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Epidemiology of childhood blindness

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**Abstract**

An estimated 1.4 million of the world's children are blind. A blind child is more likely to live in socioeconomic deprivation, to be more frequently hospitalized during childhood, and to die in childhood than a child not living with blindness. This update of a previous review on childhood visual impairment focuses on emerging therapies for children with severe visual disability (severe visual impairment and blindness or SVI/BL).

For children in higher income countries, cerebral visual impairment and optic nerve anomalies remain the most common causes of SVI/BL, whilst ROP and cataract are now the most common avoidable causes. The constellation of causes of childhood blindness in lower income settings is shifting from infective and nutritional corneal opacities, and congenital anomalies, to more resemble the patterns seen in higher income settings. Improvements in maternal and neonatal health, and investment in and maintenance of national ophthalmic care infrastructure is key to reducing the burden of avoidable blindness. New therapeutic targets are emerging for childhood visual disorders, although the safety and efficacy of novel therapies for diseases such as retinopathy of prematurity or retinal dystrophies are not yet clear. Population based epidemiological research, particularly on cerebral visual impairment and optic nerve hypoplasia, is needed in order to improve understanding of risk factors, and to inform and support the development of novel therapies for disorders currently considered 'untreatable'.

## Introduction

An estimated 1.4 million of the world's children are blind.<sup>1</sup> A blind child is more likely to live in socioeconomic deprivation,<sup>1-3</sup> to have delayed or disordered development, to be more frequently hospitalized during childhood and to die in childhood than a child not living with blindness.<sup>1 4 5</sup> The differential between the blind and non-blind child is more pronounced in developing nations: whilst 10% of UK children die in the first year following the diagnosis of blindness, in lower income countries the equivalent mortality is 60%.<sup>2</sup>

This article updates our previous review on childhood visual impairment,<sup>6</sup> by summarising new evidence on the global epidemiology of, and the emerging therapies for, severe visual impairment and blindness (or SVI/BL, table 1). It is now recognised that in adults even mild visual impairment is associated with lower socioeconomic status and poorer general and mental health status.<sup>7</sup> The evidence base regarding children is inconclusive. Moderate visual impairment (table 1) may impact on educational opportunities, with half of the UK's moderately visually impaired children educated within specialised schools for children with physical or learning deficits.<sup>8</sup> However, there is still a paucity of research on the epidemiology and impact of childhood moderate visual impairment. For example, it is well recognised that the majority of blind children will have other non-ophthalmic disorders or impairments,<sup>5</sup> but it is unknown whether the same is true of those with moderate VI.

## Defining blindness

The 1972 WHO taxonomy still forms the basis of the International Classification for Disease (ICD) definition (table 1) of blindness.<sup>9</sup> The recent creation of an additional diagnosis of 'monocular blindness' is important as these individuals have a lifelong increased risk of binocular blindness due to visual loss in the seeing eye,<sup>10</sup> but the impact on global development for children with monocular blindness is unclear.

Table 1. World Health Organisation ICD Classification of visual impairment (VI), severe visual impairment (SVI) and blindness (BL)<sup>11</sup>

<b>Category of impairment</b>	
Mild or no visual impairment	<i>Vision better than or equal to 0.48 logMAR (6/18 Snellen)</i>
Moderate visual impairment (VI)	<i>Vision worse than 0.48, but equal to or better than 1.0 (6/60 Snellen)</i>
Severe sight impairment (SVI)	<i>Vision worse than 1.0, but equal to or better than 1.3 (3/60 Snellen)</i>
Blindness (BL)	<i>Vision worse than 1.3</i>

All humans are born with vision below adult acuity norms, as the average neonate having acuity worse than 1.0 logMAR. This improves rapidly in the first year of life (figure 1).<sup>12 13</sup> There is no child specific taxonomy for visual disability. As age and cognition may be obstacles to quantification of a child's acuity level, childhood severe visual impairment (SVI) and blindness (BL) are often categorised together (SVI/BL).<sup>2 5</sup> Children diagnosed in the first year of life, who constitute the majority of blind children in many populations, invariably have clinical signs consistent with very poor vision, such as absence of preferential looking behaviour when presented with high contrast visual stimuli, or obvious severe ocular anomalies.<sup>5</sup> Although SVI/BL children often have similar causative disease profiles and similar ocular phenotypes, by definition this grouping includes both children with vision sufficient to navigate around the world independently (eg 1.1 logMAR) and those with absolutely no perception of light ('NPL'). The life experiences, cognitive, developmental and educational outcomes for children at the two ends of this spectrum may differ, and until very recently there was a paucity of child-centric measures of experiences and outcomes.<sup>14 15</sup>

### **Global burden of childhood blindness**

The major challenge to quantifying burden is the rarity of the disability and the individual causative conditions. Population based approaches are required to capture a representative picture. Additionally, there are varying definitions of both childhood (<14, WHO), <16, UNICEF and <18, UN Convention of the Child) and blindness.

