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REVIEW

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# Prevalence and risk factors of retinopathy of prematurity in Africa: A systematic review and meta-analysis

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**Abstract:** *Background*
Improvement in neonatal services across Africa has led to increased survival of preterm and low birth weight neonates with consequent rising incidence of ROP. We review the reported prevalence and risk factors associated with ROP in Africa.
*Methods:* Databases were searched systematically between December 2018 and February 2019, using relevant search terms. Primary studies done between 1948 and February2019 in Africa reporting prevalence and/or risk factors for ROP were included. Eligible articles were reviewed and discrepancies resolved by consensus. We conducted random -effects meta-analyses to estimate the overall ROP prevalence. Inter-study heterogeneity, potential confounding variables, publication bias, and small-study bias were explored using Galbriath plot, sensitivity analysis, meta-regression, and Egger's regression tests while temporal trends from accumulating studies were explored using cumulative meta-analysis.
*Results:* Twenty-four studies from six African countries were included. To address heterogeneity, we grouped the studies by prevalence: High (> 45%) – four; Medium (20% to 44%) - twelve; Low (< 20%) – eight studies. The commonest risk factors were very low birth weight and lower gestational ages. The combined prevalence of ROP in Africa was 30%. Cumulative meta-analysis indicated an increasing ROP prevalence in the last 2 decades.
*Conclusion:* The prevalence of ROP in Africa is 30% with commonest risk factors being lower gestational age and very low birth weight. Increasing prevalence is possibly related to better survival of preterm neonates while risk management remains static.

**Keywords:** Retinopathy of prematurity, Africa, Prevalence, Risk factors, Meta-analysis

**Plain English Summary**

Retinopathy of Prematurity (ROP), a potentially blinding eye disease is on the increase, affecting mainly premature babies who are having better survival because of improving healthcare in Africa. This study looked at what factors cause it and the number of babies currently affected.
Papers on the subject from 1948 to February 2019 were reviewed between December 2018 and February 2019, looking for total percentage of babies currently affected as well as factors leading to the development of disease. Articles were chosen by pre-specified criteria and different analyses to demonstrate specific outcomes were performed We included twenty-four articles from six African countries which were grouped into high, medium and low prevalence, depending on current numbers of babies with the disease as reported in the studies. The duration of pregnancy at the time of birth and birth weight of the baby were the commonest factors leading to development of the disease at any point in time.
Overall, 30% of preterm babies develop the disease in Africa. We also found a steady increase over the past two decades in the number of babies having the disease at any point in time. The tendency for the increasing numbers of babies developing the disease may be related to better survival as the factors causing it and its management largely remain unchanged.

## Background

Sixty percent of the world's premature births occur in sub-Saharan Africa and survival was previously very poor[1]. There has however been a significant improve-

ment in facilities and manpower for newborn care not only in developed, but also in developing countries[1]. With
increasing survival of premature babies across various parts of the world, retinopathy of prematurity (ROP) has emerged a leading cause of preventable childhood blindness[2-4]. Retinopathy of prematurity (ROP) is a vision-threatening disease associated with abnormal retinal vascular development at the boundary of the vascular and avascular peripheral retina resulting from preterm birth[2 5]. Retinal vascular development begins in the 16th week of gestation, starting from the optic disc centrifugally to the retinal periphery and is completed at about 36 weeks[2]. Therefore, the retina and retinal vasculature are fully developed in healthy term infants, often obviating the risk of retinopathy of prematurity. Conversely, in preterm babies, the development of the retina is incomplete making them vulnerable, with risk of disease severity increasing with decreasing gestational age at birth[5 6]. Other morbidities like asphyxia, sepsis, failure to thrive, fluctuating plasma glucose levels, and most significantly, fluctuating oxygen saturation levels, are associated with increased severity and rapid progression of the disease[2]. The absence of retinal vessels in the immature retina can result in retinal ischemia, leading to abnormal release of vascular growth factors with aberrant retinal vascular development. Abnormal fibrovascular proliferation results in vitreous hemorrhage, tractional retinal detachment, and blindness[2]. The disease was previously believed to be caused by high oxygen saturation in these preterm infants. However, studies strictly regulating oxygen supply to these babies now point to a multifactorial pathogenesis that includes oxygen fluctuations, poor growth, oxidative stress, nutritional deficiencies [2 3 7 8].

