Fourteen years of retinopathy of prematurity in KwaZulu-Natal, South Africa

by

Dr Jerusha Shanthi John

Submitted in partial fulfilment of the academic requirements

for the degree of MMed

in the Department of Ophthalmology

School of Clinical Medicine

College of Health Sciences

University of KwaZulu-Natal

Durban

2024

As the candidate's supervisors, we have approved this thesis for submission.

Signed: [redacted] Name: Dr Magritha du Bruyn Date: 23 September 2025

Signed: [redacted] Name: Dr Carl-Heinz Kruse Date: 23 September 2025

DECLARATION

I, Jerusha Shanthi John, declare that

(i) The research reported in this dissertation, except where otherwise indicated, is my original work.

(ii) This dissertation has not been submitted for any degree or examination at any other university.

(iii) This dissertation does not contain other persons' data, pictures, graphs or other information unless specifically acknowledged as being sourced from other persons.

(iv) This dissertation does not contain other persons' writing unless specifically acknowledged as being sourced from other researchers. Where other written sources have been quoted, then:

a) their words have been re-written but the general information attributed to them has been referenced;

b) where their exact words have been used, their writing has been placed inside quotation marks, and referenced.

(v) Where I have reproduced a publication of which I am an author, co-author or editor, I have indicated in detail which part of the publication was actually written by myself alone and have fully referenced such publications.

(vi) This dissertation does not contain text, graphics or tables copied and pasted from the Internet, unless specifically acknowledged, and the source is detailed in the dissertation and the References sections.

Signed: _____ Date: 23 September 2025

DEDICATION

There is a darkness that looms with doom, threatening to steal our vision,

But there are those who resist this foe,

The quest for light our mission.

So, to all premature infants at risk of ROP,

May your future be bright as we win the fight,

All for your right to see.

ACKNOWLEDGEMENTS

This mammoth project is incomplete without thanking all those involved who offered their unwavering support:

First, to God for the blessing of sight and the motivation of vision.

To my husband, my pillar, Albert, and my light-filled children, Samuel and Lydia, who have the utmost patience and understanding – your *joie de vivre* has been my saving grace.

To my parents, Eric and Vijie John, constant in chaos, who model the joy of academia and paying it forward.

To all my UKZN ophthalmology colleagues who have diligently recorded their findings on this vulnerable group of patients over all these years, making this audit possible.

To my supervisors:

Dr Magritha du Bruyn, whose calm advice and guidance have been pure gold throughout;

and finally, Dr Carl-Heinz Kruse, who painstakingly sat with me collecting and organising the data, which he also then statistically analysed, was moved to tears with me at the stories of these children, and who helped me navigate the labyrinth of putting it all together.

Thank you endlessly.

OVERVIEW OF THE THESIS

This thesis addresses a critical need in neonatal healthcare: preventing blindness and severe vision impairment caused by retinopathy of prematurity (ROP) among preterm infants in KwaZulu-Natal, South Africa. With advances in neonatal care enabling the survival of smaller, more vulnerable infants, ROP has become a pressing public health issue. This project aimed to evaluate the impact of the South African ROP screening guidelines introduced nearly a decade ago and to assess the current state of ROP detection and screening in KwaZulu-Natal. By analysing referral patterns, patient demographics, and screening outcomes, the study aimed to understand the effects of the guidelines and identify areas where care could be further improved.

To achieve these objectives, the study followed an approach that involved analysing clinical data on ROP referrals from neonatal intensive care units (NICUs) across eastern KwaZulu-Natal. This included examining ROP referral rates, patient demographics, screening compliance, and treatment numbers to capture trends before and after implementing the guidelines, the identification of trends and areas requiring intervention.

The project's outputs include an evaluation of the effectiveness of the ROP screening guidelines, revealing notable reductions in treatable ROP cases and improvements in neonatal eye health overall. However, it also uncovered persistent challenges, such as inconsistent referral practices across facilities, large variability in guideline adherence, and a concerning rate of missed follow-up appointments. These insights have implications for healthcare policy and practice, suggesting that while the guidelines are largely beneficial, targeted efforts are needed to address gaps in referral practices and patient follow-up.

The impact of this project is important for both clinical practice and public health policy. The project advocates for focused education and monitoring efforts, especially in facilities with high inappropriate referral rates, to enhance ROP screening efficacy. In doing so, the study supports ongoing improvements to neonatal care, aiming to safeguard vision health among the most vulnerable infant populations in South Africa and beyond.

TABLE OF CONTENTS

PART 1: THE REVIEW OF LITERATURE

The human retina, in its embryologic form, remains avascular until the fourth month of gestation. It is at this point when normal retinal vascularisation is expected to begin.[1] Retinopathy of prematurity (ROP) is a vasoproliferative disorder affecting the developing retinal vasculature of premature babies.[2] These infants are often of very low (1000g – 1500g) or extremely low (<1000g) birth weight (BW), very pre-term (28 – 32 weeks) or extreme pre-term (<28 weeks) gestational age (GA), may have other systemic conditions, and are potentially exposed to a hyperoxic environment because of this. It is postulated that this ambient higher concentration of oxygen retards the normal growth of retinal vessels and that the subsequent hypoxic state of the retina results in anomalous vascularisation.[1] It is also important to note that "larger" (1500g – 2500g BW) and "older" (>32 weeks GA) pre-term babies are not immune to this condition.[3, 4]

Blindness from ROP is a devastating, life-long burden on patients, their families, and society as a whole, the potentially profound visual impairment contributes to the need for sometimes inaccessible non-mainstream/special schooling, deepening unemployment levels, and lowering the socio-economy.[3] Initially named retrolental fibroplasia when first recognized as an epidemic in the 1940s in high-income countries (HICs) secondary to unrestricted and unmonitored 100% oxygen supplementation, then again as a second epidemic in the 1970s due to a deeper focus on bettering neonatal care,[5] ROP has subsequently ushered in a further epidemic around the world in middle-income countries(MICs) as a result of waves of varying improvement in neonatal management and increased survival of pre-term babies.[6] As advances continue to be made in various pockets around the developing world in the way of enhanced attention to and therefore greater survival for the premature neonate, so too grows the need for faster, wider, and more effective screening programs for ROP detection.[5, 7] In 2011, Tasman argued that the world may have indeed been on the brink of another ROP epidemic,[8] therefore we as health care workers in MICs must be ready to engage this inevitable opponent.[5]

ROP rates differ across countries all over the world. Middle-income countries (MICs) are in the process of up-scaling neonatal services, albeit in varying degrees, and therefore have higher rates of ROP than high-

income countries (HICs), where neonatal care is advanced and access to screening and treatment for ROP is well-established; and babies who develop ROP in MICs also have a higher average birth weight and gestational age. [4, 6, 9] It is thus generally considered that the 3rd epidemic wave of ROP has fallen on the shores of the developing world, where country-specific guidelines for screening are required.[6] In contrast, low-income countries (LICs) have lower rates of ROP. This is most likely linked to an inferior, or absence of, functional and infrastructural levels of neonatal services in these countries, resulting in higher preterm neonatal mortality rates. [3, 6]

In HICs such as Canada and the UK, screening guidelines are aimed at babies ≤30 weeks GA or ≤1250g BW[10], and <32 weeks GA or <1501g BW[11] respectively. Jefferies reported, according to data from the Canadian Neonatal Network in 2016, that in babies born at <31 weeks GA, 40% – 50% develop ROP, 7% – 8% are severe, and 5% – 6% need treatment.[12] In 2014 in the UK, the median GA of babies who received treatment was 25 weeks (extreme pre-term), while the median BW was 706g (extremely low birth weight – ELBW).[6] The American Academy of Paediatrics (AAP) policy of 2013 in the USA recommends screening infants born at ≤30 weeks GA or ≤1500g BW, or selected babies at >30 weeks GA or 1500g – 2000g BW who have had an unstable clinical course and are therefore at high risk of developing ROP.[13]

The Postnatal growth and retinopathy of prematurity study (G – ROP),[14] the largest study to date, with a cohort of 11,261 screened babies, and conducted in 30 hospitals across the USA and Canada, showed a treatable ROP rate of 12.9%, which occurred mostly in those infants with a BW of <1251g. Quinn *et al.* conducted a secondary analysis of data from the G-ROP study and found the mean GA of babies with Type 1[15, 16] (treatable) ROP to be 24-25 weeks, the mean BW 604g – 741g, echoing the UK findings of extreme pre-term GA and ELBW, while the overall ROP rate was 43.1%.[17] According to Yu *et al.*, who also secondarily analysed data from the G-ROP study, the rate of type 1 ROP in North America was 5.9% and decreased with older GA at birth (28.8% for GA ≤23 weeks, 0.2% for GA of 31–32 weeks) and no infants with GA >32 weeks developed type 1 ROP[18], again reflecting the sentiment of extreme pre-term infants requiring treatment.

The picture appears different in developing countries or MICs, where there is variable up-scaling of neonatal care and ROP screening regimes.[6, 9] Yan *et al.* report that in Northwest China, the rate of ROP

detection had increased from 2.3% to 16.12%, whereas that of treatable ROP had increased from 0% to 5.6% during the period from 2008 to 2019.[19] In Bangladesh, national ROP screening began in 2010 and increased in 2013.[20] At a leading ROP screening unit there, 50 babies were screened in 2012, which swelled to 296 babies in 2018. There, Niyonzima *et al.*[20] showed that 60% of infants with ROP were >32 weeks (moderate to late pre-term GA),[21] while the mean BW was 1563g (low birth weight – LBW), 37% were at stage 2 ROP,[22] and 61% needed treatment. The ROP incidence among referrals was 34.9%, and 53% of these required treatment (10.5% of these being aggressive ROP). Of note was that 14 babies were older than 37 weeks GA (not pre-term), and 4 of these infants needed treatment for ROP. Onyango[23] showed Kenya's ROP rate to be 41,7% (mean GA 29.9 weeks – very pre-term; mean BW 1280g – very low birthweight, VLBW), while the treatable ROP rate was 20.9%. Ojaghi[24] showed Iran's ROP incidence among referrals to be 26.8%, the treatable ROP rate was 21.5%, while risk factors were a GA of <32.5weeks (up to moderate pre-term) and BW <1725g (up to LBW).

In South Africa, the rate of treatable ROP also differs amongst different provinces. In Pretoria, Delport *et al.*[25] described an incidence of ROP of 24.5%, whereas that of treatable ROP was 4.3% (3.2% in infants <1250 g). In Cape Town, Keraan *et al.*[26] found the prevalence of ROP was 29.6% (mean GA 29.2 weeks – very pre-term; mean BW 988g - ELBW) and that of treatable ROP was 1.5%. In Johannesburg, Dadoo and Ballot[27] found the incidence of ROP among inpatients screened was 11.1%; and among those who returned for follow-up as outpatients, the rate was 17%; and the rate of treatable ROP was just over 4%. These differences amongst the provinces might also be an indication of the level of neonatal services in different parts of our country. However, most of these studies were performed several years ago and results may be different now.

Treatable ROP rates also change over time, as outlined by du Bruyn and Visser,[4] where the number of preterm babies in KZN requiring treatment for ROP decreased two-fold from 2011 to 2015, after the implementation of ROP screening and management guidelines for South Africa.[28] Timeous referrals to the ophthalmologist, with the regulation of oxygen administration and monitoring of the premature infant, were the most important factors responsible for this decrease in ROP rates, as found in their study.

This present study is aimed at comparing current treatable ROP rates over a 14-year period at Inkosi Albert Luthuli Central Hospital, the quaternary health institution in KwaZulu-Natal, making inferences regarding the quality and propitiousness of ROP referrals, with a view to further understand and continue to improve the impact we make on the vision of our children in KZN, through our own ROP screening programs.

References

1. Kanski JJ, Bowling B. Kanski's clinical ophthalmology e-book: a systematic approach: Elsevier Health Sciences; 2015.
2. Zin A, Gole GA. Retinopathy of prematurity-incidence today. Clinics in perinatology. 2013;40(2):185-200.
3. Ademola-Popoola DS, Onakoya AO, Ezisi CN, Okeigbemen VW, Aghaji AE, Musa KO, *et al.* Case series of retinopathy of prematurity blindness in Nigeria: A wakeup call to policy makers, hospitals, ophthalmologists and paediatricians. Nigerian Postgraduate Medical Journal. 2021;28(4):303.
4. du Bruyn A, Visser L. Eight years of treatable retinopathy of prematurity in KwaZulu-Natal: are we winning the battle? South African Ophthalmology Journal. 2017;12(2):8 – 10.
5. Kiranmayee PS, Kalluri V. India to gear up to the challenge of "third epidemic" of retinopathy of prematurity in the world. Indian Journal of Ophthalmology. 2019;67(6):726.
6. Gilbert C, Malik AN, Nahar N, Das SK, Visser L, Sitati S, *et al.*, editors. Epidemiology of ROP update–Africa is the new frontier. Seminars in Perinatology; 2019: Elsevier.
7. Kulkarni S, Gilbert C, Zuurmond M, Agashe S, Deshpande M. Blinding retinopathy of prematurity in Western India: Characteristics of children, reasons for late presentation and impact on families. Indian pediatrics. 2018;55(8):665-70.
8. Tasman W. Retinopathy of prematurity: do we still have a problem?: the Charles L. Schepens lecture. Arch Ophthalmol. 2011;129(8):1083-6.

9. Blencowe H, Moxon S, Gilbert C. Update on blindness due to retinopathy of prematurity globally and in India. Indian pediatrics. 2016;53:S89-S92.

10. Jefferies A. Retinopathy of prematurity: recommendations for screening. Paediatrics & Child Health. 2010;15(10):667-70.

11. Wilkinson A, Haines L, Head K, Fielder A. UK retinopathy of prematurity guideline. Eye. 2009;23(11):2137-9.

12. Jefferies AL, Society CP, Fetus, Committee N. Retinopathy of prematurity: An update on screening and management. Paediatrics & child health. 2016;21(2):101-4.

13. Fierson W. American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus; American Association of Certified Orthoptists. Screening examination of premature infants for retinopathy of prematurity. Pediatrics. 2013;131(1):189-95.

14. Binenbaum G, Tomlinson LA. Postnatal growth and retinopathy of prematurity study: rationale, design, and subject characteristics. Ophthalmic epidemiology. 2017;24(1):36-47.

15. Group CfRoPC. Multicenter trial of cryotherapy for retinopathy of prematurity: preliminary results. Pediatrics. 1988;81(5):697-706.

16. Group ETfRoPC. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. Archives of Ophthalmology (Chicago, Ill: 1960). 2003;121(12):1684-94.

17. Quinn GE, Ying G – s, Bell EF, Donohue PK, Morrison D, Tomlinson LA, *et al.* Incidence and early course of retinopathy of prematurity: secondary analysis of the postnatal growth and retinopathy of prematurity (G – ROP) study. JAMA ophthalmology. 2018;136(12):1383-9.

18. Yu Y, Tomlinson LA, Binenbaum G, Ying G – s. Incidence, timing and risk factors of type 1 retinopathy of prematurity in a North American cohort. British Journal of Ophthalmology. 2021;105(12):1724-30.