Much of the literature on the epidemiology of childhood blindness is based on study populations drawn from schools for children with disabilities or children seen within health care centres.<sup>6</sup> These methodologies are often at risk of under-ascertainment and bias particularly in lower income settings,<sup>16</sup> where there are significant obstacles to accessing education or health care.<sup>17</sup> There is evidence that research has failed to capture girls, rural communities, or children with multi-system impairments.<sup>16 17</sup> Children may also fail to present to health care services because families do not recognise that there is a problem,<sup>18</sup> or because access to health care for children is limited by their carer's own blindness.<sup>18</sup> There can also be a lack of awareness amongst health care givers, with half of a group of primary care workers in Tanzania unaware of the urgent nature of referrals for congenital cataract, or that children with albinism may have visual impairment.<sup>19</sup>

Key informant (KI) studies, in which trained volunteers with a pre-existing 'key' role identify children with disorders in their community, enabling referral to health care professionals, have been validated as a low-cost alternative to other population based approaches. KI methods enable researchers to capture a more representative study population, but are still likely to underestimate the true burden.<sup>20</sup>

Using the available estimates of childhood blindness, derived through robust population based approaches, the prevalence of blindness in individuals aged under 16 years (the definition used most consistently within the research) has been estimated at 12-15 per 10,000 children in very poor regions, and 3-4/10,000 in affluent areas (figure 2).<sup>1</sup> As the birth rate remains higher within lower income countries, these countries have a disproportionately higher absolute number of blind children.<sup>1</sup>

### **Trends in the global causes of childhood blindness**

For children in higher income countries, cerebral visual impairment and optic nerve anomalies remain the most common causes of SVI/BL, whilst ROP, cataract, glaucoma and non-accidental injury are now the most common avoidable causes.<sup>3 21</sup> Recent work from the UK has suggested an increasing certification of children with

severe visual impairment and blindness.<sup>22</sup> This suggests either a true increase in new cases, or an increasing awareness of the benefit of certification leading to registration, which brings with it increased support for the child and family (although it is not a prerequisite for access to early educational and developmental support for UK children with visual disabilities). However, this voluntary register has been found to be incomplete.<sup>3</sup> Much of the data on the epidemiology of childhood blindness in an industrialised setting is derived from the 2001 British Childhood Visual Impairment Study.<sup>5</sup> A follow up study, which aims to investigate the epidemiology of the full spectrum of childhood visual impairment, is currently underway.<sup>23</sup>

Over the last two decades, with the establishment of national programmes of vitamin A supplementation, vaccination and sanitation improvements, the constellation of causes of childhood blindness in lower income settings has shifted from infective and nutritional corneal opacities, and congenital anomalies, to more resemble the pattern of causes seen in higher income settings.<sup>17 24 25</sup> In countries which have relatively recently moved up from the lower to the middle economic strata, there has been improved survival following premature or complicated birth, with an attendant increase in visual morbidity, due not only to retinopathy of prematurity (ROP), but also cerebral visual impairment.<sup>26 27</sup> Of 231,000 children (aged under 16 years) examined as part of a major recent Indian rural population based, 8 per 10,000 had vision worse than 3/60 (95% CI 40-110/10,000).<sup>28</sup> Almost half of the blind children had retinal disorders, the most common being retinopathy of prematurity. Cataract (28%) and globe anomaly (11%) were the next most common blinding disorders.<sup>28</sup> Amongst blind children in regions of Nigeria, 30% were blind due to an event in the perinatal period.<sup>26</sup> In Turkey perinatal birth injury related cerebral visual impairment (CVI) is now the most common cause of childhood blindness with significant decreases in blindness secondary to ROP, and cataract.<sup>29</sup>