Retinopathy of prematurity (ROP) has an estimated global incidence of 20,000 infants per year. Previous studies have reported prevalence of retinopathy of prematurity ranging from 14% to 69% in different parts of the world[1 4 9-13]. In the United States, about 14,000 preterm infants are affected each year[2].Certain Latin American and East European countries recorded incidences of childhood blindness due to ROP as high as 38.6 and 25.9%, respectively[9 14]. In South Africa, an estimated 16,000 infants are at risk of ROP and require screening each year[15]. In Sub-Saharan Africa, there is also an increasing prevalence of retinopathy of prematurity[15]. A hospital- based retrospective review of the records of premature infants screened for ROP between January 2010 and December 2015 in Kenya revealed that 41.7% of infants were diagnosed with retinopathy of prematurity[4]. A prospective study to determine the frequency and risk factors associated with ROP in preterm infants in Lagos University Teaching Hospital reported that 15% of the 80 infants examined had any ROP[10].Another prospective study carried out at the Special Care Baby Unit (SCBU) and Pediatric Outpatient Clinics of the University of Port Harcourt Teaching Hospital between January 1 and October 31, 2012 revealed that 47.2% had different degrees of ROP[16].

Several studies have reported risk factors associated with retinopathy of prematurity some of which include gestational age (strongest risk factor), low birth weight, sepsis, oxygen therapy, female gender, and frequent blood transfusions[4 9 10 12 13].As a result of the heterogeneity in prevalence, it is essential to summarize the evidence on the prevalence of retinopathy of newborn to aid in strategic planning and health policy making for better patient care. A good understanding of the risk factors of retinopathy of prematurity will enhance prevention and treatment. This review aims to elucidate the prevalence and risk factor associated with retinopathy of prematurity in Africa.

## Methods

*Search strategy and selection criteria*

A systematic search for literature was conducted between December 2018 and February 2019. The databases searched include PUBMED, Ovid MEDLINE,EMBASE Classic plus EMBASE, CINAHL, Web of Science, AJOL and Google Scholar. The search terms used included prevalence, risk factors, incidence, determinants, burden, screening, predictors, retinopathy of prematurity, retrolental fibroplasia and Africa. Also, searches were conducted with the same search terms including specific names of each African country and the African regions such as West Africa, sub-Saharan Africa, etc. Bibliographies of the retrieved articles were carefully reviewed for any relevant articles published within the time frame. The search strategy is displayed in Additional file 1

*Inclusion and exclusion criteria*

We included primary studies that were carried out in Africa and published in English language, published between the years 1948 and February2019 which reported prevalence and/or risk factors of retinopathy of prematurity. Review articles and studies in other languages were excluded.

*Study Selection*

A total of 213 publications were identified from the search including 6 from Google Scholar and 14 from African Journal online. After duplicates were removed, the number of remaining publications was 67 articles, and these were reviewed for inclusion based on information contained in titles and abstracts.
Studies not addressing the topic of review were excluded to givea total of 27 full text articles. These were assessed further, and 3 studies removed because they either did not estimate the prevalence nor report risk factors. One of them included Africa as part of a global study. All authors agreed on the inclusion of 24 studies in the final review. See figure 1 for PRISMA flow diagram[17].

*Data extraction*

A data extraction form was developed and reviewed by all authors. Data was extracted for each paper using the standardised form with the following domains: the name of first author and year of publication, study location, study design, prevalence, birth weight, and risk factors. Two of the reviewers extracted the data independently and discrepancies were resolved by discussion and consensus. The references were tracked using End Note reference manager where duplicates were also removed.

*Meta-analysis*

A random-effects weighted meta-analysis was conducted to determine the combined prevalence of ROP in the included studies. Random-effects weighting was employed considering the between-study differences in setting and prevalence. Inter-study heterogeneity was assessed using I-squared statistics. Subgroup meta-analysis with analysis of variance (ANOVA) was performed to examine differences between high prevalence (HP), medium prevalence (MP) and low prevalence (LP) subgroups. Meta-regression analysis was used for moderator analysis i.e. to test whether mean birth weight confounded ROP prevalence meta-analysis. Forest plots and bubble plots were utilized to display the meta-analysis and meta-regression results, respectively. A *p*-value of 0.05 was used as significant threshold. Publication bias and small-study biaswere explored using Galbriath plot, sensitivity analysis, meta-regression, and Egger's regression tests. Cumulative meta-analysis was done to elucidate temporal trend from accumulating studies. Meta-Essentials package Version 1.4 [18] and Open Meta [Analyst] Version 10.12 [19]were used for computing statistical analysis. Forest plots were generated using the online tool Distiller SR Forest Plot Generator from Evidence Partners[20].

*Ethical Considerations*

Ethical approval was not required for this study because it is a systematic review with no direct involvement of human or animal study participants. This review was registered in PROSPERO with registration number CRD42018117536.

