a disease of the developing retina in preterm infants that has become a leading cause of blindness in children. The main risk factors for ROP are lower gestational age and low birthweight, and unregulated exposure to oxygen. Thus, as the age of viability of preterm infants decreases worldwide with advances in neonatal care, the incidence of ROP is increasing. Case detection among high risk newborns requires screening to permit timely, specialized treatment, which can be sight-saving.

Several “epidemics” of blindness due to ROP have been described with a more recent “third epidemic” occurring in middle-income countries.1 The epidemiology of childhood blindness in general, and ROP-related blindness in particular, varies by geography and socioeconomic status.1,2,3,4 As has been evidenced in the United States over the last 60 years, the incidence of blindness from ROP can be reduced with the optimization of oxygen management and ROP screening and treatment based on protocols, however ROP still occurs, particularly in the most preterm, smallest, and sickest infants.4 Middle-income countries have (1) a higher proportion of preterm birth,2 (2) often lack medical equipment and standard clinical protocols for proper supplemental oxygen monitoring to prevent ROP, (3) a shortage of neonatal health care staff who often lack awareness about ROP, (4) a shortage of trained ophthalmologists and healthcare providers with appropriate skills to screen for and manage ROP, and (5) inadequate or inconsistently applied screening programs for ROP.2 In lower income country settings where child mortality and neonatal mortality remain high, ROP-related blindness is an emerging problem.4 However, as countries achieve the United Nations Sustainable Development Goals and survival increases among infants born preterm, we anticipate a rising incidence of ROP and ROP-related blindness in regions where it has not been a problem, such as certain parts of sub-Saharan Africa.5 Therefore, urgent implementation and evaluation of evidence-based programs targeted at primary, secondary, and tertiary prevention especially in middle income countries is essential to mitigate the rising incidence of childhood blindness.

Case Example of a Preterm Infant Who Developed Complications from Unregulated Oxygen Management and Inadequate ROP Care

A preterm infant was born at 32 weeks gestation and weighed 1650 grams at birth. The infant was started on 100% supplemental oxygen during the first 24 hours of life for respiratory distress. The infant’s condition worsened on day 2, and was managed with continuous positive airway pressure (CPAP) with 100% oxygen for 8 days. The infant then transitioned to 2 L/min oxygen by nasal cannula oxygen. During the hospital stay the infant was given a blood transfusion and also developed hospital-acquired sepsis which was treated with IV antibiotics. He was discharged on day 35 at a weight of 1900 grams. A month later his mother noticed that the pupils of the infant’s eyes were white and took the infant to an ophthalmologist. The ophthalmologist diagnosed total detachment of the retina and referred the infant for surgery at a tertiary care eye hospital. Ultimately, the child was functionally blind in both eyes.

Why is retinopathy of prematurity (ROP) important?

Retinopathy of prematurity (ROP) occurs in premature and low birth weight (LBW) infants when abnormal blood vessels and scar tissue grow over the retina leading to visual impairment/blindness. The incidence of ROP is increasing as more preterm and extremely LBW babies are surviving due to expanding provision of neonatal care services, and advances in medical technology and therapeutics. The incidence of ROP and visual impairment and blindness from ROP is also increasing, and all regions of the world are now affected.1,2 Primary prevention through improved neonatal care, and secondary prevention through appropriate ROP screening of at-risk infants with timely treatment of those with severe ROP can prevent nearly all cases of blindness.

What are the major risk factors for the development of ROP and what practices promote ROP development?

The major risk factors for ROP are premature birth, low birth weight (LBW), and supplemental oxygen exposure. According to multi-center international studies, approximately 70% of children who are born ≤ 1500 grams and 30-weeks gestational age are at risk of developing ROP. Up to 10% of preterm infants develop sight-threatening ROP, which if not detected and treated in time, can lead to blindness. Rates of sight-threatening ROP are higher when oxygen management is not optimized, such as with the unregulated delivery of supplemental oxygen, and inappropriate delivery of supplemental oxygen when it is not needed (during initial resuscitation or later). While oxygen may be necessary for adequate newborn resuscitation to reduce neonatal mortality, inappropriate oxygen supplementation can lead to ROP, chronic lung disease and other medical sequelae. Other risk factors for ROP include sepsis, poor weight gain, and blood transfusions which can be prevented through quality improvement strategies, supported by protocols.