Whilst maternal (vertical) and 'horizontal' transmission of potentially blinding diseases such as measles and rubella has fallen, other infectious diseases may come to the fore. For example, a third of Brazilian children with suspected Zika associated microcephaly have ocular abnormalities, the commonest being pigmented change or retinochoroidal atrophy.<sup>30</sup> There have also been reports of ocular changes in exposed infants with normal head circumference.<sup>31</sup> However,

cerebral visual impairment associated with severe micropcephaly is likely to be sufficient cause of poor visual function for most affected children, who are also likely to have severe global brain dysfunction

The review will now summarise key developments in the epidemiology and management of the most important causes of childhood severe visual impairment / blindness (table 2), i.e. those which are responsible for the highest proportion of affected children globally, and those which carry the highest burden of avoidable blindness.<sup>1 3 6 16 22 26 28 29 32-34</sup>

Table 2: the most important causes of childhood blindness<sup>1,2,9,11</sup> (which may co-exist):

The most common avoidable causes of childhood blindness globally	ROP
	Cataract
	Corneal opacity
The most common causes of childhood blindness in high and middle income countries	Cerebral Visual Impairment
	Optic nerve hypoplasia
	Inherited retinal disorders

### Retinopathy of prematurity (ROP)

ROP develops when the vasoconstrictive response to hyperoxia, i.e. the immature retina of the eyes of premature children, is followed by a vasoproliferative phase which is driven by the surge in endothelial growth factors (EGFs) on the return to normal oxygenation. In industrialised settings CVI is a more important cause of visual impairment for a preterm child, but globally, ROP remains the major threat to vision for preterm infants. Approximately 170,000 preterm babies worldwide developed some degree of ROP in 2010, and 54,000 required treatment for potentially blinding severe disease, but only an estimated 42% of these babies received this treatment.<sup>24</sup> Globally, an estimated third of surviving children with ROP requiring treatment (20,000; 95% CI 15,500–27,200) are severely visually impaired or blind secondary to ROP.<sup>24</sup>

Developments in neonatal care in regions such as Western Europe and North America have led to a reduction in the proportion of moderately preterm children (32-28 weeks) developing ROP.<sup>25 35</sup> However, in less developed health settings older and heavier preterm babies are still at significant risk of developing ROP.<sup>36 37</sup> Of Iranian children with ROP requiring treatment, 8% would never have been examined if American or UK screening guidelines had been in place.<sup>38</sup> This finding, consistent with others from low/middle-income countries demonstrates the power of epidemiology in determining setting-specific policy and practice.<sup>25</sup>

Primary prevention of blindness due to ROP requires identification of the risk factors underlying disease development. Prematurity and low birthweight are the most important determinants of disease and may be addressed through maternal health care. Genetic and environmental factors are likely to play a role in the degree and duration of hyperoxia necessary to trigger the process, the resultant surge in vascular growth factors, and the severity of disease which develops. Balancing oxygen supplementation is key: lower supplementation (85% - 89% versus 91% - 95%) reduces the risk of sight threatening ROP (RR of 0.72, 95% CI, 0.51–1.00) but increases the risk of mortality (RR 1.17, 95% CI, 1.03–1.32).<sup>39</sup> The role of nutrition, haemoglobin transfusion or EPO administration is unclear, though meta-analysis of RCTS of early nutritional supplementation indicates a protective effect (RR 0.22, 0.09 – 0.55 95% CI, and RR 0.67, 0.46 - 0.97 respectively).<sup>37 39</sup>

Secondary prevention strategies involve early identification, and early and appropriate treatment of children with ROP to prevent blindness. The required infrastructure can be a challenge in higher income settings, where approximately 55 infants are examined for every infant treated.<sup>35</sup> Over 8 years, the co-ordination of care over 36 rural centres in India involved more than 75 000 imaging sessions on more than 23 000 preterm infants.<sup>40</sup> 1 in every 15 examined infants required urgent treatment. Telemedicine techniques may allow more babies to be examined,<sup>36 41 42</sup> but suitably trained ophthalmologists are still required to confirm diagnosis and deliver treatment. Reliable prediction of those at risk will be key to delivering a sustainable service: the Weight, IGF-1, Neonatal, ROP (WINROP) study used serum IGF levels and post-natal weight gain to successfully predict all children who



required ROP treatment.<sup>43</sup> The WINROP algorithm is undergoing validation across different countries and settings to determine its utility as a universal screening tool.