## Results

Twenty-four studies enrolling a total of 1848 patients met the inclusion criteria and were reviewed in this study. The studies reviewed were carried out in six countries. South Africa (9) and Egypt (7) had the highest number of studies. Prospective cohort, retrospective cohort and cross-sectional study designs were the commonly used study designs (Table 1). The prevalence of ROP was determined at varying mean birth weights in the individual studies (Table 1). The study findings are presented based on the prevalence of ROP usefully categorized into 3 groups namely: low prevalence (≤20%), medium prevalence (21-45%) and high prevalence of ROP (≥46%) (Table 1). A summary all studies with number of ROP cases is shown in table 2. The risk factors for ROP are presented in Table 3.

**Table 1:** Prevalence of retinopathy of prematurity in Africa

| Author/date | Country | Prevalence | Subgroup | Mean birth weight | Study design |
|---|---|---|---|---|---|
| Ali et al., 2017 | Egypt | 69% | HP | 1200 | Retrospective |
| Bassiouny et al., 2017 | Egypt | 59% | HP | 1514 | Prospective |
| Ademola et al., 2013 | Nigeria | 89.6% | HP | 1500 | Retrospective |
| Adio et al., 2014 | Nigeria | 47.2% | HP | 1411 | Prospective |
| El-Mekawey et al., 2011 | Egypt | 23% | MP | NA | Prospective |
| Bedda et al.,2014 | Egypt | 33.74% | MP | 1223 | Non-comparative nonrandomized interventional prospective study |
| Hadi et al., 2013 | Egypt | 34.40% | MP | 1329 | Prospective study |
| Nassar,2016 | Egypt | 36.50% | MP | 1234 | Prospective study |
| Onyango et al.,2018 | Kenya | 41.7% | MP | 1280 | Retrospective |
| Delport et al., 2002 | South Africa | 24.40% | MP | 1200 | Cross-sectional |
| Kirsten et al.,1995 | South Africa | 32% | MP | 1184 | Prospective |
| Jacoby et al.,2016 | South Africa | 25.90% | MP | NA | Retrospective |
| VisserKift et al.,2016 | South Africa | 33.40% | MP | 930 | Cross-sectional |
| Keraan et al.,2016 | South Africa | 29.60% | MP | 1056 | Prospective cohort study |
| Van der Merwe et al., 2013 | South Africa | 21.80% | MP | 949 | Retrospective Study |
| Omer et al., 2014 | Sudan | 37% | MP | NA | Prospective study |
| Hakeem et al.,2012 | Egypt | 19.2 | LP | 1510 | Prospective |
| Wanjala et al., 2007 | Kenya | 17.40% | LP | 1375 | Non-comparative cohort |
| Baiyeroju et al.,1998 | Nigeria | 5.50% | LP | 870-1500 | Prospective |
| Fajolu et al., 2015 | Nigeria | 15.00% | LP | 1231 | Prospective Cohort |
| Uwizihiwe, 2016 | Rwanda | 14.90% | LP | NA | Cross sectional |
| Kana et al., 2017 | South Africa | 1.20% | LP | 1074 | Cross sectional |
| Mayet et al.,2006 | South Africa | 16.30% | LP | 800-1250 | Prospective |
| Dadoo et al.,2016 | South Africa | 15.64% | LP | 1127 | Retrospective |