In many regions where neonatal resuscitation and intensive neonatal care are nascent, the primary focus has been on reducing
neonatal mortality. The lack of skilled health care providers and appropriate equipment often limit attention to the secondary goals of reducing morbidities in preterm survivors, including blindness from ROP. As more countries develop and neonatal mortality rates decline, action must be taken to establish a skilled workforce and infrastructure that focuses not just on improving mortality but on both primary and secondary prevention of the sequelae of prematurity, including ROP to reduce the incidence of blindness.

Factors contributing to an increased incidence of ROP and ROP-related blindness in low resource settings are:

- Improved access to neonatal care and increased survival of premature infants;
- Failure of primary prevention due to unrestricted use of supplemental oxygen in neonatal care;
- Exposure to other modifiable risk factors, such as infection and poor weight gain and blood transfusions;
- Failure of secondary prevention to identify ROP in the earliest stages; and
- Failure of secondary prevention through referral for appropriate and timely treatment.

What are the current WHO recommendations for ROP?

The control of blindness due to ROP was recommended by the World Health Organization’s (WHO’s) Prevention of Blindness Program in 1999. The most pressing problem is lack of ability or awareness of the importance of regulating and monitoring oxygen. The WHO has recommendations for the use of oxygen during resuscitation and its relationship to the occurrence of ROP. However, there are no specific WHO recommendations for the use of oxygen following resuscitation, or specific recommendations for the prevention and management of ROP.

What are the current evidence-based best practices?

Primary prevention: Oxygen management and ROP

The association between exposure to unregulated oxygen and ROP in premature infants has been clearly established. The opposing goals are that lower oxygen levels may result in death or impaired neurodevelopment, whereas higher oxygen levels may increase severe ROP or chronic lung disease. The optimal management of oxygen supplementation has been summarized in a Do No Harm Technical Brief on the safe use of oxygen, which promotes the lowest effective oxygen concentration by using blended oxygen or room air, monitoring oxygen concentration with pulse oximetry, and providing appropriate timely titration of oxygen levels. In addition, reduced incidence of respiratory disease is associated with use of antenatal corticosteroids for threatened preterm birth, and quality newborn care practices that include appropriate newborn resuscitation, feeding support with human breast milk, skin-to-skin contact, and good infection control.

Secondary prevention: ROP screening, treatment, and follow-up programs

ROP screening and treatment programs have been shown to be cost-effective and proven to reduce blindness associated with ROP. Screening and early detection of ROP requires a process of initial early examination of at-risk infants (criteria for which may vary by setting), followed by repeat examinations until the developing retina fully matures.

Screening criteria: According to the joint statement from the American Academy of Ophthalmology (AAO), American Academy of Pediatrics (AAP), American Association of Pediatric Ophthalmology and Strabismus (AAPOS), and American Association of Certified Orthoptists (AACO), children born ≤ 30 weeks or ≤ 1500 grams, and selected infants with gestational age of >30 weeks or a birth weight between 1500 and 2000 grams with an unstable clinical course should have a retinal screening examination. The initial retinal exam should be performed at 31 weeks if born at ≤ 27 weeks, or 4 weeks after birth for children born after 27 weeks. Follow-up examinations should be recommended by the examining ophthalmologist on the basis of retinal findings. Because unmonitored ROP can lead to blindness, all infants meeting ROP screening criteria should be examined in a timely fashion.