Retinal laser ablation therapy is challenging, time consuming and implicitly destructive, but remains the gold standard intervention to prevent central sight loss in children with severe RO. 1 in 12 babies undergo disease progression despite laser treatment.<sup>35</sup> Anti-VEGF agents have recently emerged as a therapeutic option. Bevacimab (Avastin) is now used as a first line treatment by up to a quarter of ophthalmologists following early studies suggesting superiority of over laser in more central disease.<sup>41</sup> However, the long term neurodevelopmental and cardiovascular impact of the associated suppression of systemic VEGF levels, which can last for up to 8 weeks after intravitreal bevacizumab injection, is unclear. A recent retrospective analysis of a cohort of very premature children showed that, adjusted for maternal education, systemic status and gestational age, children who had undergone intravitreal treatment were, by 6-7 years of age, more likely to have severe neurodevelopmental impairment (RR 3.1 (1.2–8.4)).<sup>44</sup>

## **Cataract**

Cataract related to prenatal rubella infection is still an issue globally, for example accounting for 20% of childhood cataract in the Phillipines.<sup>45</sup> However, for the majority of affected children with bilateral cataract (and therefore at risk of blindness), aetiology is unknown, and prevention of blindness is focused on the prompt detection and treatment of visually significant lens opacity before deprivation amblyopia becomes intractable. The Chinese Childhood Cataract Program (CCPMOH), established with the support of the V2020 programme, resulted in earlier diagnosis of cases of congenital / infantile cataract, and an apparent increase in prevalence of childhood cataract, as a result of improved case detection in remote regions.<sup>46</sup>

However, there are still many obstacles to prompt treatment for affected children. In several countries patients need to supplement health costs, putting treatment beyond the means of many families.<sup>47</sup> In many settings, proximity to a hospital is an independent predictor of better visual outcome following childhood cataract surgery.<sup>48</sup>

## **Corneal opacity**

Corneal opacity secondary to vitamin A deficiency (VAD), infection or toxicity from traditional remedies, remains the most common cause of childhood severe visual impairment / blindness in Sub-Saharan Africa and areas of extreme deprivation,<sup>1</sup> despite recent V2020 programmes on nutritional supplementation, measles and rubella vaccination and health education. The only current treatment for established corneal scarring is corneal transplantation. Childhood corneal transplants have a high failure rate, due to rejection, new scar formation, or infection.<sup>49</sup> They require frequent re-operation, and even when the transplant successfully retains its clarity, the complex refractive aberrations can result in intractable severe amblyopia.<sup>49</sup> Stem cell therapeutic approaches to corneal transplantation will reduce the incidence of graft rejection, but will not overcome the other challenges of paediatric corneal transplantation.

## **Cerebral Visual Impairment (CVI)**

CVI ('cortical' and 'central' visual impairment are terms previously used by some as an alternative to cerebral) is visual impairment due a heterogenous group of disorders affecting the optic radiations, visual cortex or associated visual areas). This encompasses a spectrum of visual problems from blindness through to children with normal acuity but disabling visual processing defects (such as object confusion or non-recognition). Although CVI can co-exist with ophthalmic abnormalities, it can be a challenge to determine whether a child with normal eyes and apparently severely reduced visual acuity has CVI unless non-visual causes for poor visual response, such as severe global brain problems, are excluded. For two thirds of children who have vision worse than 1.0 logMAR due to CVI, visual impairment is part of a global developmental sequelae to hypoxic ischaemic encephalopathy (HIE).<sup>50</sup> As HIE is strongly associated with birth complication, primary prevention of CVI blindness requires improvement of maternal and infant perinatal health. As with many other early childhood disorders, the incidence of HIE is a marker for the socioeconomic development of a region, being much lower in a high income setting (6 per 1000 live births),<sup>51</sup> than that seen in lower income settings (26 per 1000 live births).<sup>51</sup> It is postulated that the first 48 hours are the 'golden window' for interventions to prevent further neuronal and white matter injury, and that a multi-target approach is

necessary to reverse the multi-phasic ischaemic, apoptotic, inflammatory and angiogenic pathways underlying HIE.<sup>52</sup> The advent of hypothermia (head cooling or whole body cooling) as a therapy for HIE within the 'golden window' has resulted in modest improvements in neurodevelopmental outcomes.<sup>52</sup> There are several currently underway trials of adjuvant therapies hoped to further improve outcome, including noble gases (NCT 00934700, NCT 01545271), melatonin (NCT01862250) and erythropoietin derivatives (NCT 01913340).