HP: High Prevalence, MP: Middle Prevalence LP: Low Prevalence NA: Not Available

**Table 2:** Summary of all studies with number of ROP cases

| Author name | Country | Prevalence of ROP | Subgroup | Number of ROP cases | Sample size |
|---|---|---|---|---|---|
| Ali et al., 2017 | Egypt | 69% | HP | 75 | 108 |
| Bassiouny et al., 2017 | Egypt | 59% | HP | 237 | 402 |
| Ademola et al., 2013 | Nigeria | 89.6% | HP | 26 | 29 |
| Adio et al., 2014 | Nigeria | 47.2% | HP | 25 | 53 |
| El-Mekawey et al., 2011 | Egypt | 23% | MP | 226 | 981 |
| Bedda et al.,2014 | Egypt | 33.74% | MP | 73 | 223 |
| Hadi et al., 2013 | Egypt | 34.40% | MP | 52 | 152 |
| Nassar,2016 | Egypt | 36.50% | MP | 19 | 52 |
| Onyango et al.,2018 | Kenya | 41.7% | MP | 43 | 103 |
| Delport et al.,2002 | Pretoria | 24.40% | MP | 23 | 94 |
| Kirsten et al.,1995 | South Africa | 32% | MP | 40 | 127 |
| Jacoby et al.,2016 | South Africa | 25.90% | MP | 239 | 919 |
| Visser-Kift et al.,2016 | South Africa | 33.40% | MP | 369 | 1104 |
| Keraan et al.,2016 | South Africa | 29.60% | MP | 40 | 135 |
| Van Der Merwe et al., 2013 | South Africa | 21.80% | MP | 75 | 356 |
| Omer et al.,2014 | Sudan | 37% | MP | 34 | 92 |
| Hakeem et al.,2012 | Egypt | 19.2 | LP | 33 | 172 |
| Wanjala et al., 2007 | Kenya | 17.40% | LP | 21 | 120 |
| Baiyeroju et al.,1998 | Nigeria | 5.50% | LP | 1 | 18 |
| Fajolu et al., 2015 | Nigeria | 15.00% | LP | 12 | 80 |
| Uwizihiwe, 2016 | Rwanda | 14.90% | LP | 22 | 148 |
| Kana et al., 2017 | South Africa | 1.20% | LP | 23 | 1911 |
| Mayet et al.,2006 | South Africa | 16.30% | LP | 84 | 514 |
| Dadoo et al.,2016 | South Africa | 15.64% | LP | 23 | 147 |

**Table 3:** Risk factors associated with retinopathy of prematurity in Africa.

| Risk factor | Number of studies | Author/date | Predisposing |
|---|---|---|---|
| Female gender | 1 | Merwe et al., 2013 | (+) |
| Supplemental oxygen | 2 | Bassiouny et al., 2017 | (+) |
| | | Hakeem et al.,2012 | (+) |
| Sepsis | 3 | Ali et al 2017 | (+) |
| | | Hakeem et al.,2012 | (+) |
| | | Uwizihiwe, 2016 | (+) |
| Blood transfusion | 2 | Keraan et al.,2017 | (+) |
| | | Hakeem et al.,2012 | (+) |
| Ventilation | 1 | Ali et al., 2017 | (+) |
| Birth weight | 4 | Bassiouny et al., 2017 | (+) |
| | | Visser-kift et al.,2016 | (+) |
| | | Keraan et al.,2017 | (+) |
| | | Uwizihiwe, 2016 | (+) |
| Gestational age | 4 | Visser-kift et al.,2016 | (+) |
| | | Keraan et al.,2017 | (+) |
| | | Hakeem et al.,2012 | (+) |
| | | Uwizihiwe, 2016 | (+) |
| Severe apnoea | 1 | Merwe et al., 2013 | (+) |
| Respiratory distress syndrome | 2 | Wanjala et al., 2007 | (+) |
| | | Uwizihiwe, 2016 | (+) |

*Quality Appraisal*

Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [21]was used to appraise the quality of the studies included in this review (Additional file 2). This quality assessment tool has been used in other systematic reviews[22-24]. The tool is made up of fourteen questions which assess different aspects of a study including but not limited to definition of objectives, study population, sampling strategy, sample size and statistical analyses. Each question is scored as Yes (1) or No (0), and others (CD, cannot determine; NA, not applicable and NR, not reported). The elements of the criteria which did not apply to a particular study were marked as not applicable. The quality assessment was done by the first author and two other co-authors.

All the 24 studies fulfilled the quality criteria although20 studies did not report on sample size justification, power description, or variance and effect estimates. In four studies the exposures of interest were not measured prior to the outcome being measured, and in 19 studies, key potential confounding variables were not measured.

*Prevalence of ROP*

*High ROP prevalence*

A high prevalence of ROP was documented in four studies with a total of 363 patients from 2 countries (Nigeria and Egypt)[16 25-27].The prevalence of ROP was 47.2%-89.6% (Table 2).

*Medium ROP prevalence*

In twelve (12) of the studies with a total of 1253 patients from 4 countries, ROP prevalence was medium. The lowest prevalence in this category was 23% from a study in Egypt while the highest was 41.7% from a similar study in Kenya [4 11 15 28-36](Table 2).

*Low ROP prevalence*

Eight of the studies with a total of 232 patients in this review found a low prevalence of ROP of 1.2%-19.2%[10 13 37-42]. (These studies were conducted in 5 African countries, i.e. Egypt, Kenya, Nigeria, Rwanda, and South Africa) (Table 2).

*Risk factors for ROP*

A total of nine risk factors were identified in this review as reported by some of the included studies.