Importantly, screening criteria will vary based on regional differences in the population of babies at risk for ROP, due to variation in the quality of neonatal care and variation in reliability of gestational age assessment. (See Figure 1). In more developed

Figure 1: Gestational age and birthweight indications for screening for retinopathy of prematurity in different countries.
countries, every child born at ≤ 32 weeks or ≤ 1500 grams is screened for ROP. In lower and middle income countries (LMICs), extrapolating from the previous published guidelines, the first examination is often recommended by 30 days of life for all infants exposed to neonatal intensive care. However, this may not be conservative enough in certain settings where unrestricted oxygen can lead to aggressive ROP within a few weeks of birth, thus it is important for each region to develop criteria that are sensitive enough to identify all infants at risk of blindness. Other clinical considerations that inform the decision to screen an infant are intraventricular hemorrhage, bronchopulmonary dysplasia, sepsis, unstable hospital course, and prolonged oxygen exposure. Screening should take place within the neonatal unit for in-patients, or in eye or neonatal outpatient departments for those who have been discharged.

**Screening eye examinations:** ROP screening requires timely examination of the retina through a dilated pupil, using special lenses. Delay in detection can result in irreversible changes, such as retinal detachment and permanent loss of sight. ROP screening examinations may be performed by either indirect ophthalmoscopy or by telemedicine diagnosis. Both examination techniques pose the same risks as outlined below from eye dilation, but telemedicine may be preferable in settings with limited ophthalmology access. It is important that retinal examinations be performed by healthcare providers who are properly equipped and skilled to identify the relevant features of ROP as defined by the International Classification of Retinopathy of Prematurity and recognize the signs which indicate that treatment is required. 

**Risks and safety of ROP screening:** There are potential risks involved in the examination of preterm infants. Close monitoring of premature infants undergoing eye exams is necessary because they may experience changes in blood pressure, decreased heart rate, and pauses in breathing. Comfort measures should also be provided during eye examinations and unnecessary examinations minimized.

**Tertiary Prevention: Treatment of ROP**

**Treatment:** Timely treatment within 48-72 hours of diagnosis is essential to save sight of infants with progressive ROP. Laser of the avascular peripheral retina has been considered as the gold standard for treatment. Cryotherapy may be considered if laser is not available. Recent evidence suggests anti-vascular endothelial growth factor injection treatment for ROP can be effective; however long-term safety has not yet been determined. If there is progression of ROP to retinal detachment, surgery can be performed with scleral buckler or vitrectomy if the appropriate skilled personnel and equipment are available.

**What systems are needed for ROP screening and treatment programs?**

*Improved neonatal care:* Health systems should continually improve the standard of neonatal care and resuscitation and include the safe use of oxygen to ensure primary prevention. Morbidity and mortality outcome measures and clinical service indicators for premature infants should be collected and analyzed to inform quality improvement interventions.

**Clinical service indicators for monitoring and evaluation of effective primary, secondary, and tertiary ROP prevention:**

1. Number of newborns identified who meet ROP screening criteria/total number of live births.
2. Number of infants initially examined for ROP who meet screening criteria/total number of infants who meet screening criteria.
3. Number of infants who complete the appropriate follow up examination with the eye care provider after the initial screening exam/total number of infants who received initial screening exam.
4. Number of infants treated for ROP/total number of infants who meet ROP treatment criteria.

**Establishment of effective programs:** Introduction of national newborn and child health policy for ROP screening, treatment and follow-up is an important driver of health system changes. Hospitals that provide inpatient care for newborns/neonatal intensive care should establish programs to ensure babies at risk for ROP are screened and followed after discharge from hospital care according to regionally appropriate guidelines. This requires additional staff and resources dedicated to the screening and treatment program. Training of specialists in the management of ROP is also essential when developing an ROP program.

Blindness prevention through ROP screening and treatment programs is only effective if there are systems in place to ensure that 1) all at-risk infants are identified for screening and are screened, 2) there is a qualified examiner available, and 3) there is a mechanism to initiate a response in the case of a patient with severe ROP in need of treatment. Appropriate timing of the examination is crucial to the success of the treatment. In telemedicine systems, this means having a provider available on a timely basis to examine neonates at risk for ROP and interpret retinal images, and having the resources to manage infants with conditions requiring treatment.