Other causes of CVI include central nervous system (CNS) malformations, neoplasia or infection, and metabolic neurodegenerative disease.<sup>53</sup> Genome studies have also revealed aetiological insights: a whole exome study of 25 children with CVI and cognitive impairment revealed that 16 had a related underlying genetic abnormality: five had a recognised genetic cause, and eleven had mutations within candidate genes coding for neurometabolic functions, or brain / optic nerve development.<sup>54</sup>

Demonstrable improvements in visual function in some children with CVI have resulted in suggestions that various 'visual stimulation' therapies may be of benefit, but the population who improve may be a separate subgroup in whom CVI is a manifestation of a delayed or interrupted rather than aborted trajectory of 'normal' visual development.<sup>55</sup> Further research into pathogenesis, or the identification of therapeutic targets, is hampered by the absence of a clinically meaningful taxonomy with which to classify the different CVI phenotypes.

### **Optic nerve anomalies**

Anterior visual pathway disorders are responsible for almost a quarter of childhood SVI/BL in some higher income settings, and optic nerve hypoplasia (ONH), is the commonest single cause of severe visual impairment / blindness in industrialised nations.<sup>3 21 56 57</sup> In most cases the cause is unknown, but ONH is independently associated with younger maternal age and nulliparity.<sup>56-58</sup> It may also be a marker of poorer maternal health,<sup>56 57</sup> with a UK study finding case clusters within areas of socio-economic deprivation.<sup>59</sup> ONH is a clinical diagnosis based on the appearance of the optic nerve, and the absence of a standardised clinical phenotype for the classification of hypoplasia limits epidemiological research. There is evidence of the relatively frequent co-existence of ONH and CVI, but the aetiological or clinical

significance of this is unclear.<sup>53</sup> There is a paucity of normative data on optic nerve appearance in early childhood, or optic nerve volume on neuroimaging during childhood. Hand-held optical coherence tomography devices, which are non-contact diagnostic tools able to produce biomicroscopical images of the paediatric eye, are an emerging technology which may be able to aid the classification of paediatric optic nerve disease.<sup>60</sup>

### **Inherited retinal disorders**

Photoreceptor dystrophies are the most common inherited retinal disorders amongst children with SVI/BL.<sup>5 61</sup> These constitute the global photoreceptor dystrophy of Leber's amaurosis (LCA), dystrophies affecting rod photoreceptors more than cones (the retinitis pigmentosas), and the cone dystrophies.<sup>5</sup> The RPE65 gene, mutations of which cause LCA type 2 and retinitis pigmentosa, has been a target for gene therapies. Following intraretinal injection of adenoviral delivered copies of functioning RPE65, children with LCA2 initially had improved visual function. This improvement was not maintained in follow up studies, due to degeneration of treated retina.<sup>62</sup> Further human trials of genetic therapeutics are underway. Next generation sequencing technologies have resulted in a deeper understanding of the genetic bases of this group of disorders, but as genetic heterogeneity is a challenge to gene therapy, further work on mutation independent approaches is necessary.

### **Summary**

Childhood visual impairment and blindness remains an important public health issue, and alongside local or disease specific successes, there has been an emergence, or re-emergence, of other causes of early onset visual impairment, particularly retinopathy of prematurity (in middle income settings) and cerebral visual impairment (within higher income settings). Improvements in maternal and neonatal health, and investment in and maintenance of national ophthalmic care infrastructure is key to reducing the burden of avoidable blindness. Therapeutic targets are emerging for childhood visual disorders, although novel therapies for diseases such as retinopathy of prematurity or retinal dystrophies are not without risk, and the hypothermic therapies which address CVI are still at an early stage. In order to reduce the burden of childhood blindness attributable to diseases previously considered 'untreatable',

particularly cerebral visual impairment and optic nerve hypoplasia, population based epidemiological studies are needed. Such research will determine natural history and putative risk factors, necessary for the elucidation of the pathogenetic mechanisms which will form the basis of future treatments.

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Figure legends:

Figure 1: Maturation of vision in the first two years of life

Derived from Salomao et al<sup>12</sup> and Mayer et al<sup>13</sup>

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Figure 2: Global prevalence of Childhood Blindness

Figures presented by economic region. Derived from Rahi et al<sup>1</sup>.

Prevalence per 10,000

Numbers of children affected in millions