19. Yan H-X, Li M-H, Wang L, Wu L, Fan J, Zhou Y, *et al.* Twelve-year profile of screening results of retinopathy of prematurity at a tertiary care institute in Northwest China. International Journal of Ophthalmology. 2022;15(2):312.

20. Niyonzima JC, Nahar N, Chowdhury M, Das SK, Rahman M. Characteristics of babies referred for Retinopathy of prematurity screening and management to a tertiary eye hospital of Bangladesh, a database analysis. 2019.

21. Vogel JP, Chawanpaiboon S, Moller A-B, Watananirun K, Bonet M, Lumbiganon P. The global epidemiology of preterm birth. Best Practice & Research Clinical Obstetrics & Gynaecology. 2018;52:3-12.

22. Chiang MF, Quinn GE, Fielder AR, Ostmo SR, Paul Chan RV, Berrocal A, *et al.* International Classification of Retinopathy of Prematurity, Third Edition. Ophthalmology. 2021;128(10):e51-e68.

23. Onyango O, Sitati S, Amolo L, Murila F, Wariua S, Nyamu G, *et al.* Retinopathy of prematurity in Kenya: prevalence and risk factors in a hospital with advanced neonatal care. Pan African Medical Journal. 2018;29(1):1-7.

24. Ojaghi H, Fekri Y, Momeni N, Amani F. Retinopathy of prematurity (ROP) in Ardebil (North West of Iran): Prevalence and Risk factors. Pakistan Journal of Medical and Health Sciences. 2021;15(5):1557-63.

25. Delport SD, Swanepoel JC, Odendaal PJ, Roux P. Incidence of retinopathy of prematurity in very-low-birth-weight infants born at Kalafong Hospital, Pretoria. South African Medical Journal. 2002;92(12):986-90.

26. Keraan Q, Tinley C, Horn A, Pollock T, Steffen J, Joolay Y. Retinopathy of prematurity in a cohort of neonates at Groote Schuur Hospital, Cape Town, South Africa. South African Medical Journal. 2017;107(1):64-9.

27. Dadoo Z, Ballot D. An evaluation of the screening for retinopathy of prematurity in very-low-birth-weight babies at a tertiary hospital in Johannesburg, South Africa. South African Journal of Child Health. 2016;10(1):79-82.

28. Visser L, Singh R, Young M, Lewis H, McKerrow N. Guideline for the prevention, screening and treatment of retinopathy of prematurity (ROP). S Afr Med J. 2013;103(2):116-25.

PART 2: SUBMISSION READY MANUSCRIPT

Trends over fourteen years of retinopathy of prematurity referrals in KwaZulu-Natal, South Africa

John JS[§], Kruse C[§], du Bruyn M[§]

§ Department of Ophthalmology, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa

Corresponding author: Jerusha Shanthi John

https://orcid.org/0009-0007-0709-7836

JerushaJohn+ROP@gmail.com

Co-authors: Carl-Heinz Kruse

https://orcid.org/0000-0002-8805-8383

RuralEye@gmail.com

Magritha du Bruyn

https://orcid.org/0000-0002-0120-3438

aritha2@gmail.com

Synopsis

This article explores retinopathy of prematurity (ROP), a serious eye condition that primarily affects premature infants and can lead to blindness if untreated. The study investigates the current landscape of ROP screening and management, especially within middle-income countries, where access to standardized screening and treatment is often limited.

Study question

How have the new South African screening and treatment guidelines for retinopathy of prematurity (ROP) affected the screening and detection of the condition, in this middle-income country with limited healthcare resources?

What's already known

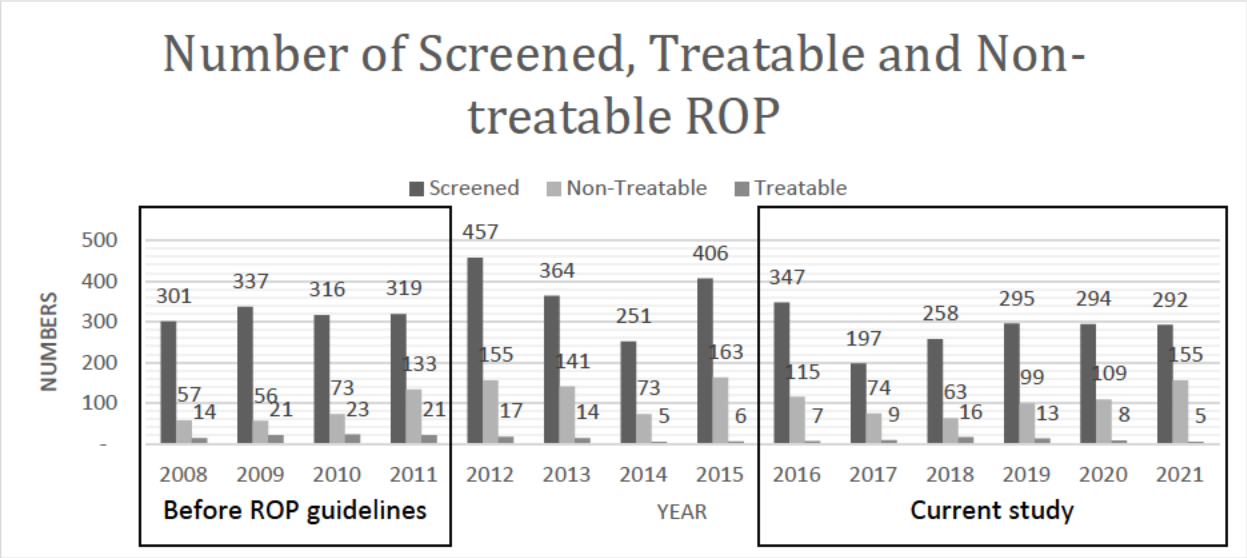
Retinopathy of prematurity is a (mostly) preventable cause of blindness in preterm infants, but the incidence rates remain high in those born in low- and middle-income regions. Standardized screening protocols and timely interventions can prevent or mitigate severe visual impairment. However, access to resources and consistency in applying guidelines vary significantly, leading to disparities in care and outcomes.

What this study adds

This study emphasizes the critical need for accessible, country-specific ROP screening and management protocols in middle-income regions. By reviewing existing guidelines and highlighting gaps in current healthcare infrastructure, the study advocates for screening and treatment guidelines tailored to each country or region. The findings reinforce the importance of ROP education, early detection and appropriate referral pathways, which could significantly reduce the burden of blindness in affected populations.

Tweetable quote

New guidelines on retinopathy of prematurity (ROP) have halved treatable cases in KwaZulu-Natal, thanks to oxygen mixers in NICUs and better screening protocols. While progress is clear, missed follow-ups and inconsistent referrals show there's more to do to protect neonatal eye health. #ROP #NeonatalCare



Abstract

Background

New Retinopathy of Prematurity (ROP) guidelines were introduced in South Africa in 2012.

Objectives

This study examines ROP referral trends a 14-year period at a quaternary state hospital in South Africa.

Methods

We retrospectively compared the rate of ROP referrals in the final six-year period (2016 to 2021), to two previous periods: 2008 to 2011, (before ROP guidelines), and 2012 to 2015 (after South African ROP guideline implementation). Raw data from the first study were re-analysed to ensure parity with our new data. We also ascertained referral appropriateness for the treated babies and compared the rates of treatable ROP between referring hospitals.

Results

Referrals were received from seven hospitals. One-third of all cases were inappropriately referred, ranging from 22.8% to 60.6% per facility. The level of the hospital had no bearing on the appropriateness of the referrals. The birth gestational age of the average referred patient has been steadily decreasing. The mean birthweight, however, has remained unchanged. Despite an increase in population size in the province, the referral numbers for ROP screening stayed the same. Between a fifth and a third of all babies referred for ROP screening defaulted follow-up visits before it was safe to stop.

Conclusions

The introduction of the South African Guidelines on ROP seems to have made improvements in referrals. Treatable ROP numbers have halved, and this reduction has endured for almost a decade. There is, however, still much room for augmenting interdisciplinary communication and enhancing efforts to prevent the worsening of current trends.

Keywords

Retinopathy of prematurity (ROP)

Premature

Screening guidelines

Neonatal care

Middle-income countries

Referral

Word count:

2 952 (Main text, excluding tables, figures and references)

Main Text

Background

The embryologic retina is avascular until the fourth month of gestation, when normal retinal vascularisation should begin,[1] reaching its full extent around gestational week 40. Retinopathy of prematurity (ROP) is a vasoproliferative disorder affecting the developing retinal vasculature of preterm babies.[2] These infants are often of very low (1000g – 1500g) or extremely low (<1000g) birthweight (BW), very pre-term (28 – 32 weeks) or extreme pre-term (<28 weeks) gestational age (GA), may have other systemic conditions and, hence, be exposed to a relatively hyperoxic environment. It is postulated this ambient higher concentration of oxygen retards normal retinal vessel growth, the subsequent hypoxic retinal state resulting in its anomalous vascularisation.[1] It is important to note that "larger" (1500g – 2500g BW) and "older" (>32 weeks GA) pre-term babies are not immune to this condition,[3, 4] the end-stage of which is retinal detachment, yielding total/near-total loss of vision.

Blindness from ROP is a devastating life-long burden on patients, their families, and society as a whole, the potentially profound visual impairment contributes to the need for often inaccessible non-mainstream/special schooling, deepening unemployment levels, and depression of the socio-economy.[3] Initially named retrolental fibroplasia when first recognised as an epidemic in the 1940s in high-income countries (HICs) secondary to unrestricted and unmonitored 100% oxygen supplementation, then again as a second epidemic in the 1970s due to a deeper focus on bettering neonatal care,[5] ROP has subsequently ushered in a further epidemic around the world in middle-income countries (MICs) due to the varying improvement in neonatal management and increased survival of pre-term babies there.[6] As advances continue to be made in various pockets around the developing world in the way of enhanced attention to and therefore greater survival for the preterm neonate, so too grows the need for faster, wider, and more effective screening programs for ROP detection.[5, 7] In 2011, Tasman argued that the world may have indeed been on

the brink of another ROP epidemic,[8] therefore we as health care workers in MICs must be ready to engage this inevitable opponent.[5]

ROP rates differ across countries all over the world. Middle-income countries (MICs) are in the process of up-scaling neonatal services, albeit in varying degrees, and therefore have higher rates of ROP than high-income countries (HICs), where neonatal care is advanced and access to screening and treatment for ROP is well-established. Babies who develop ROP in MICs also have a higher average birthweight and gestational age. [4, 6, 9] It is thus generally considered that the 3rd epidemic wave of ROP has fallen on the shores of the developing world, where country-specific guidelines for screening are required.[6] In contrast, low-income countries (LICs) have lower rates of ROP. This is most likely linked to an inferior, or absence of, functional and infrastructural levels of neonatal services in these countries, resulting in higher preterm neonatal mortality rates. [3, 6]

In HICs such as Canada and the UK, screening guidelines are aimed at babies ≤30 weeks GA or ≤1250g BW,[10] and <32 weeks GA or <1501g BW respectively.[11] Jefferies reported, according to data from the Canadian Neonatal Network in 2016, that in babies born at <31 weeks GA, 40% – 50% develop ROP, 7% – 8% are severe, and 5% – 6% need treatment.[12] In 2014 in the UK, the median GA of babies who received treatment was 25 weeks (extreme pre-term), while the median BW was 706g (extremely low birthweight – ELBW).[6] The American Academy of Paediatrics (AAP) policy of 2013 in the USA recommends screening infants born at ≤30 weeks GA or ≤1500g BW, or selected babies at >30 weeks GA or 1500g – 2000g BW who have had an unstable clinical course and are therefore at high risk of developing ROP.[13]

The postnatal growth and retinopathy of prematurity study (G – ROP),[14] the largest study to date, with a cohort of 11 261 screened babies, and conducted in 30 hospitals across the USA and Canada, showed a treatable ROP rate of 12.9%, which occurred mostly in those infants with a BW of <1251g. Quinn *et al.* conducted a secondary analysis of data from the G-ROP study,[15, 16] and found the mean GA of babies with Type 1 (treatable) ROP to be 24-25 weeks, the mean BW 604g – 741g, echoing the UK findings of extreme pre-term GA and ELBW, while the overall ROP rate

was 43.1%.[17] According to Yu *et al.*,[18] who also secondarily analysed data from the G-ROP study, the rate of type 1 ROP in North America was 5.9% and decreased with older GA at birth (28.8% for GA ≤23 weeks, 0.2% for GA of 31 – 32 weeks) and no infants with GA >32 weeks developed type 1 ROP, again reflecting the sentiment of extreme pre-term infants requiring treatment.

The picture appears different in developing countries or MICs, where there is variable up-scaling of neonatal care and ROP screening regimes.[6, 9] Yan *et al.* report that in Northwest China, the rate of ROP detection had increased from 2.3% to 16.2%, whereas that of treatable ROP had increased from 0.0% to 5.6% during the period from 2008 to 2019.[19] In Bangladesh, national ROP screening began in 2010 and increased in 2013.[20] At one of their leading ROP screening units, 50 babies were screened in 2012, which swelled to 296 babies in 2018. There, Niyonzima *et al.*[20] showed that 60% of infants with ROP were >32 weeks (moderate to late pre-term GA),[21] while the mean BW was 1563g (low birthweight - LBW), 37% were at stage 2 ROP[22], and 61% needed treatment. The ROP incidence among referrals was 34.9%, and 53% of these required treatment (10.5% of these being aggressive ROP). Of note was that 14 babies were older than 37 weeks GA (not pre-term), and 4 of these infants needed treatment for ROP. Onyango[23] showed Kenya's ROP rate to be 41.7% (mean GA 29.9 weeks – very pre-term, mean BW 1280g – very low birthweight, VLBW), while the treatable ROP rate was 20.9%. Ojaghi[24] showed Iran's ROP incidence among referrals to be 26.8%, the treatable ROP rate was 21.5%, while risk factors were a GA of <32.5weeks (up to moderate pre-term) and BW <1725g (up to LBW). Collectively these rates are higher in MICs than HICs, including "larger" and "older" pre-term infants.

In South Africa, the rate of treatable ROP also differs amongst provinces. In Pretoria, Delport *et al.*[25] described an incidence of ROP of 24.5%, whereas that of treatable ROP was 4.3% (3.2% in infants <1250 g). In Cape Town, Keraan *et al.*[26] found the prevalence of ROP was 29.6% (mean GA 29.2 weeks – very pre-term, mean BW 988g - ELBW) and that of treatable ROP was 1.5%. In Johannesburg, Dadoo and Ballot[27] found the incidence of ROP among inpatients screened was 11.1%, and among those who returned for follow-up as outpatients, the rate was 17%, and the rate of treatable ROP was just over 4%. These differences amongst the provinces might also be

an indication of the level of neonatal services in different parts of our country. However, most of these studies were performed several years ago and results may be different now.

Treatable ROP rates also change over time, as outlined by du Bruyn and Visser,[4] where the number of preterm babies in KZN requiring treatment for ROP was halved from 2011 to 2015, after the implementation of ROP screening and management
for South Africa.[28] Timeous referrals to the ophthalmologist, with the regulation of oxygen administration and monitoring of the preterm infant, were the most important factors responsible for this decrease in ROP rates, as found in their study.