*Birth Weight*

Four of the studies found that birth weight was a predictor of developing ROP in the patients surveyed. Lower birth weight babies were more at risk of ROP [11 15 26 41]. (Table 3)

*Gestational age*

Four of the studies found that gestational age was a risk factor for developing ROP. The studies showed that babies born at lower gestational age were more likely to have ROP[11 13 15 41]. (Table 3)

*Female gender*

One of the studies found that females were more likely to be affected by ROP compared to males[35].(Table 3)

*Supplemental oxygen*

Oxygen therapy was found to be a predictor of increased likelihood of development ROP in two studies[13 26]. (Table 3)

*Sepsis*

In three of the studies, sepsis increased the riskof developing ROP in the surveyed patients[13 25 41].(Table 3)

*Blood transfusion*

Two of the studies found that patients who received blood transfusion were more likely to develop ROP compared to those who were not transfused[11 13].(Table 3)

*Ventilation*

Receiving mechanical ventilation therapy increased the risk of development of ROP[25].(Table 3)

*Severe apnoea*

Severe apnoea was reported as a risk factor for experiencing ROP in one of the studies[35]. (Table 3)

*Respiratory distress syndrome*

Two studies reported respiratory distress syndrome as a risk factor for retinopathy of prematurity[37 42].

*Meta-analysis, Heterogeneity, Subgroup Meta-analysis Results*

Meta-analysis revealed the combined prevalence of ROP in Africa to be 30% (95% CI 22%, 39%), with significant heterogeneity of 95% $I^2$ ($p< 0.0001$) (Figure2a). In order to address heterogeneity, we grouped the studies into 3 groups of high (> 45%), medium (20% to 44%), and low (< 20%) prevalence. Subgroup meta-analysis showed that only the medium prevalence (MP) subgroup (12 studies) with a combined prevalence of 29% exhibited insignificant heterogeneity ($I^2$ = 36.5%; p = 0.09, Figure 2d). High prevalence (HP) subgroup (4 studies) featured a combined prevalence of 67% and significant heterogeneity ($I^2$ = 87.6%; $p< 0.0001$, Figure 2b). Low prevalence (LP) subgroup (8 studies) with 11% combined prevalence similarly showed significant heterogeneity ($I^2$ = 60%; p = 0.01, Figure 2c). ANOVA analysis showed significant differences among the 3 subgroups ($p< 0.0001$, Figure 2e).

**Fig 1:** PRISMA flow diagram

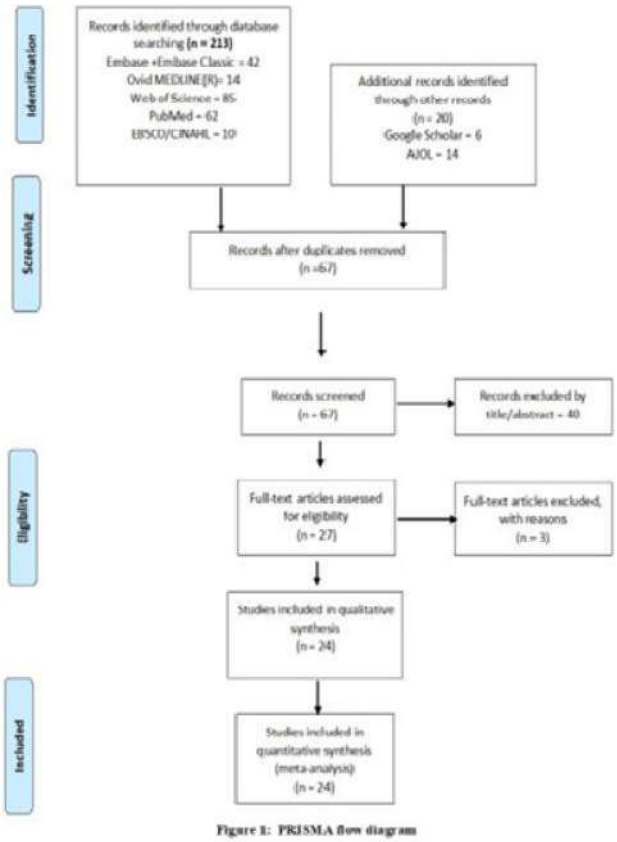



Figure 1: PRISMA flow diagram

*Meta-regression Results*

Meta-regression within the homogenous MP subgroup showed that there was no statistically significant association between birth weight and ROP prevalence (p =