It is important for the neonatal team to take primary responsibility for ROP screening program planning and include documentation of ROP screening protocols as part of quality assurance checks for neonatal care units. All babies at risk for ROP (based on current guidelines appropriate for that population) should receive screening. In addition, quality control would include ensuring follow up for all at risk babies with eye care providers and collecting data to ensure that the screening guidelines are appropriate for the regional context and are not missing babies with disease.

The ROP examination can be challenging even for experienced examiners and there is a growing awareness of quality and training differences between examiners. Improved systems of training and/or certification may improve the quality and consistency of ROP screening and treatment. In addition, mechanisms to overcome the logistical challenges of potentially transporting babies for treatment need to be in place.

The International Pediatric Ophthalmology and Strabismus Council (IPOS) has developed a Task Force with the goal of establishing strategies to address the emerging epidemic of ROP that is occurring globally and beginning to develop in Sub-Saharan Africa. The Task Force is implementing initiatives focusing on education, research, and clinical service, and collaborating with local partners to develop centers of excellence for ROP in Sub-Saharan Africa. Through the development of centers of excellence, improved capacity for ROP care and education can be achieved by local experts. Other efforts, through support from the Queen Elizabeth Diamond Jubilee Trust, to increase the workforce for ROP in Sub-Saharan Africa involve partnerships between institutions in Africa and India to train physicians in ROP management.
What actions can be taken to reduce ROP and improve health outcomes?

Policy Makers
- Establish clear national newborn and child health policy for ROP prevention
- Develop neonatal care unit quality indicators including indicators of effective primary, secondary, and tertiary ROP prevention
- Develop clinical guidelines for safe oxygen use and ensure staffing levels are adequate for effective oxygen monitoring
- Commit to capital investments and ongoing financing of safe oxygen use and ROP screening and treatment
- Develop regionalization of care across different levels of the health system with referral and transport to centers providing ROP screening and treatment
- Improve access to subspecialist ophthalmologists/retinal specialists/pediatric ophthalmologists

Program Planners and Implementers
- Understand the epidemiology of ROP in the region
- Develop location-specific ROP guidelines based on available data
- Build capacity of health workers through pre-service and in-service training on safe oxygen use and screening and treatment of ROP
- Procure equipment for neonatal ROP screening, and devices and drugs for treatment of ROP that match the level of care
- Train end users on the use and maintenance of equipment for safe oxygen delivery, equipment for neonatal ROP screening and devices for treatment of ROP, including procurement plans for spare parts

Facility Managers and Administrators
- Recognize that effective implementation of ROP blindness prevention measures is an inherent responsibility of neonatal care units
- Increase human resource staffing levels to improve primary prevention, including safe oxygen use and improved neonatal care practices
- Implement and evaluate secondary prevention measures with ROP screening, and ensure access to treatment for neonates with severe ROP
- Develop and track indicators to monitor compliance with ROP screening, ROP screening, and patient outcomes

Clinicians and Nurses
- Educate staff on the role of oxygen in neonatal survival and the development of ROP
- Adopt and follow clinical guidelines for safe oxygen use for newborn care and resuscitation
- Adopt and follow ROP screening and treatment guidelines
- Provide human breastmilk
- Administer antenatal corticosteroids for threatened preterm birth from gestational age >32 weeks to <34 weeks at appropriate facilities
- Ensure infection control practices
- Promote skin-to-skin contact between newborn and mother and/or other caretakers, where feasible and appropriate

Nepal
Helen Keller International (HKI), Tilganga Institute of Ophthalmology, and GEN-ROP, with support of the USAID Child Blindness Program, are collaborating to develop a ROP teleseconing program and improve neonatal care to help reduce the incidence of ROP and childhood blindness. The approach utilizes the latest technology (pulse oximetry, CPAP, electronic health records, retina imaging) to improve the quality of care provided to preterm babies in Nepal. Three selected hospitals and NICUs are working with a core team of experts from pediatrics, neonatology, anesthesia, nursing and ophthalmology in order to establish a system that will effectively identify and treat babies at risk of ROP. This program will utilize the 3nethra neo (Forus Health, Bangalore, India) camera for ROP teleseconing.

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