This present study is aimed at comparing current treatable ROP rates over a14-year period at Inkosi Albert Luthuli Central Hospital, the quaternary health institution in KwaZulu-Natal province, making inferences regarding the quality and propitiousness of ROP referrals, with a view to further understand and continue to improve the impact we make on the vision of our children in KZN, through our own ROP screening programs.

Methods

This study was a quantitative, retrospective, observational, descriptive audit by chart review of all preterm babies referred to Inkosi Albert Luthuli Central Hospital (IALCH) for retinopathy of prematurity (ROP) screening. IALCH is a quaternary-level referral state hospital in the coastal province of KwaZulu-Natal, South Africa. Ethical approval was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BREC/00005453/2023), as well as the provincial and facility ethics committees.

This study follows a previous study that investigated ROP referrals between 2008 and 2015. The primary aim was to compare the rate of treatable ROP in the final six-year period (2016 – 2021) at this hospital, to two previous periods: 2008 to 2011, (before ROP guidelines), and 2012 to 2015 (after South African ROP guideline implementation) at the same hospital. The raw data of the first study were re-analysed to ensure parity with our new data. The secondary objectives were to ascertain the referral appropriateness for the treated babies and compare the rate of treatable ROP between the referring hospitals.

The considered variables included appropriateness of referral as per South African guidelines (Figure 1), gestational age at birth, at the first screening visit and the last screening visit, birthweight, stage of ROP at presentation and before treatment, treatable disease numbers and treatment type.[*]

[*] Treatment of ROP is dependent on the stage and extent of ROP:

In type 1 disease, treatment is aimed at reducing or halting the drive of vascular endothelial growth factor (VEGF), either by direct injection of an anti-VEGF drug into the vitreous cavity, or by suppressing the source of the expression of VEGF by lasering the remaining signalling ischaemic or poorly developing avascular retinal tissue.

Type 2 disease on the other hand, is that which does not need treatment, yet is serious enough to require closer observation on a biweekly basis to detect if the disease is progressing to Type 1/treatable disease.

If ROP progresses, advanced stages involve consequences of untreated/relentless neovascularisation – gliotic traction on the young retina, with resultant detachment thereof. This would require surgery – pars plana vitrectomy – to attempt repair of the damaged retina under general anaesthesia, if not already inoperable.

According to the South African guidelines for ROP screening, appropriate screening criteria include:

Whom to screen:

Low birth weight (LBW) <1500g, or

Prematurity <32 weeks' gestational age, or

Birth weight between 1500g – 2000g

and sub-optimal oxygen monitoring

and at least one of the following:

- cardio-respiratory arrest
- severe HIE
- more than 2 neonatal blood transfusions
- a total blood transfusion
- family history of ROP

When to screen: (whichever comes later)

4 – 6 weeks chronological age, or

31 – 33 weeks corrected gestational age

Figure 1: South African guidelines on appropriate ROP referral

Maternal and HIV status were captured to explore any association with ROP. The authors are not aware of any research associating HIV with ROP, but HIV has been associated in multiple countries with preterm birth, low birth weight, and being small for gestational age.[29, 30] Notably, these associations persisted regardless of antiretroviral treatment status, income level, or geographic region. Although HIV has no known association with ROP, its influence on prematurity justifies HIV status inclusion in data collection.

Only babies that were referred to IALCH were included in this study. Babies not referred, even if inappropriately so, were not included. The effects of this confounder were minimised since both groups being compared will have the same class of missing cases.

Data were manually entered and collated onto an Excel® spreadsheet (Microsoft Corp., USA). All data at the institution are kept on electronic health records. As confirmation, theatre notes were searched for treatment of ROP.

The Excel spreadsheet was exported to R (R Studio®, USA) for analysis. Categorical variables were expressed as frequencies and percentages and compared using the Chi-squared test. Continuous variables were expressed as medians and interquartile range (IQR) as the distribution was expected to be non-normal. The Wilcoxon test was used for comparison of non-parametric data. The alpha level was set at 0.05 and a p-value of less than 0.05 was deemed significant.

Results

The demographics of our study cohort are summarised in Table 1. A total of 1710 cases were included in the study and no cases were excluded. 49.9% were female and the majority (93.3%) were of Black African descent. Data on maternal HIV status were available in 824 patients of which 46% were positive. PCR test results for HIV on the neonates (n 171) had a positivity rate of 2.9%.

	n	%
Sex (n = 1710)		
Male	855	50.0%
Female	854	49.9%
Unknown	1	0.1%
Race		
African	1595	93.3%
Indian	78	4.6%
Coloured	28	1.6%
White	5	0.3%
Other	4	0.3%
HIV Exposure (n = 824)		
Exposed	382	46.4%
Not exposed	442	53.6%
HIV PCR (n = 171)		
Positive	5	2.9%
Negative	166	97.1%

Table 1: Demographics

The first full year (2016) saw the greatest number of screening cases (n 347) as shown in Figure 2. The largest number of ROP cases was seen in 2021 (n 160) which is 54.8% of all screened babies for that year. The highest number of treated cases was in 2018 (n 16) while the lowest was in 2021 (n 5).

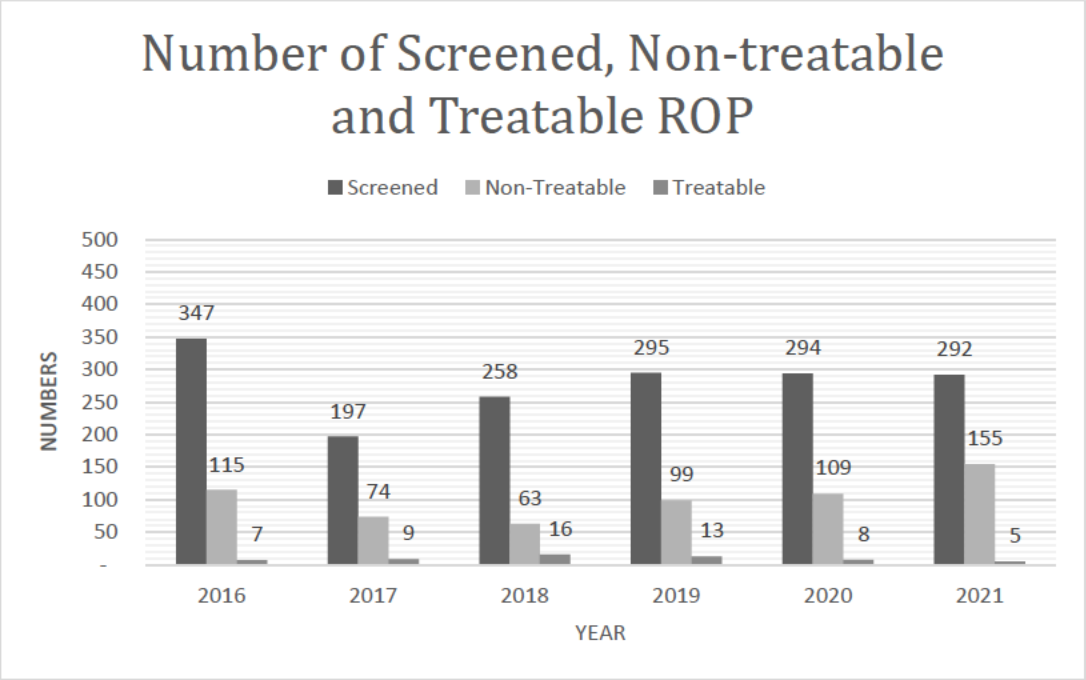


Figure 2: Number of cases screened per year, with the number of cases with clinical ROP divided into treatable cases, and cases that did not meet the criteria for treatment.

Mean gestational age at birth was 30.3 weeks (SD 2.3, Range 23, 41). Figure 3 shows the variation over the six-year study, during which the year 2018 saw the lowest mean birth gestational age recorded in all cases with ROP, both treatable and non-treatable, while the highest mean birth gestational age in non-treatable cases was seen in 2016 and 2019. In general, gestational age was lowest in the treatable ROP group.

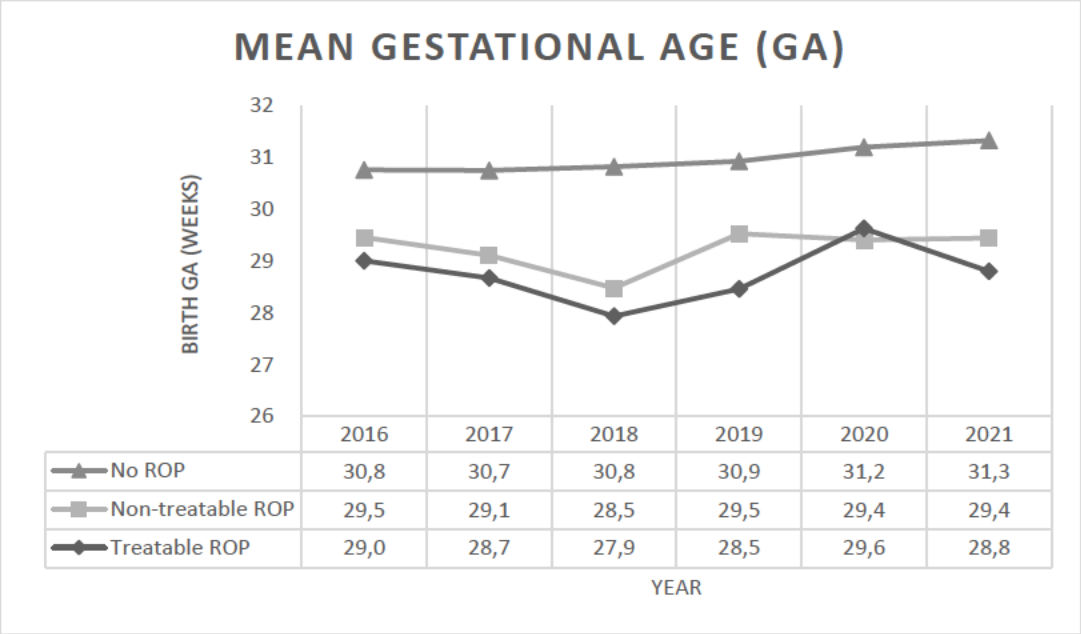


Figure 3: Mean gestational age at birth for all screened, non-treatable and treatable ROP cases.

The mean birthweight for all babies was 1271 g (SD 302, Range 550, 4580) and the variation over the study's six years is depicted in Figure 4. During this time, cases with non-treatable ROP saw the lowest mean birthweight recorded in 2018, while this group's highest mean birthweight was seen in 2016, followed closely by 2020. As expected, the treatable ROP group recorded the lowest mean birth weights during all study years.

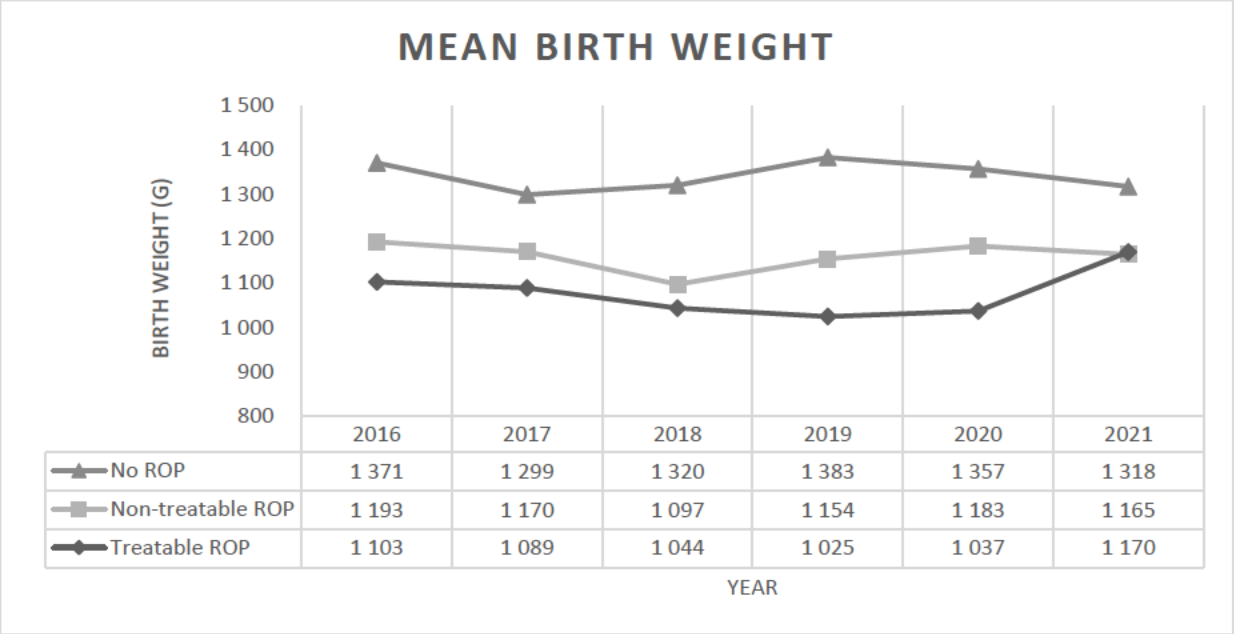


Figure 4: Mean birth weight for all screened, treatable and non-treatable ROP cases.

Referrals were received from seven different hospitals, outlined in Table 2, ranging from primary facilities (n 3) to one quaternary service-level hospital. Of these, two hospitals (one secondary and one tertiary level) referred the majority of patients (71.4%). Overall, one-third of cases were inappropriately referred, ranging from 22.8% to 60.6%. The level of the hospital had no bearing on the appropriateness of the referrals.

Incorrect referrals included 190 babies (11.1%) that were both more than 32 weeks birth gestational age as well as a birth weight more than 1499g, two babies (0.1%) who were referred too early and 480 (28.1%) who were referred later than the guidelines recommend. For some of these babies, several referral errors were found, so the actual number of incorrect referrals totals 641 (37.5%).

Contingency Tables

Referral Hospital	Level	Appropriate referral			Total
		Yes	No		
A	4	28	43	60.6%	71
B	3	281	166	37.1%	447
C	2	281	134	32.3%	415
D	2	71	21	22.8%	92
E	1	49	21	30.0%	70
F	1	37	18	32.7%	55
G	1	24	33	57.9%	57
Total		771	436	36.1%	1207

χ^2 Tests

	Value	df	p
χ^2	42	6	< .001
N	1207		

Table 2: Referral hospitals – appropriate referral according to the official South African guidelines

Table 3 shows the variation in the percentage of babies with ROP from each of the facilities. Treatable ROP ranged from 0.2% to 5.2% of all referrals. The number of babies that had ROP not requiring treatment, ranged from 30.4% to 50.0% of referrals from each referring centre. Hospital level was not an indicator of the percentage of referrals with clinical ROP.

Contingency Tables

Referral Hospital	Level	Diagnosis					
		ROP for treatment		ROP not for treatment		No ROP	Total
A	4	3	4.2%	35	49.3%	33	71
B	3	16	3.6%	206	46.1%	225	447
C	2	1	0.2%	128	30.8%	286	415
D	2	2	2.2%	28	30.4%	62	92
E	1	1	1.4%	12	17.1%	57	70
F	1	3	5.2%	29	50.0%	26	58
G	1	2	3.5%	25	43.9%	30	57
Total		28	2.3%	463	38.3%	719	1210

χ^2 Tests

	Value	df	p
χ^2	65.8	12	< .001
N	1210		

Table 3: Referral hospitals – Breakup of referral numbers into treatable ROP, ROP not requiring treatment and referrals with no evidence of ROP.

The number of patients that defaulted (did not return to the eye clinic despite being given a follow-up appointment) was 458 of the 1 710 (26.8%), and ranged from 20.7% in 2020, to 34.0% in 2017.

Analysis of HIV status of the mother and child showed that these made no difference to the presence of ROP (p 0.088) and had no effect on treatable ROP (p 0.219).

Comments

These data can be directly compared to a similar study at the same institution which was done in the preceding eight years (n 2 345). In the first study, the data were divided into two periods: 2008 – 2011 were the four years prior the adoption of the South African ROP Guidelines. The second period (2012 – 2015) was used comparatively to see if the guidelines had made any difference to referral and disease patterns, which was undeniably the case, with the number of cases requiring treatment decreasing by half. Our data for 2016 – 2021 are displayed as the third group in figures 4 – 6.

Figure 4 shows that the mean number of referrals per year stayed the same after the guidelines had been instituted (period 1: 346, period 2: 349) (p 0.201). The decrease in the period over the final six-year period did not reach significance (p 0.087).

The number of referred babies had a positive correlation with the numbers that had clinical ROP. It did not, however, correlate with the number of ROP patients that required treatment. The mean number of babies that met the criteria for ROP treatment, fell from 19.2 in the first period, to 8.7 and 9.7 in the following two periods respectively (p 0.05). This is a 45.3% decrease in treatable ROP since the introduction of the South African ROP Guidelines, and this improvement has indeed lasted for at least a decade.

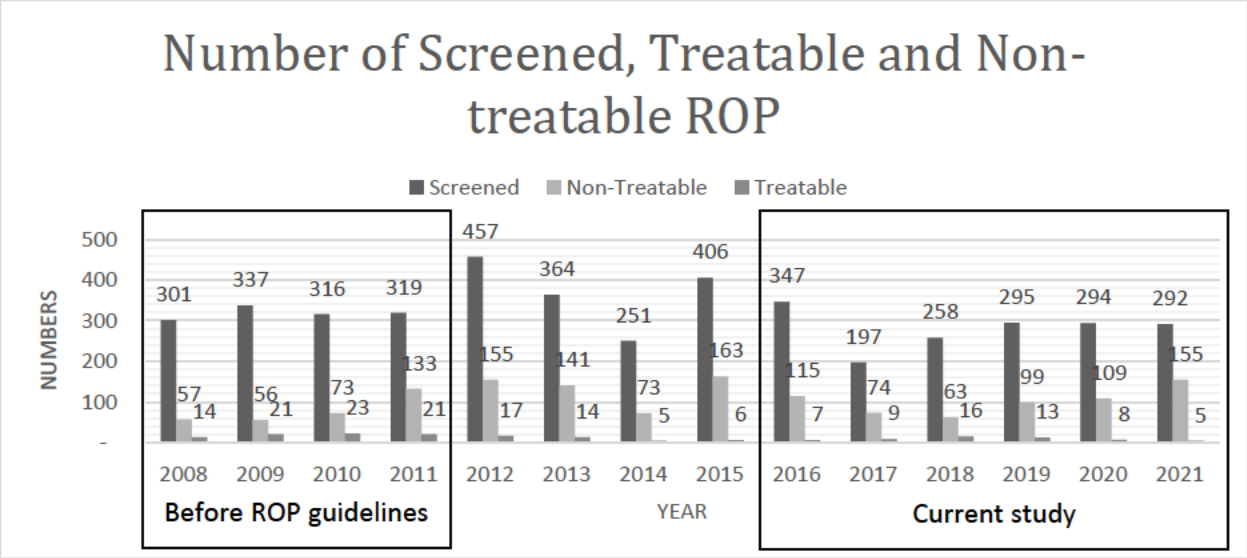


Figure 5: Comparison of three periods - Number of cases screened per year, with the number of cases with clinical ROP divided into treatable cases, and cases that did not meet the criteria for treatment.

The mean birthweight for all cases (Figure 5) decreased over the three periods, from 1335 g to 1307 g (p 0.044) and then to 1271 g (p 0.002). This is most likely related to the improving survival of very low-weight babies, as technology, services and/or neonatology skills improve.

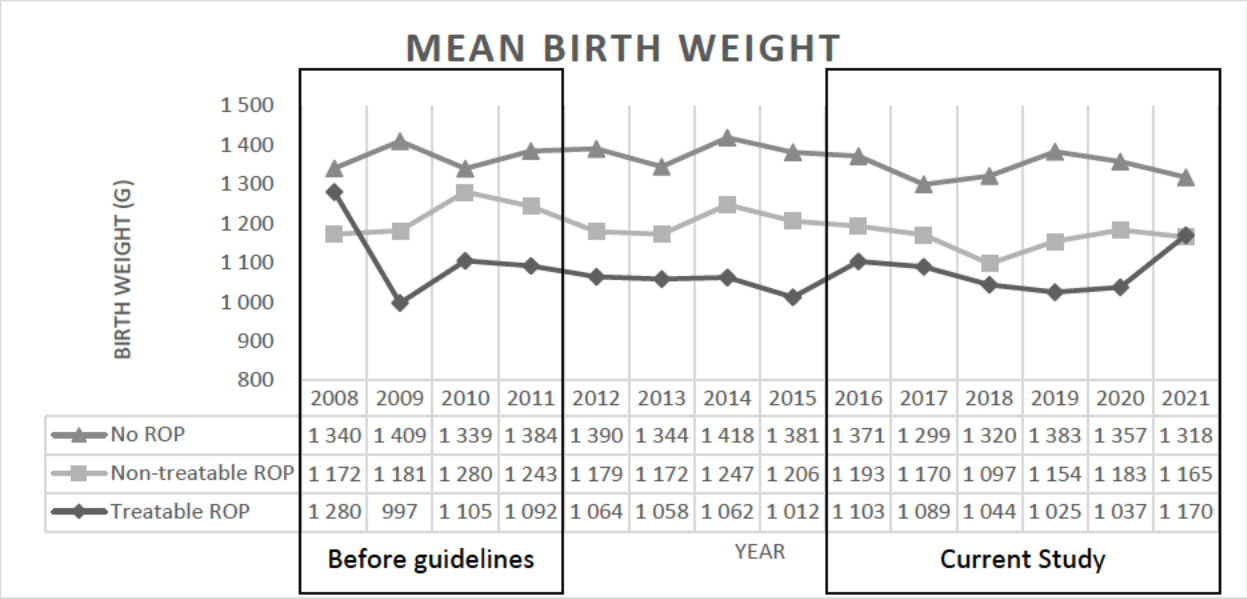


Figure 6: Comparison of three periods - Mean birth weight for all screened, treatable and non-treatable ROP cases.

The mean gestational age at birth for all screened babies (figure 5) decreased from 30.4 weeks to 30.1 weeks in the periods straddling the ROP guideline intervention ($p<0.001$), but counter-intuitively, increased back to 30.3 weeks in the final period (p 0.349 to the first period).

The reasons for older but smaller babies in the final six years are unknown. An increased rate of improper referrals of larger babies is not the cause, since the referral rates of babies with a birthweight >1 499 g, dropped from 24.1% and 23.1% in the first two periods respectively, to 19.5% in the last. However, according to Chu *et al.*,[31] it would appear that intra-uterine growth retardation plays a considerably more substantial role in producing severe and treatable disease, independent of gestational age.

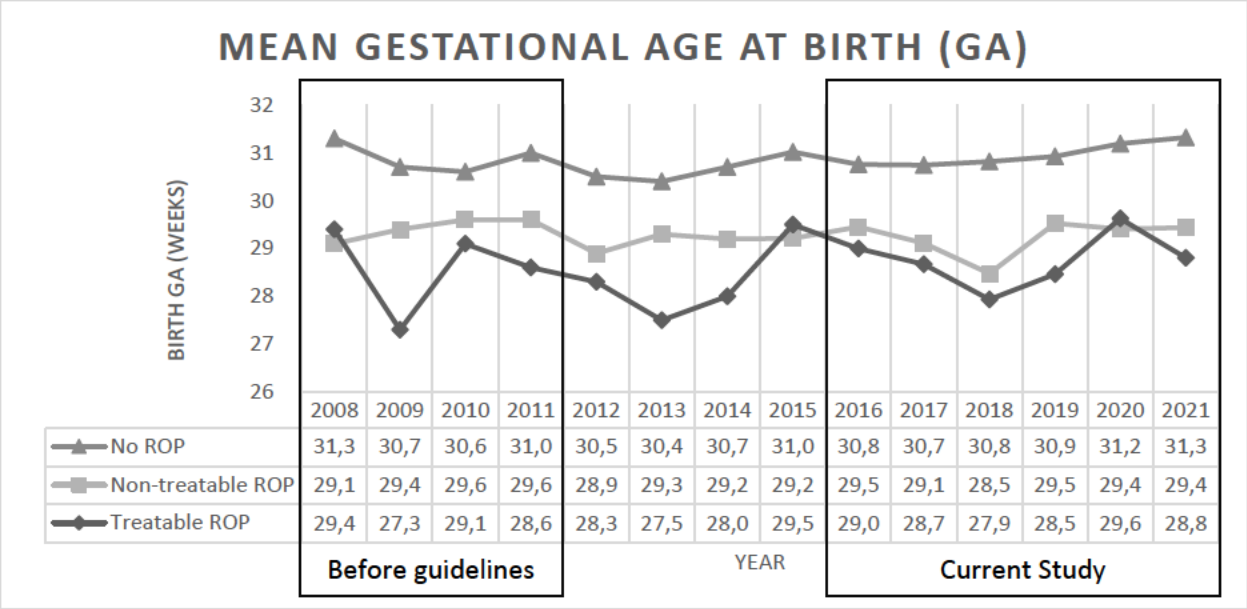


Figure 7: Comparison of three periods – Mean gestational age at birth for all screened, non-treatable, and treatable ROP cases.

The weight and age means for the treatable ROP subsets, seem to vary greatly over the years, but the numbers are too small to yield reliable results.

Principal Findings

The introduction of the South African Guidelines on ROP[28] has led to a sustained reduction in treatable retinopathy of prematurity (ROP) cases in KwaZulu-Natal over the past decade. The authors attribute this improvement primarily to the implementation of oxygen mixers in neonatal intensive care units (NICUs) across the province. Although the birth gestational age of referred patients has declined over time, the mean birth weight of these patients has remained consistent. This may indicate advances in saving babies born at lower gestational age, but not necessarily the smaller, growth-restricted infants. HIV status had no effect on ROP.

Strengths of the Study

This study provides long-term data on the impact of the South African ROP guidelines in a real-world setting, giving insight into how policy changes and resource allocation (such as oxygen mixers) affect ROP patterns. It highlights differences in referral appropriateness across institutions, suggesting that targeted ROP education and monitoring initiatives could lead to improved screening and treatment outcomes in facilities where referral processes are less optimal.

Limitations of the Data

The study does not account for factors potentially affecting referral rates, such as changes in population size or healthcare access over time. The study also does not differentiate between patients who required only one visit and those who missed necessary follow-ups, which may underestimate the impact of non-compliance on screening outcomes.

Care should be taken when comparing data from this study to past or future South African studies. Although the South African ROP Guidelines were formally published at the end of 2012/ beginning of 2013, the hospital and referring institutions in this study implemented the new guidelines at the beginning of 2012, and the data and statistics reflect this. We would assume

that most South African hospitals would have only implemented the guidelines after publication one year later.

Interpretation

The results suggest that the introduction of standardized ROP guidelines has been instrumental in reducing treatable ROP cases in KwaZulu-Natal. However, the steady referral numbers despite population growth, as well as the high rates of missed follow-up visits, indicate a need to strengthen the referral and follow-up systems. This highlights the importance of targeted education and feedback initiatives in hospitals with lower referral vigilance, which could lead to improvements in ROP screening and outcomes.

Conclusions

While significant progress has been made in reducing treatable ROP cases in KwaZulu-Natal, there remains room for improvement, particularly in the areas of follow-up adherence and institutional consistency in referrals. Efforts should focus on enhancing interdisciplinary communication, reinforcing ROP education in specific institutions, and ensuring that referral and follow-up protocols are robustly implemented to further reduce the ROP tide and improve neonatal ocular health. These measures could help in achieving more comprehensive prevention and management of ROP in vulnerable neonatal populations.

References

1. Kanski JJ, Bowling B. Kanski's clinical ophthalmology e-book: a systematic approach: Elsevier Health Sciences; 2015.
2. Zin A, Gole GA. Retinopathy of prematurity-incidence today. Clinics in perinatology. 2013;40(2):185-200.
3. Ademola-Popoola DS, Onakoya AO, Ezisi CN, Okeigbemen VW, Aghaji AE, Musa KO, et al. Case series of retinopathy of prematurity blindness in Nigeria: A wakeup call to policy makers, hospitals, ophthalmologists and paediatricians. Nigerian Postgraduate Medical Journal. 2021;28(4):303.
4. du Bruyn A, Visser L. Eight years of treatable retinopathy of prematurity in KwaZulu-Natal: are we winning the battle? South African Ophthalmology Journal. 2017;12(2):8-10.
5. Kiranmayee PS, Kalluri V. India to gear up to the challenge of “third epidemic” of retinopathy of prematurity in the world. Indian Journal of Ophthalmology. 2019;67(6):726.
6. Gilbert C, Malik AN, Nahar N, Das SK, Visser L, Sitati S, et al., editors. Epidemiology of ROP update–Africa is the new frontier. Seminars in Perinatology; 2019: Elsevier.
7. Kulkarni S, Gilbert C, Zuurmond M, Agashe S, Deshpande M. Blinding retinopathy of prematurity in Western India: Characteristics of children, reasons for late presentation and impact on families. Indian pediatrics. 2018;55(8):665-70.
8. Tasman W. Retinopathy of prematurity: do we still have a problem?: the Charles L. Schepens lecture. Arch Ophthalmol. 2011;129(8):1083-6.
9. Blencowe H, Moxon S, Gilbert C. Update on blindness due to retinopathy of prematurity globally and in India. Indian pediatrics. 2016;53:S89-S92.
10. Jefferies A. Retinopathy of prematurity: recommendations for screening. Paediatrics & Child Health. 2010;15(10):667-70.
11. Wilkinson A, Haines L, Head K, Fielder A. UK retinopathy of prematurity guideline. Eye. 2009;23(11):2137-9.
12. Jefferies AL, Society CP, Fetus, Committee N. Retinopathy of prematurity: An update on screening and management. Paediatrics & child health. 2016;21(2):101-4.
13. Fierson W. American Academy of ophthalmology; American Association for Pediatric Ophthalmology and Strabismus; American Association of Certified Orthoptists. Screening examination of premature infants for retinopathy of prematurity. Pediatrics. 2013;131(1):189-95.
14. Binenbaum G, Tomlinson LA. Postnatal growth and retinopathy of prematurity study: rationale, design, and subject characteristics. Ophthalmic epidemiology. 2017;24(1):36-47.
15. Group CfRoPC. Multicenter trial of cryotherapy for retinopathy of prematurity: preliminary results. Pediatrics. 1988;81(5):697-706.
16. Group ETfRoPC. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. Archives of Ophthalmology (Chicago, Ill: 1960). 2003;121(12):1684-94.
17. Quinn GE, Ying G-s, Bell EF, Donohue PK, Morrison D, Tomlinson LA, et al. Incidence and early course of retinopathy of prematurity: secondary analysis of the postnatal growth and retinopathy of prematurity (G-ROP) study. JAMA ophthalmology. 2018;136(12):1383-9.
18. Yu Y, Tomlinson LA, Binenbaum G, Ying G-s. Incidence, timing and risk factors of type 1 retinopathy of prematurity in a North American cohort. British Journal of Ophthalmology. 2021;105(12):1724-30.

19. Yan H-X, Li M-H, Wang L, Wu L, Fan J, Zhou Y, et al. Twelve-year profile of screening results of retinopathy of prematurity at a tertiary care institute in Northwest China. International Journal of Ophthalmology. 2022;15(2):312.
20. Niyonzima JC, Nahar N, Chowdhury M, Das SK, Rahman M. Characteristics of babies referred for Retinopathy of prematurity screening and management to a tertiary eye hospital of Bangladesh, a database analysis. 2019.
21. Vogel JP, Chawanpaiboon S, Moller A-B, Watananirun K, Bonet M, Lumbiganon P. The global epidemiology of preterm birth. Best Practice & Research Clinical Obstetrics & Gynaecology. 2018;52:3-12.
22. Chiang MF, Quinn GE, Fielder AR, Ostmo SR, Paul Chan RV, Berrocal A, et al. International Classification of Retinopathy of Prematurity, Third Edition. Ophthalmology. 2021;128(10):e51-e68.
23. Onyango O, Sitati S, Amolo L, Murila F, Wariua S, Nyamu G, et al. Retinopathy of prematurity in Kenya: prevalence and risk factors in a hospital with advanced neonatal care. Pan African Medical Journal. 2018;29(1):1-7.
24. Ojaghi H, Fekri Y, Momeni N, Amani F. Retinopathy of prematurity (ROP) in Ardebil (North West of Iran): Prevalence and Risk factors. Pakistan Journal of Medical and Health Sciences. 2021;15(5):1557-63.
25. Delport SD, Swanepoel JC, Odendaal PJ, Roux P. Incidence of retinopathy of prematurity in very-low-birth-weight infants born at Kalafong Hospital, Pretoria. South African Medical Journal. 2002;92(12):986-90.
26. Keraan Q, Tinley C, Horn A, Pollock T, Steffen J, Joolay Y. Retinopathy of prematurity in a cohort of neonates at Groote Schuur Hospital, Cape Town, South Africa. South African Medical Journal. 2017;107(1):64-9.
27. Dadoo Z, Ballot D. An evaluation of the screening for retinopathy of prematurity in very-low-birth-weight babies at a tertiary hospital in Johannesburg, South Africa. South African Journal of Child Health. 2016;10(1):79-82.
28. Visser L, Singh R, Young M, Lewis H, McKerrow N. Guideline for the prevention, screening and treatment of retinopathy of prematurity (ROP). S Afr Med J. 2012;103(2):116-25.
29. Atowoju I, Dawer P, Asrani M, Panjiyar B. Impact of maternal HIV infection on perinatal outcomes: A systematic review. International Journal of Gynecology & Obstetrics. 2024;166(1):35-43.
30. Asferie WN, Aytenew TM, Kassaw A, Hailemeskel HS, Kebede SD, Gashaw BT, et al. Effect of maternal HIV infection on birth outcomes among HIV positive women in Sub Saharan Africa: a systematic review and meta-analysis. BMC Public Health. 2025;25(1):459.
31. Chu A, Dhindsa Y, Sim MS, Altendahl M, Tsui I. Prenatal intrauterine growth restriction and risk of retinopathy of prematurity. Scientific reports. 2020;10(1):17591.

Funding statement

No funding was received for this research

Data availability statement

The data underlying this research will be made available upon reasonable request. To preserve confidentiality, identifying data will not be made available.

Conflict of interest disclosure

No conflict of interest to declare

Ethics approval statement

Ethical approval was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BREC/00005453/2023), as well as the provincial and facility ethics committees.

Patient consent statement

This was a retrospective chart review and therefore no patient consent is applicable.

Permission to reproduce material from other sources

No additional permissions

Figures and Legends

According to the South African guidelines for ROP screening, appropriate screening criteria include:

Whom to screen:

Low birth weight (LBW) <1500g, or

Prematurity <32 weeks' gestational age, or

Birth weight between 1500g – 2000g

and sub-optimal oxygen monitoring

and at least one of the following:

- cardio-respiratory arrest
- severe HIE
- more than 2 neonatal blood transfusions
- a total blood transfusion
- family history of ROP

When to screen: (whichever comes later)

4 – 6 weeks chronological age, or

31 – 33 weeks corrected gestational age

Figure 8: South African guidelines on appropriate ROP referral

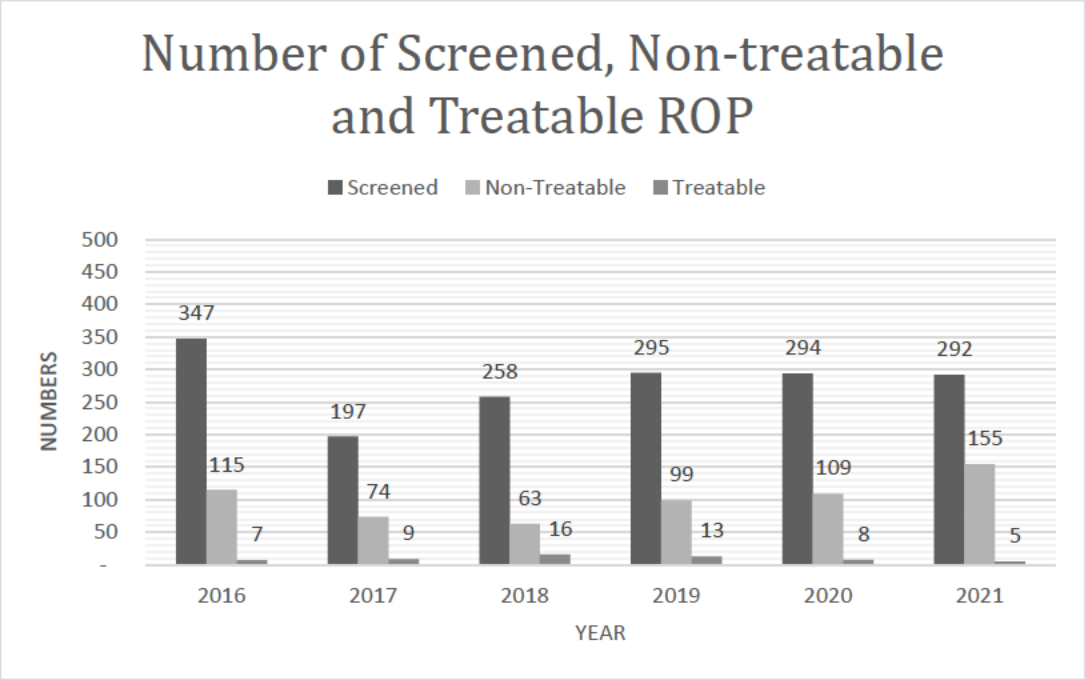


Figure 9: Number of cases screened per year, with the number of cases with clinical ROP divided into treatable cases, and cases that did not meet the criteria for treatment.

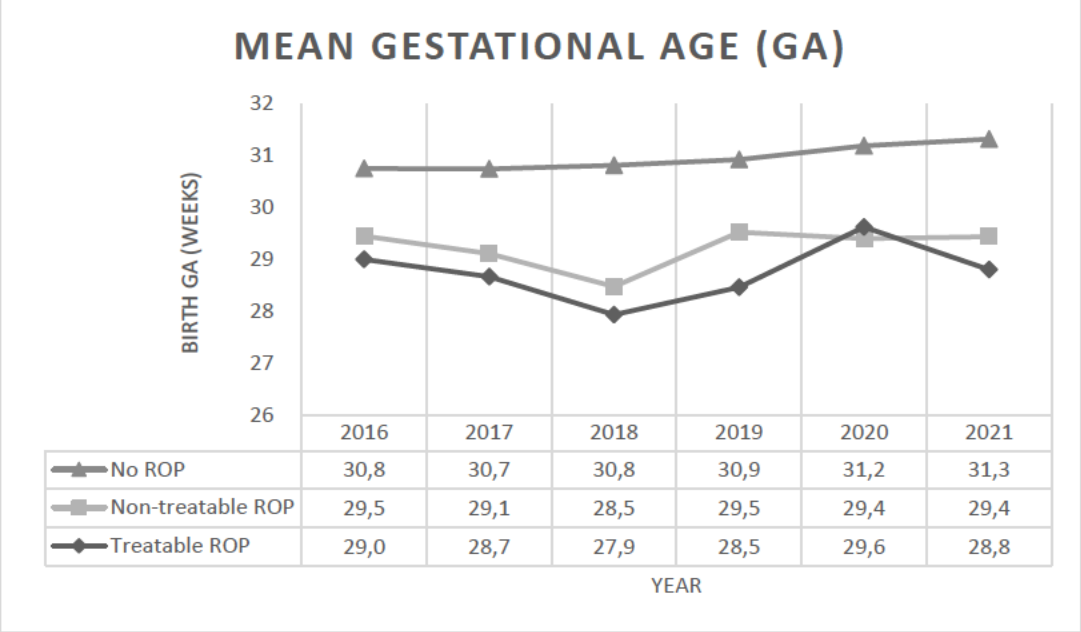


Figure 10: Mean gestational age at birth for all screened, non-treatable and treatable ROP cases.

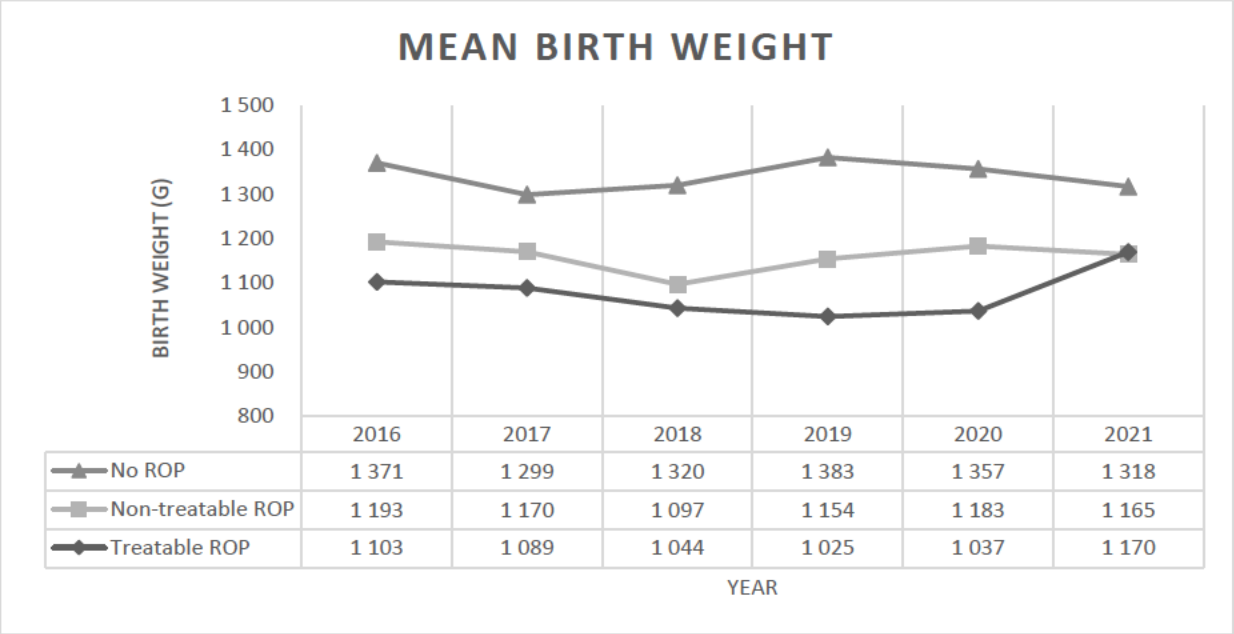


Figure 11: Mean birth weight for all screened, treatable and non-treatable ROP cases.

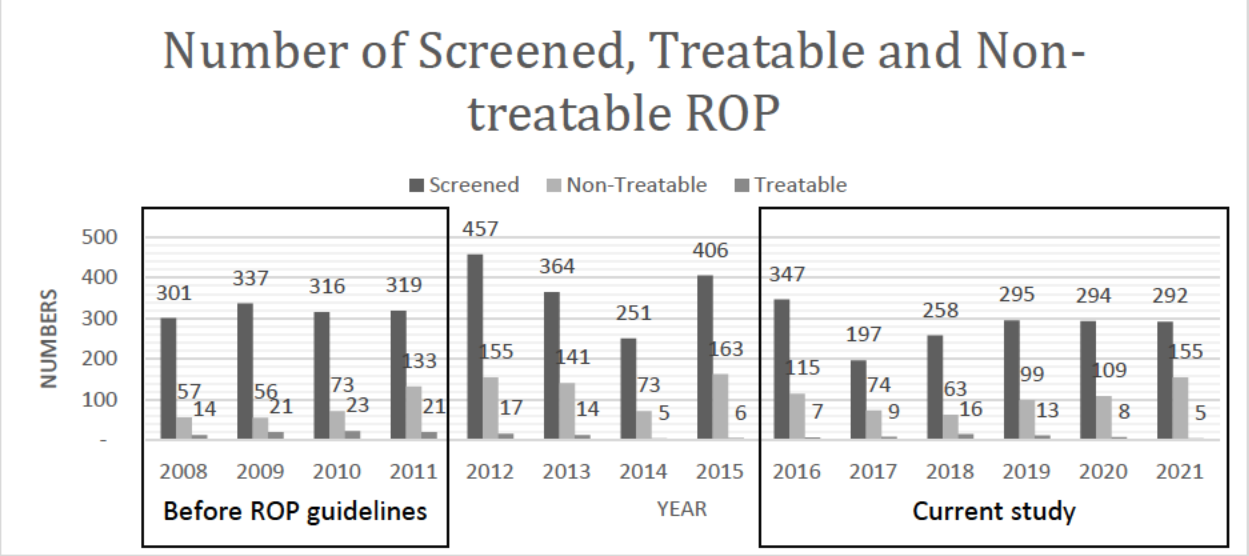


Figure 12: Comparison of three periods - Number of cases screened per year, with the number of cases with clinical ROP divided into treatable cases, and cases that did not meet the criteria for treatment.

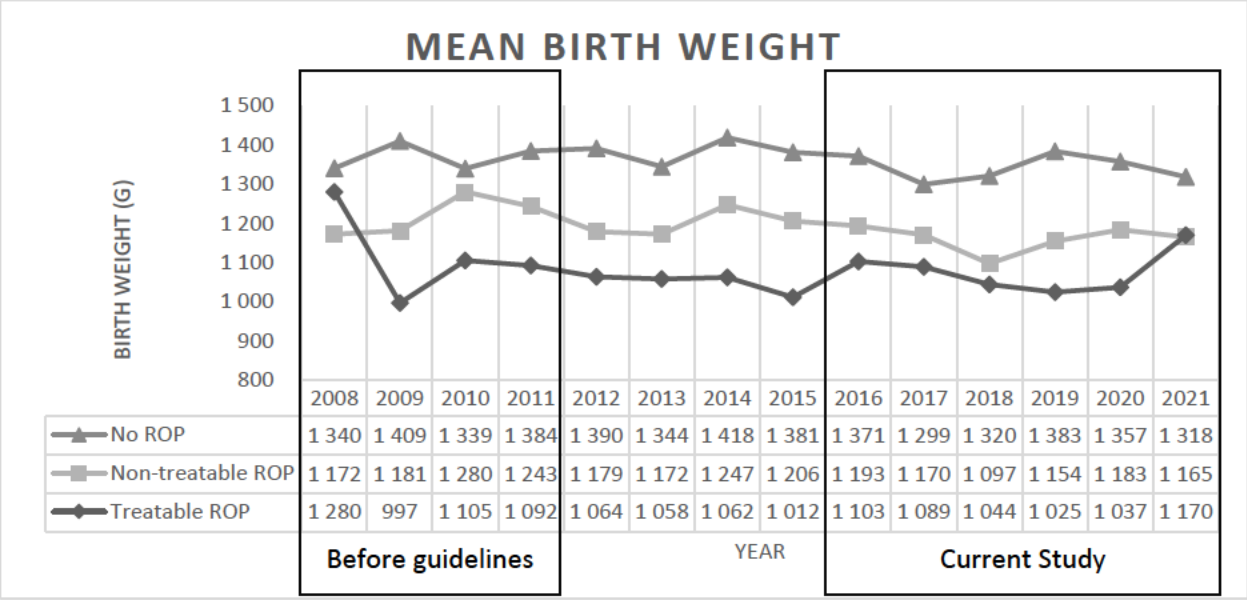


Figure 13: Comparison of three periods - Mean birth weight for all screened, treatable and non-treatable ROP cases.

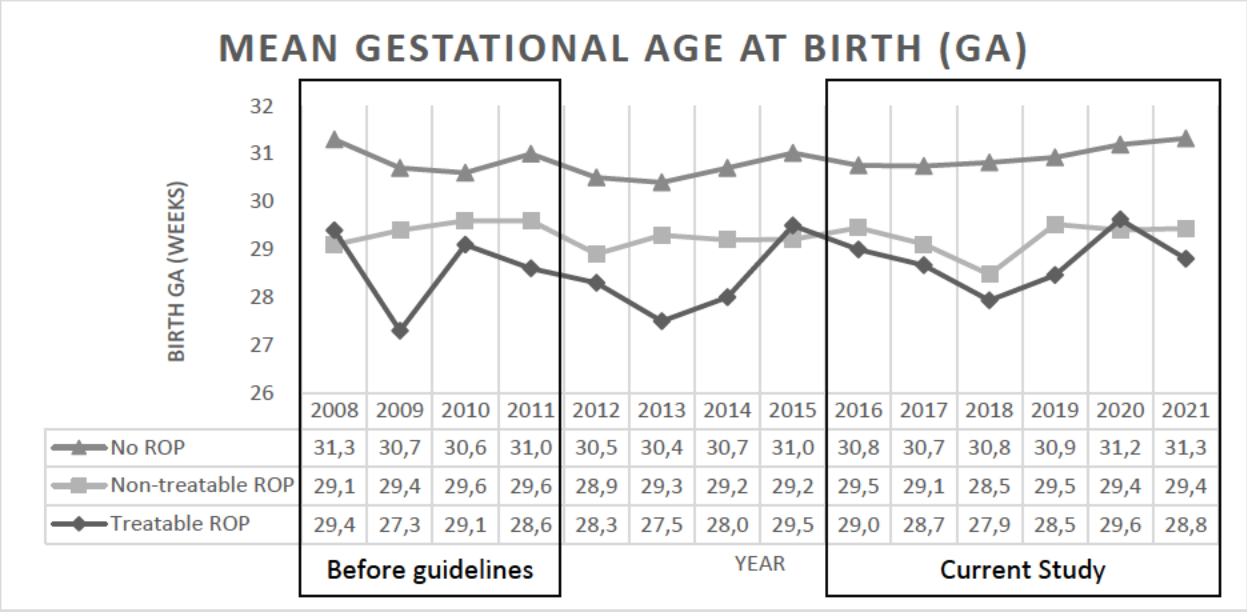


Figure 14: Comparison of three periods – Mean gestational age at birth for all screened, non-treatable and treatable ROP cases.

Tables and Legends

	n	%
Sex (n = 1710)		
Male	855	50.0%
Female	854	49.9%
Unknown	1	0.1%
Race		
African	1595	93.3%
Indian	78	4.6%
Coloured	28	1.6%
White	5	0.3%
Other	4	0.3%
HIV Exposure (n = 824)		
Exposed	382	46.4%
Not exposed	442	53.6%
HIV PCR (n = 171)		
Positive	5	2.9%
Negative	166	97.1%

Table 4: Demographics

Contingency Tables

Referral Hospital	Level	Appropriate referral			Total
		Yes	No		
A	4	28	43	60.6%	71
B	3	281	166	37.1%	447
C	2	281	134	32.3%	415
D	2	71	21	22.8%	92
E	1	49	21	30.0%	70
F	1	37	18	32.7%	55
G	1	24	33	57.9%	57
Total		771	436	36.1%	1207

χ^2 Tests

	Value	df	p
χ^2	42	6	< .001
N	1207		

Table 5: Referral hospitals – appropriate referral according to the official South African guidelines

Contingency Tables

Referral Hospital	Level	Diagnosis					
		ROP for treatment		ROP not for treatment		No ROP	Total
A	4	3	4.2%	35	49.3%	33	71
B	3	16	3.6%	206	46.1%	225	447
C	2	1	0.2%	128	30.8%	286	415
D	2	2	2.2%	28	30.4%	62	92
E	1	1	1.4%	12	17.1%	57	70
F	1	3	5.2%	29	50.0%	26	58
G	1	2	3.5%	25	43.9%	30	57
Total		28	2.3%	463	38.3%	719	1210

χ^2 Tests

	Value	df	p
χ^2	65.8	12	< .001
N	1210		

Table 6: Referral hospitals – Breakup of referral numbers into treatable ROP, ROP not requiring treatment and referrals with no evidence of ROP.

APPENDICES

Appendix 1: The Final Study Protocol

PROTOCOL (MMED) – DR JERUSHA JOHN

TITLE OF STUDY

Treatable retinopathy of prematurity in KwaZulu-Natal, South Africa: How far have we come in the last 14 years?

PROBLEM STATEMENT

We do not know whether the amount of treatable ROP seen at a quaternary state hospital in KwaZulu-Natal has continued to decrease since the implementation of the South African ROP screening guidelines and also if the ROP referrals to IALCH have been improving or deteriorating over the last 6 years, in comparison to the 8 years prior to this period.

AIM OF STUDY

To compare the rate of treatable ROP in the last 6 years (1 January 2016 – 31 December 2021) at a South African quaternary state hospital, to two previous periods: 2008 to 2011, (before new ROP guidelines), and 2012 to 2015 (after implementation of South African ROP guidelines) at the same hospital.

SPECIFIC OBJECTIVES

PRIMARY OBJECTIVES

The primary objectives are to quantify the amount of treatable ROP, and to compare the last 6 years of data to two previous time periods (before and after the implementation of new South African screening guidelines) at Inkosi Albert Luthuli Central Hospital (IALCH).

SECONDARY OBJECTIVES

The secondary objectives of this study are to ascertain the referral appropriateness for the treated babies, and compare the rate of treatable ROP between the referring hospitals.

BACKGROUND AND LITERATURE

Retinopathy of prematurity (ROP) is a potentially life-long sight-threatening condition, the impact of which can potentially be reduced or avoided with early detection through adequate referral, screening and treatment of at-risk babies. It remains an area of concern for vigilance as younger gestational age or greater prematurity at birth is

better managed as medical therapy improves through the years – these babies being born earlier and have an ever-increasing chance at survival.(1) (2) ROP rates are expected to increase(3).

The recently revised international classification of ROP (ICROP) screening and treatment protocols, ICROP 3(4), are instrumental in managing this vulnerable group of patients. Fundamentally, it assists in subdividing the retina into zones I, II, and III (least to most mature), and stratifying ROP severity into stages 1-5. These features are searched throughout the circumference of the retina for accurate location, diagnosis and documentation of presence/absence, progression/regression or reactivation of disease, including long-term sequelae. In South Africa, guidelines for screening were further refined to be specifically relevant to our developing country, to combat the particular burden of this entity to middle-income-countries(5).

Treatment for ROP had been reserved for those babies with the previously-titled "threshold" disease as outlined by the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) Study(6). This entailed trans-scleral peripheral retinal cryotherapy ablation for severe disease deemed to carry a 50% risk for retinal detachment – the threshold for treatment[*].

Although cryotherapy at this point was shown to significantly reduce the risk of retinal detachment in the long term, the numbers of detachments were still unacceptably high(7), prompting calls for earlier treatment. Treatable ROP was therefore re-defined as per the Early Treatment for Retinopathy of Prematurity (ET-ROP) Study(8)[†]. They showed that earlier treatment significantly reduced unfavourable visual acuity and structural outcomes(9). A new treatment modality had also been introduced – ablation of ischaemic retina by trans-pupillary laser.

The BEAT-ROP Cooperative Group then showed intravitreal injection of Bevacizumab to be superior to conventional laser therapy in the most severe ROP (Zone 1 disease with Stage 3+). It also showed that continued normal retinal vascularisation continued after Bevacizumab injection, as compared to the permanent destruction incurred with laser treatment(10). As such, treatment with intravitreal Bevacizumab has become the standard of care in most centres for the most severe, Type 1, disease.

Early treatment is paramount. Screening is aimed at early identification of those babies who need treatment to avoid development of advanced ROP with unfavourable outcomes (retinal detachment requiring surgery, macular folds or dragging, retro-lenticular masses, or those deemed inoperable and permanently blind). However, centres seem to still be seeing babies with advanced stages of ROP at the point of referral. These late referrals often require lengthy, difficult, and/or multiple procedures necessitating general anaesthesia for retinal detachment repair, which further compounds the morbidity risk.

This then poses questions – are we reaching the right babies timeously? Are referrals appropriate? Which part of the system needs to be streamlined to ensure long-term sighted quality of life for these premature babies?

---

[*] Threshold disease was defined by at least 5 contiguous or 8 cumulative clock hours (or 30˚ sectors) of stage 3 ROP in zone 1 or 2, with "plus disease" (posterior vessel tortuosity and dilation in at least 2 retinal quadrants regarded as equal to or greater than that of a given standard photograph).

[†] Treatable ROP was re-defined Type 1 disease (defined as Zone I any stage with plus disease, or Zone I stage 3 with or without plus, or Zone II stage 2 or 3 with plus); and frequent observation for Type 2 disease (defined as Zone I, stage 1 or 2 without plus, or Zone II stage 3 without plus disease), should these babies progress to Type 1 or threshold disease.

A retrospective audit reviewing electronic case notes, conducted by M. du Bruyn and L. Visser, spanning Jan 2008 to Dec 2015, assessed the number of preterm babies that required treatment for retinopathy of prematurity before

and after the South African screening guidelines were implemented in 2012. (11) They also looked at the impact that the guidelines had on the management of these babies and their referral for screening. Their results showed that after this implementation, the amount of treatable ROP had drastically decreased.

The period of January 2016 until December 2021 remains an unanalysed gap and the current neonatal care and adequacy of referrals for screening is unknown.

REFERENCES

Organization WH. World health statistics 2018: monitoring health for the SDGs, sustainable development goals: World Health Organization; 2018.

Beauthier J-P. [Forensic approach of infanticide and neonatal death]. Revue médicale de Bruxelles. 2007;28:431-8.

Tasman W. Retinopathy of prematurity: do we still have a problem?: the Charles L. Schepens lecture. Arch Ophthalmol. 2011;129(8):1083-6.

Chiang MF, Quinn GE, Fielder AR, Ostmo SR, Paul Chan RV, Berrocal A, *et al.* International Classification of Retinopathy of Prematurity, Third Edition. Ophthalmology. 2021;128(10):e51-e68.

Visser L, Singh R, Young M, Lewis H, McKerrow N. Guideline for the prevention, screening and treatment of retinopathy of prematurity (ROP). S Afr Med J. 2012;103(2):116-25.

Tasman W. Multicenter trial of cryotherapy for retinopathy of prematurity. Archives of Ophthalmology. 1988;106(4):463-4.

Group CfRoPC. Multicenter trial of cryotherapy for retinopathy of prematurity: ophthalmological outcomes at 10 years. Archives of Ophthalmology. 2001;119(8):1110-8.

Good WV, Hardy RJ. The multicenter study of Early Treatment for Retinopathy of Prematurity (ETROP). Ophthalmology. 2001;108(6):1013-4.

Good WV, Group ETfRoPC. Final results of the Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial. Transactions of the American Ophthalmological Society. 2004;102:233.

Mintz-Hittner HA, Kennedy KA, Chuang AZ. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. New England Journal of Medicine. 2011;364(7):603-15.

du Bruyn A, Visser L. Eight years of treatable retinopathy of prematurity in KwaZulu-Natal: are we winning the battle? South African Ophthalmology Journal. 2017;12(2):8 – 10.

STUDY DESIGN

This will be a quantitative, retrospective, observational, descriptive audit by chart review.

STUDY POPULATION

All premature babies referred to Inkosi Albert Luthuli Central Hospital (IALCH) for retinopathy of prematurity (ROP) screening.

SAMPLING STRATEGY

Non-probability sampling: Purposive/Judgmental sampling – all patients in the time periods will be included.

STATISTICAL PLANNING (VARIABLES / CONFOUNDERS)

VARIABLES

Appropriateness of referral (Figure 1)

Gestational age at birth, 1st screening visit and at last screening visit

Birth weight

Stage of ROP at presentation and before treatment

Treatable disease numbers • Treatment type‡

According to the South African guidelines for ROP screening, appropriate screening criteria include:
A. Who to screen:
Low birth weight (LBW) <1500g
Prematurity <32 weeks' gestational age
Birth weight between 1500g – 2000g and sub-optimal oxygen monitoring and at least one of the following:
cardio-respiratory arrest
severe HIE
more than 2 neonatal blood transfusions
a total blood transfusion
family history of ROP
B. When to screen (whichever comes later): 4 – 6 weeks chronological age, or
31 – 33 weeks corrected gestational age

Figure 1: South African guidelines on appropriate ROP referral

CONFOUNDERS

Only babies that were referred to IALCH will be included in this study. Babies not referred, even if inappropriately so, will not be included. The effect of this confounder will be minimised since both groups being compared will have the same class of missing cases.

‡ Treatment of ROP is dependent on the stage and extent of ROP:

In type 1 disease, treatment is aimed at reducing or halting the drive of vascular endothelial growth factor (VEGF), either by direct injection of anti-VEGF drug into the vitreous cavity, or by suppressing the source of the expression of VEGF by lasering the remaining signalling ischaemic or poorly developing avascular retinal tissue.

If ROP progresses, advanced stages involve consequences of untreated neovascularisation – gliotic traction on the young retina, with resultant detachment thereof. This would require surgery – pars plana vitrectomy – to attempt repair of the damaged retina under general anaesthesia, if not already inoperable.

SAMPLE SIZE

Roughly 4000 patients (2800 during the period of 1 January 2008 – 31 Dec 2015, and 1200 during the period of 1 January 2016 – 31 December 2021)

INCLUSION / EXCLUSION CRITERIA

INCLUSION CRITERIA

All babies who have been referred to IALCH and who fulfil the criteria for ROP screening, whether treated or untreated, will be included, from 1 January 2008 until 31 December 2021.

EXCLUSION CRITERIA

Babies that do not fulfil criteria for ROP screening.

DATA COLLECTION METHODS AND TOOLS

Retrospective chart review, and manual entering and collation of data onto a data collection sheet using Microsoft Excel Spreadsheet software.

All data at the institution is kept on electronic health record. The database will be searched for “ROP” or “retinopathy of prematurity” as diagnosis. As confirmation, theatre notes will be searched for treatment of ROP. All notes will be manually filtered to exclude cases that do not fulfil the entrance criteria.

DATA ANALYSIS AND STATISTICAL TECHNIQUES

The Excel (Microsoft Corp., USA) spreadsheet will be exported to R (R Studio, USA) for analysis. Categorical variables will be expressed as frequencies and percentages and compared using the Chi-squared test. Continuous variables will be expressed as medians and interquartile range (IQR) as the distribution is expected to be nonnormal. The Wilcoxon test will be used for comparison of non-parametric data. Alpha level is set at 0.05.

STUDY LOCATION

Inkosi Albert Luthuli Central Hospital, KwaZulu-Natal, South Africa

STUDY PERIOD

1 January 2008 to 31 December 2021 (new data will be collected from the period of 1 January 2016 to 31

December 2021, and compared to older data collected from the period of 1 January 2008 to 31 December 2015)

LIMITATIONS TO THE STUDY

Retrospective study limitations – possibility of incorrect or incomplete record keeping/missing data and poor recall of detail. This limitation is limited by the electronic medical record used throughout this hospital which decreases the chance of lost notes.

ETHICAL CONSIDERATIONS

Patients' personal details will be kept confidential. Results will be reported on anonymously (no personal/private information of patients will be linked to reported results). Identifying source datasheets will be destroyed after 5 years.

The data and conclusions gained from this research will directly advantage the population involved. By improving the understanding of which babies require treatment for retinopathy of prematurity, subsequent decisions, revisions, and establishment of screening guidelines and policies (local and national) can be addressed to streamline the system amongst clinics and hospitals in both the public and private sectors. Budget allocation to combat the burden of this disease can also be adjusted accordingly. It is hoped that the referral appropriateness will be maintained or improved, which speaks to enhanced collaboration between various fields of health (ophthalmology, paediatrics, obstetrics, nursing), to aid in prevention of the avoidable burden of life-long blindness from this condition.

Appendix 2: The Journal Guidelines for Authorship:

Paediatric and Perinatal Epidemiology

https://onlinelibrary.wiley.com/page/journal/13653016/homepage/forauthors.html

Author Guidelines

1. SUBMISSION

Authors should kindly note that submission implies that the content has not been published or submitted for publication elsewhere except as a brief abstract in the proceedings of a scientific meeting or symposium.

Data protection:

By submitting a manuscript to or reviewing for this publication, your name, email address, and affiliation, and other contact details the publication might require, will be used for the regular operations of the publication, including, when necessary, sharing with the publisher (Wiley) and partners for production and publication. The publication and the publisher recognise the importance of protecting the personal information collected from users in the operation of these services, and have practices in place to ensure that steps are taken to maintain the security, integrity, and privacy of the personal data collected and processed. You can learn more at https://authorservices.wiley.com/statements/data-protection-policy.html.

Social Media Quote:

When submitting an original article, you will be asked to also include a social media information

We will post the quote on both Twitter and Facebook.

We require that you provide a Tweetable quote of 280 characters or less, (in the manuscript and at the submission online portal), summarising the main findings of the paper.

Identify a single Figure or a small Table in the manuscript that will be posted along with the quote on social media.

We look forward to your submission.

2. AIMS AND SCOPE

Paediatric and Perinatal Epidemiology welcomes original research, brief reports, reviews (including systematic reviews and meta-analysis), letters to the editor, and debates, as well as papers describing the methods of large epidemiological studies or novel cohort or longitudinal study designs. Topics of interest include the application of epidemiologic methods to studies of fertility, pregnancy and obstetrical complications, birth outcomes, child health and development, and the influence of the foetal and early environment on child or adult health. We also encourage submissions on the development and applications of new and innovative methods.

All authors are expected to meet the International Committee of Medical Journal Editors Uniform Criteria for Authorship (http://www.icmje.org/), which they confirm by their signature on the letter of submission.

1. MANUSCRIPT CATEGORIES AND REQUIREMENTS

Manuscript submission

Paediatric and Perinatal Epidemiology requires all manuscripts to be submitted electronically at https://mc.manuscriptcentral.com/ppe. Login or click the "Create Account" option if you are a first-time user of the ScholarOne system. Full instructions and support for authors (and reviewers) are available on the site. Support can be contacted by email at support@scholarone.com or at http://authorservices.wiley.com/bauthor/journal.asp. If you have trouble submitting online, PPE's Editorial Assistant (PPEoffice@wiley.com) will be able to assist.

Word and references limits

Except where noted below, all manuscripts are to include a structured abstract and uniform section and subsection headings. The structured abstract (no more than 300 words) should include the following: Background, Objectives, Methods, Results, and Conclusions.

Original articles: Submissions may not exceed 3500 words, with a maximum of 6 tables and figures combined, and up to 60 references. They should include a structured abstract (no more than 300 words; see "original submission" format below).

Methodology: Submissions should not exceed 3500 words, with a maximum of 6 tables and figures combined and up to 60 references. They should include a structured

4. PREPARING YOUR SUBMISSION

Free Format submission

PPE now offers Free Format submission for a simplified and streamlined submission process. Before you submit, you will need:

Your **manuscript**: this should be an editable file including text, figures, and tables, or separate files – whichever you prefer. All required sections should be contained in your manuscript, including abstract (which does need to be correctly styled), introduction, methods, results, and conclusions. Figures and tables should have legends. Figures should be uploaded in the highest resolution possible. [If the figures are not of sufficiently high quality your manuscript may be delayed.] References may be submitted in any style or format, as long as it is consistent throughout the manuscript. Supporting information should be submitted in separate files. If the manuscript, figures or tables are difficult for you to read, they will also be difficult for the editors and reviewers, and the editorial office will send it back to you for revision. Your manuscript may also be sent back to you for revision if the quality of English language is poor.

The **title page** of the manuscript, including:

Your co-author details, including affiliation and email address. (Why is this important? We need to keep all co-authors informed of the outcome of the peer review process.)

Statements relating to our ethics and integrity policies, which may include any of the following (Why are these important? We need to uphold rigorous ethical standards for the research we consider for publication):

data availability statement

funding statement

conflict of interest disclosure

ethics approval statement

patient consent statement

permission to reproduce material from other sources

To submit a new paper, login at wiley.atyponrex.com/journal/PPE and create a new submission. Follow the submission steps as required and submit the manuscript.

General style conventions and formatting requirements

All manuscripts should be submitted in English using United Kingdom spelling and grammar conventions. Manuscripts should be typed with double spacing in Calibri font, 12 points. Pages should be numbered consecutively in the bottom centre. Do not fully justify the text.

Style conventions

In an effort to standardise language use throughout the journal, *Paediatric and Perinatal Epidemiology* has adopted the following style conventions:

Birthweight not birth weight; stillbirth not still birth.

Breast feeding (noun) not breastfeeding; and breast-feeding mothers (adjective).

Preterm or low birthweight never premature.

Confidence intervals; not confidence limits.

Multivariable not multivariate, for regression models with a single outcome variable.

Parts of the Manuscript

The manuscript should be submitted in separate files: main text file; figures.

Main Text File

The text file should be presented in the following order:

A short informative title containing the major key words. The title should not contain abbreviations;

A short running title of less than 40 characters;

The full names of the authors;

The author's institutional affiliations where the work was conducted, with a footnote for the author's present address if different from where the work was conducted;

Abstract and keywords;

Main text;

Acknowledgments;

References;

Tables (each Table complete with title and footnotes);

Figure legends;

Appendices (if relevant).

Figures and supporting information should be supplied as separate files.

Body of text

Do NOT indent paragraphs. Instead, separate paragraphs with a blank extra line between paragraphs.

Confidence intervals should be put in round brackets, separated by a comma (not a dash). For example, RR 2.31, 95% CI 1.90, 2.74; or RR 2.31 (95% CI 1.90, 2.74).

Do not insert line numbers in the document.

Ethics/human subjects' statement (e.g., institutional review board approval) is required; it should be included as the last sentence of the first paragraph under Methods.

Reporting of numerical data

Report percentages and risks with one digit, and risk estimates and CIs to two significant digits. Round accordingly, reporting numbers appearing more than once consistently.

Confidence intervals should be put in round brackets, separated by a comma (see example above).

P-values and confidence intervals

We strongly discourage the use of **P-values** or statements that reflect "statistical significance" testing. The use of P-values is permitted for the following three scenarios only: (a) tests for linear and non-linear trends; (b) tests of interactions; and (c) multiple degrees of freedom tests (e.g., ANOVA).

All ratio (OR, RR, HR) and difference measures should be accompanied by a 95% confidence interval.

Title page

Title: Be concise; declaring the type of study design is encouraged; do not specify the study (sample) size.

List of authors (do not list qualifications or academic titles), with full names, each followed by a superscript number (not letter) to link with the institution at which the authors were affiliated when the work was completed.

For the corresponding author, please list: Full name, department, institution, city and state of location, and country and email address only; do not list the full mailing address, telephone, or fax numbers.

Authorship

The journal follows the ICMJE definition of authorship, which indicates that authorship be based on the following 4 criteria:

Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

Drafting the work or revising it critically for important intellectual content; AND

Final approval of the version to be published; AND

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he or she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged. These authorship criteria are intended to reserve the status of authorship for those who deserve credit and can take responsibility for the work. The criteria are not intended for use as a means to disqualify colleagues from authorship who otherwise meet authorship criteria by denying them the opportunity to meet criterion #s 2 or 3. Therefore, all individuals who meet the first criterion should have the opportunity to participate in the review, drafting, and final approval of the manuscript.

Conflict of Interest Statement

Authors will be asked to provide a conflict-of-interest statement during the submission process. For details on what to include in this section, see the 'Conflict of Interest' section in the Editorial Policies and Ethical Considerations section below. Submitting authors should ensure they liaise with all co-authors to confirm agreement with the final statement.

Abstract

Original submissions and brief reports, follow this structure.

Background: Briefly state the reason(s) or justification for undertaking the study.

Objectives: Spell out the primary objective of the study. A hypothesis statement can also accompany an objective.

Methods: Begin by declaring the type of study design, time frame of study, population, and data source. Describe the primary exposure and outcome. Provide a brief description of analytic method, and how threats to study validity, including but not limited to, confounding, were addressed (if applicable). If space permits, declare alternate exposure definitions and secondary outcome(s).

Results: Begin by providing the study size, exposure and outcome prevalence (or other appropriate descriptive measure). Statement of effect measures (for the primary outcome) must be preceded by the outcome prevalence conditional on the exposure. Do not report P-values (see exceptions "P-value" section below); instead, difference and ratio measures must be accompanied by 95% confidence intervals.

Conclusion(s): Declare the primary finding of the study—if you have declared a hypothesis earlier, state if the study supports or does not support the hypothesis. Conclusions should not be overstated, and do not present any new findings here without declaring them in the "Results" section. Do not declare any policy-based implications or recommendations unless the study and/or the objective is policy-related. Causal language should be avoided unless fully supported by the design and statistical analysis.

Synopsis - Original submission, Brief Reports, Systematic Review/meta-analysis and Methodology ONLY

We require that you provide a brief synopsis of the paper of no more than 125 words, organised under the following headings.

Study question.

What's already known.

What this study adds.

Keywords
Insert a set of 4-6 key words, separated by semicolons, on a new page after the abstract. Keywords should be taken from those recommended by the US National Library of Medicine's Medical Subject Headings (MeSH) browser list at www.nlm.nih.gov/mesh.

Word count

Provide a word count not including the abstract, tables, figures, or references after the keywords.

Main text

The required section headings (shown in bold) are as follows:

Background, Methods, Results, Comment, and Conclusions.

The Methods section should include the following sub-sections:

Cohort or case-control selection: Preferably with a flow chart describing all exclusions.

Exposure (both primary and secondary).

Outcomes (both primary and secondary).

Statistical analysis: Clearly describe the general approach to statistical analyses and including the following to sub-sections.

Missing data (see below).

Sensitivity analyses (see below).

Ethics approval: A sentence noting the institution(s) where ethics approval was obtained.

Manuscript Structure

The manuscript should contain the following sections, in the following order, with each section beginning on a new page: Title page, Synopsis, Abstract, Key words, Main text, References, Acknowledgements, Funding, Figure legends, Tables, Table legends, Figures, Supplemental tables, and Supplemental figures.

Acknowledgments
Contributions from anyone who does not meet the criteria for authorship should be listed, with permission from the contributor, in an Acknowledgments section. Any acknowledgements should be placed at the end of the text before the references. Authors should be sure that they have obtained permission to mention any individual acknowledged by name. Financial and material support should also be mentioned. Thanks to anonymous reviewers are not appropriate.

References
References in the text should be referred to by a superscript number after the punctuation. The list of references at the end of the manuscript should be listed in the order in which they appear in the text. Note that journal names should be spelt out in full, and both the beginning and the ending page numbers should be listed in full. References to personal communications, unpublished data or manuscripts “in preparation” should not be included. If essential, such material may be incorporated at the appropriate place in the text. The style should be as follows:

For articles, give authors’ names followed by initials, full title of the article, name of journal, year of publication, volume number, first and last relevant page numbers. List all authors and if the number exceeds six give the first six, followed by *et al.*

Example: Sophist J, Paradigm K. The variation in infant sex ratio according to degree of maternal pedantry. *International Journal of Perinatal Variation* 1979; 7:143-152.

For books, give authors' names followed by initials, title of chapter/article, title of book preceded by "In:," "Editor(s):" followed by name(s) and initial(s), place of publication, publisher's name, year of publication, first and last relevant page numbers.

Example: Cart A. Patterns of illness in children living in an area of heavy pollution. In: Horse Sense. Editors: Loh J, Mee K, Soh AH. Solihull: Khyber Press, 1984; pp. 14-83.

We strongly recommend the use of a tool such as EndNote for reference management and formatting. EndNote reference styles can be found at: https://endnote.com/downloads/styles.

Tables

Tables should only be prepared in Microsoft Word using the Table function and created in a manner such that it is clear what is being shown.

Tables should be clearly labelled and able to be understood apart from the text.

Each Table should begin on a separate sheet, numbered consecutively with Arabic numerals, containing only horizontal lines (one each at the top and bottom of the Table and with additional lines to divide Table sections only as needed), and with a concise legend. Table footnotes should be denoted with superscript lowercase letters.

Aside from the column headings, none of the Table entries should be in bold.

Confidence intervals should be put in round brackets, separated by a comma not a dash.

The reference category for relative measures of effect should always be labelled as "1.00 (Reference)" (not "ref"); for absolute measures, the reference category should be labelled as "0.00 (Reference)."

Figure Legends

Legends should be concise but comprehensive – the Figure and its legend must be understandable without reference to the text. Include definitions of any symbols used and define/explain all abbreviations and units of measurement.

Figures

Authors' original artwork will be used; labelling should be in Calibri typeface, 12 points so that after reduction it is no smaller than eight points.

All figures must be at least 300 × 300 DPI.

Symbols and lines should be distinct after reduction; histograms should be black, white or hatched in distinctive ways; background lines should not be used.

In the full-text online edition of the journal, Figure legends may be truncated in abbreviated links to the full-screen version. Therefore, the first 100 characters of any legend should inform the reader of key aspects of the figure.

Complete guidance regarding the preparation and preferred file formats for figures and images are available at http://author services.wiley.com/bauthor/illustration.asp.

Supplemental Material

We accept supplemental tables and figures that support the main analyses.

All supplemental tables and figures must be referenced in the text as “eTable x” or “eFigure x.”

Other Points to Consider

• Presenting a DAG to highlight the pathways amongst variables is highly recommended.

• Standard deviations are preferred over standard errors for sample descriptions.

• Avoid statements such as “This was the first study to…” or “We were the first to…”

• When race, ethnicity, or nationality (defined as place of birth) is identified as research variables, authors should make clear the purpose for using such variables. Authors should describe their methods of definition and classification of racial, ethnic, or nationality groupings. Ethnocentricity should be avoided. For example, in choosing a reference group, it should not be assumed that the majority racial, or ethnic group is necessarily the best choice. Care should be taken to explain the choice of referent. Limitations of race, ethnicity, and nationality data and measurement should be clearly stated. Known or potential causes of the observed differences between groups should be explored and discussed.

• Sex versus gender: We are cognisant of the fact that some people do not identify their gender as the biological sex they were born with. We ask that authors be clear whether they are talking about biological sex or self-identified gender.

Additional Files

Appendices
Appendices will be published after the references. For submission they should be supplied as separate files but referred to in the text.

Supporting Information

Supporting information is information that is not essential to the article, but provides greater depth and background. It is hosted online and appears without editing or typesetting. It may include tables, figures, videos, datasets, etc.

5. EDITORIAL POLICIES AND ETHICAL CONSIDERATIONS

Editorial Review and Acceptance

The acceptance criteria for all papers are the quality and originality of the research and its significance to our readership. Except where otherwise stated, manuscripts are single-blind peer reviewed. Papers will only be sent to review if the Editors-in-Chief determine that the paper meets the appropriate quality and relevance requirements.

Wiley's policy on confidentiality of the review process is available here.

Refer and Transfer Program

Wiley believes that no valuable research should go unshared. This journal participates in Wiley’s Refer & Transfer program. If your manuscript is not accepted, you may receive a recommendation to transfer your manuscript to another suitable Wiley journal, either through a referral from the journal’s editor or through our Transfer Desk Assistant.

Guidelines on Publishing and Research Ethics in Journal Articles Please review Wiley's policies surrounding human studies, animal studies, clinical trial registration, biosecurity, and research reporting guidelines here.

Conflict of Interest

The journal requires that all authors disclose any potential sources of conflict of interest. Any interest or relationship, financial or otherwise that might be perceived as influencing an author's objectivity is considered a potential source of conflict of interest. These must be disclosed when directly relevant or directly related to the work that the authors describe in their manuscript. Potential sources of conflict of interest include but are not limited to: patent or stock ownership, membership of a company board of directors, membership of an advisory board or committee for a company, and consultancy for or receipt of speaker's fees from a company. The existence of a conflict of interest does not preclude publication. If the authors have no conflict of interest to declare, they must also state this at submission. It is the responsibility of the corresponding author to review this policy with all authors and collectively to disclose with the submission ALL pertinent commercial and other relationships.

Funding
Authors should list all funding sources in the Acknowledgments section. Authors are responsible for the accuracy of their funder designation. If in doubt, please check the Open Funder Registry for the correct nomenclature: https://www.crossref.org/services/funder-registry/. Please list all funding sources, including the grant or contract number and the funding agency

Missing data

Multiple imputation methods are required so long as the pattern of missing data satisfies the assumptions required for imputations, with a minimum of 50 imputations.

Please describe exactly the proportion of missing data for individual variables, how multiple imputation was performed and all other relevant details. Providing citations will be preferred.

Multiple imputation is generally not necessary when missing data are <5%.

Sensitivity analysis

Most observational studies suffer from two common biases: selection bias and unmeasured confounding. We ask that authors undertake and report additional sensitivity analysis that addresses the following biases.

Selection bias: Authors should provide a flow diagram to describe the exclusion categories and loss to follow-up. Authors must explicitly address selection bias by describing the characteristics of included versus excluded groups and the potential impact on results, including using statistical techniques, such as inverse probability weighting, when appropriate.

Unmeasured confounding: An additional requirement for the estimation of causal effects requires that the associations remain unaffected by unmeasured confounding. We ask authors to undertake a sensitivity analysis to address unmeasured confounding through the "E-value" method, described in VanderWeele TJ, Ding P. Sensitivity analysis in observational research: Introducing the "E-Value." Annals of Internal Medicine 2017;167(4):268 – 274.

Material and Methods

If a method or tool is introduced in the study, including software, questionnaires, and scales, the author should state the license this is available under and any requirement for permission for use. If an existing method or tool is used in the research, the authors are responsible for checking the license

and obtaining the permission. If permission was required, a statement confirming permission should be included in the Material and Methods section.

The Comment section should include the following sub-headings:

Principal findings

Strengths of the study

Limitations of the data

Interpretation

Conclusions

Data Sharing and Data Accessibility

Please review Wiley's policy here. This journal expects data sharing.

The journal expects authors to share the data and other artefacts supporting the results in the paper by archiving it in an appropriate public repository. Authors should include a data accessibility statement, including a link to the repository they have used, in order that this statement can be published alongside their paper.

Author Guidelines Updated 15 June 2020

Appendix 3: Ethical approvals

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

26 September 2023

Dr Jerusha Shanthi John (991237653)
School of Clinical Medicine
Medical School

Dear Dr John,

Protocol reference number: BREC/00005453/2023
Project title: Treatable retinopathy of prematurity in KwaZulu-Natal, South Africa: How far have we come in the last 14 years?
Degree Purposes: MMed

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application.

The conditions have been met and the study is given full ethics approval and may begin as from 26 September 2023. Please ensure that any outstanding site permissions are obtained and forwarded to BREC for approval before commencing research at a site.

This approval is valid for one year from 26 September 2023. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on RIG on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2020) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be noted by a full Committee at its next meeting taking place on 10 October 2023.

Yours sincerely,

[redacted]

Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

Biomedical Research Ethics Committee
Chair: Professor D R Wassenaar
UKZN Research Ethics Office Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DIRECTORATE:
OFFICE OF THE MEDICAL MANAGER

NKOSI ALBERT LUTHULI CENTRAL HOSPITAL
rivate Bag X03, Mayville, 4058
00 Vusi Mzimela (Bellair) Road, Mayville,4091
el: 031 240 1059 Fax: 031 240 1005 Email: Ursula.john@ialch.co.za

Reference: BREC 00005453/2023
Enquiries: Medical Management

8 June 2023

Dr J S John (991237653)
School of Clinical Medicine
Medical School

Dear Dr John

RE: PERMISSION TO CONDUCT RESEARCH AT IALCH

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: **Treatable retinopathy of prematurity in KwaZulu-Natal, South Africa: How far have we come in the last 14 years?**

Kindly take note of the following information before you continue:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Kindly ensure that this office is informed before you commence your research.
4. The hospital will not provide any resources for this research.
5. You will be expected to provide feedback once your research is complete to the Medical Manager.

Yours faithfully

[redacted]

Dr A Harrichandparsad
Acting Medical Manager

KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DIRECTORATE:

Physical Address: 330 Langalibalele Street, Pietermaritzburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email: [redacted]

Health Research & Knowledge Management

NHRD Ref: KZ_202307_019

Dear Dr J John
(UKZN)

Approval of research

1. The research proposal titled '**Treatable retinopathy of prematurity in KwaZulu-Natal, South Africa: How far have we come in the last 14 years?**' was reviewed by the KwaZulu-Natal Department of Health (KZN-DoH).

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central hospital.

2. You are requested to take note of the following:
   a. ***Kindly liaise with the facility manager BEFORE your research begins.***
      This is to ensure that conditions in the facility are conducive to the conduct of your research. These include, but are not limited to, an assurance that the numbers of patients attending the facility are sufficient to support your sample size requirements, and that the space and physical infrastructure of the facility can accommodate the research team and any additional equipment required for the research.
   b. *All research conducted in KwaZulu-Natal must comply with government regulations relating to Covid-19. These include but are not limited to: regulations concerning social distancing, the wearing of personal protective equipment, and limitations on meetings and social gatherings.*
   c. *Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.*
   d. *Provide an interim progress report and final report (electronic and hard copies) when your research is complete to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za*
   e. *Please note that the Department of Health shall not be held liable for any injury that occurs as a result of this study.*

For any additional information please contact Dr. G Shezi on 033-395 3189.

Yours Sincerely

[redacted]

Dr E Lutge

Chairperson, Provincial Health Research Committee

Date: 31/08/2023

Appendix 4: Data collection tool

Study Number	ROP present	Race	Sex	DOB	Date of 1st visit	Referral Hospital	HIV Exposed	HIV PCR	Birth GA	Birth Weight	GA at 1st visit	Age at 1st Visit
Example	Yes	African	Female	23/06/2015	03/08/2015	IALCH	Yes	Neg	26	1000	31.9	5.9

O_2 therapy	Days on O_2	NNJ	Anaemia	Transfusions	Sepsis	Anti-VEGF	Laser	PPV	Last visit	Lost to follow-up	GA at last visit	Comments
Yes	12	No	Yes	4	No	1	1		18/01/2016	Yes	55.9	Did not return

Appendix 5: Raw data (example)

Study Number	ROP present	Race	Sex	DOB	Date of 1st visit	Referral Hospital	HIV Exposed	HIV PCR	Birth GA	##	Birth Weight	>1499	Should'nt have been referred?	GA at 1st visit	<31	>33	Age at 1st Visit	<4	>6	Referred too early	Referred too late	Incorrect referral
ST0001	Yes	African	Female	23/06/2015	03/08/2015	RKKH	Yes	Neg	26		1000			31.9			5.9					
ST0002	No	African	Male	17/07/2015	15/09/2015	MGMH			28		1070			36.6		Yes	8.6		Yes		Yes	Yes
ST0003	No	African	Male	30/09/2015	30/09/2015				32	Yes	1500	Yes	Yes	32.0			0.0	Yes				Yes
ST0004	No	African	Female	08/10/2015	16/11/2015	OGH	Yes	Neg	30		1500	Yes		35.6		Yes	5.6					
ST0005	Yes	Indian	Male	17/10/2015	23/11/2015	MGMH			32	Yes	1560	Yes	Yes	37.3		Yes	5.3					Yes
ST0006	Yes	African	Male	23/10/2015	23/11/2015				33	Yes	1970	Yes	Yes	37.4		Yes	4.4					Yes
ST0007	Yes	African	Male	25/10/2015	23/11/2015		Yes		32	Yes	1300			36.1		Yes	4.1					
ST0008	No	African	Female	29/10/2015	30/11/2015		No		28		895			32.6			4.6					
ST0009	No	African	Female	13/10/2015	30/11/2015		Yes	Neg	29		1100			35.9		Yes	6.9		Yes		Yes	Yes
ST0010	No	African	Female	28/10/2015	30/11/2015		No		29		1500	Yes		33.7		Yes	4.7					
ST0011	Yes	African	Male	03/11/2015	09/12/2015	KEH			32	Yes	1390			37.1		Yes	5.1					
ST0012	Yes	African	Male	06/10/2015	14/12/2015		No		29		1980	Yes		38.9		Yes	9.9		Yes		Yes	Yes
ST0013	No	African	Female	10/10/2015	14/12/2015		No		32	Yes	1435			41.3		Yes	9.3		Yes		Yes	Yes
ST0014	Yes	African	Male	09/11/2015	14/12/2015		Yes		30		1270			35.0		Yes	5.0					
ST0015	Yes	African	Female	16/11/2015	21/12/2015	KEH	Yes		31		1120			36.0		Yes	5.0					
ST0016	Yes	African	Female	17/11/2015	21/12/2015	SMH			32	Yes	1400			36.9		Yes	4.9					
ST0017	Yes	African	Male	18/10/2015	21/12/2015		Yes		28		1090			37.1		Yes	9.1		Yes		Yes	Yes

O_2 therapy	Days on O_2	NNJ	Anaemia	Transfusions	Sepsis	Anti-VEGF	Laser	PPV	ROP Treated	Last visit	Lost to follow-up	GA at last visit	>45	GA No ROP	GA ROP No-Tx	GA ROP Tx	Weight No ROP	Weight ROP No-Tx	Weight ROP Tx	Comments
Yes	12		Yes	4					No	18/01/2016	Yes	55.9	Yes		26			1000		def Sept 2015-Jar
Yes	45								n/a	23/10/2015		42.0		28			1070			
No									n/a	11/01/2016		46.7	Yes	32			1500			
		Yes							n/a	06/01/2016		42.9		30			1500			
Yes									No	11/01/2016		44.3			32			1560		referred paeds e
Yes				2					No	23/02/2016		50.6	Yes		33			1970		
Yes									No	25/01/2016		45.1	Yes		32			1300		
Yes	4		Yes	1					n/a	15/02/2016		43.6		28			895			
No			Yes	2	Yes				n/a	04/01/2016		40.9		29			1100			
Yes	7								n/a	11/01/2016		39.7		29			1500			
Yes	6								No	18/01/2016		42.9			32			1390		
Yes				4					No	18/01/2016	Yes	43.9			29			1980		
No									n/a	04/01/2016		44.3		32			1435			
Yes	7			1					No	15/02/2016		44.0			30			1270		
No					Yes				No	15/02/2016		44.0			31			1120		
Yes	28								No	08/02/2016		43.9			32			1400		
Yes	37								No	08/02/2016		44.1			28			1090		