**Fig 2a:** Random-effects meta-analysis forest plot

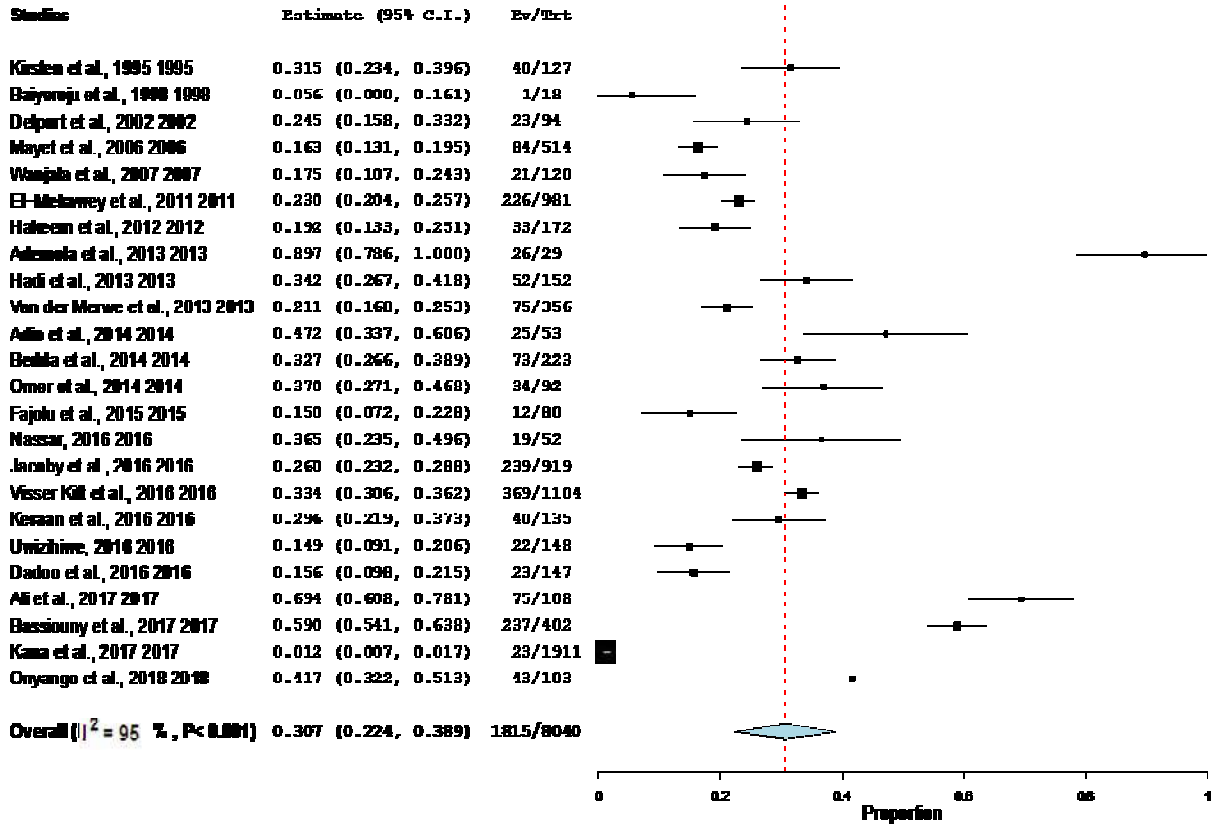



**Fig 2b**

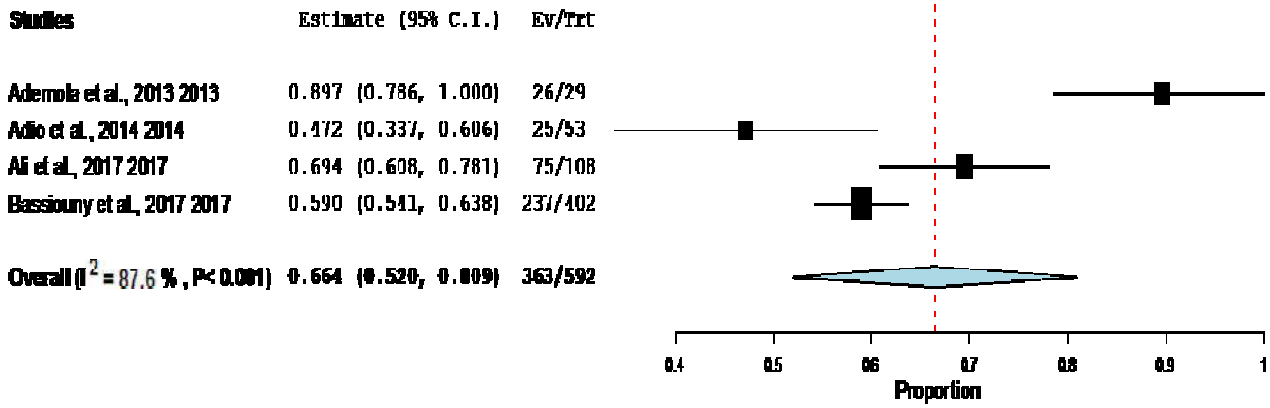



**Fig 2c**

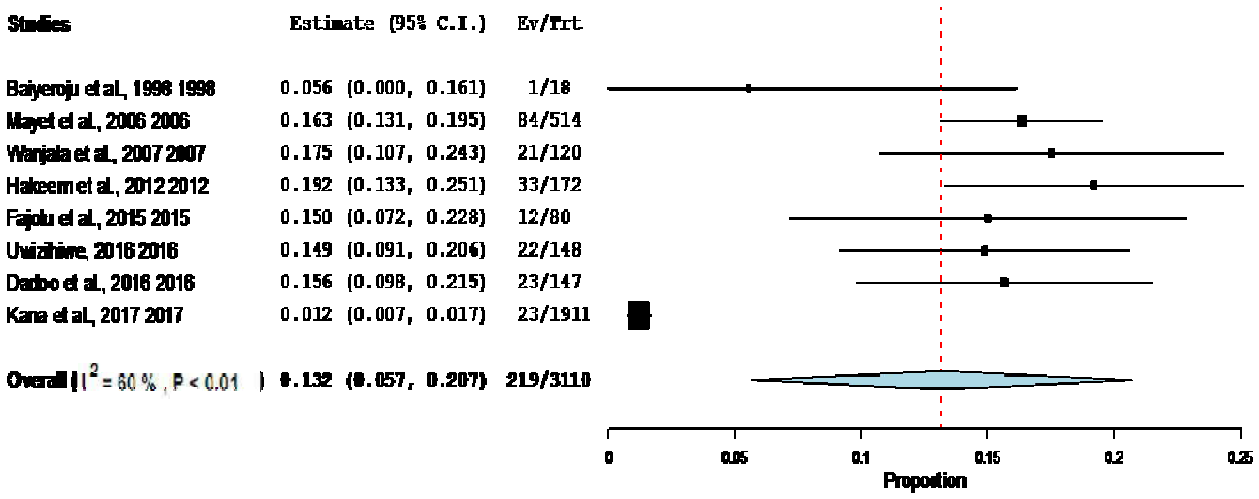


**Fig 2d**

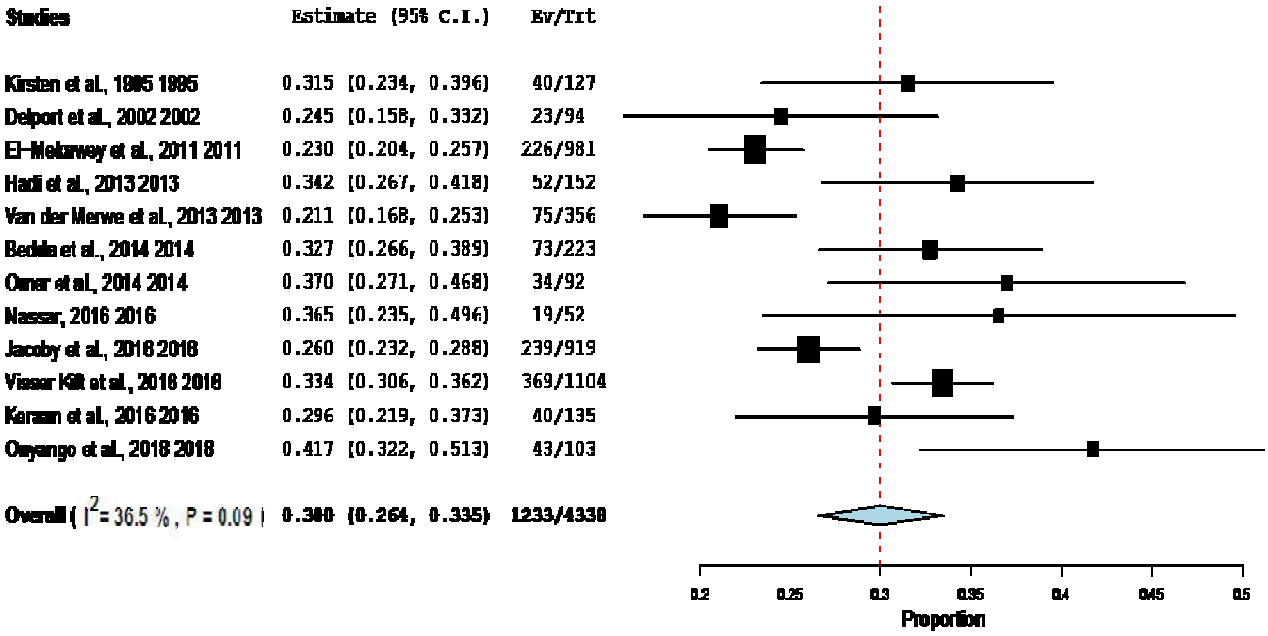
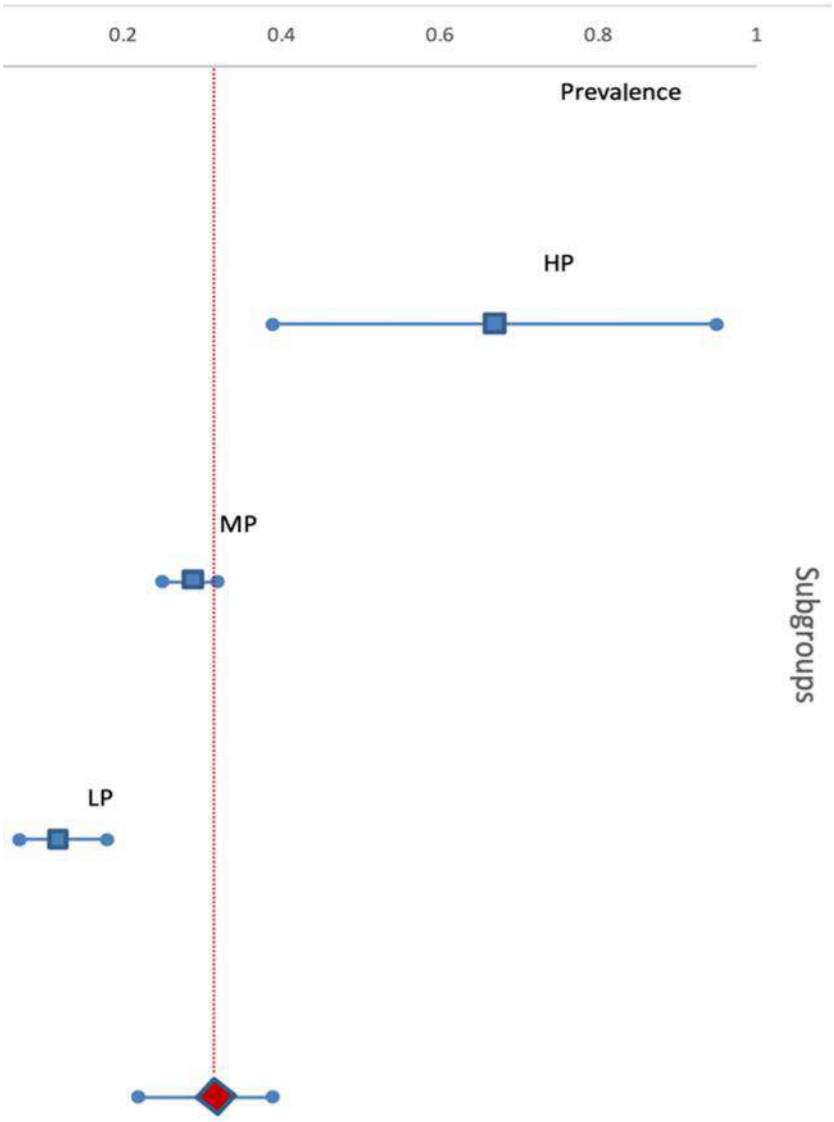

Studies
Estimate (95% C.I.)
Ev/Trt
Kirsten et al., 1995 1995 0.315 (0.234, 0.396) 40/127
Delport et al., 2002 2002 0.245 (0.158, 0.332) 23/94
El-Mekawy et al., 2011 2011 0.230 (0.204, 0.257) 226/981
Hadi et al., 2013 2013 0.342 (0.267, 0.418) 52/152
Van der Merwe et al., 2013 2013 0.211 (0.168, 0.253) 75/356
Bedda et al., 2014 2014 0.327 (0.266, 0.389) 73/223
Oner et al., 2014 2014 0.370 (0.271, 0.468) 34/92
Nassar, 2016 2016 0.365 (0.235, 0.496) 19/52
Jacoby et al., 2016 2016 0.260 (0.232, 0.288) 239/919
Visser Kilt et al., 2016 2016 0.334 (0.306, 0.362) 369/1104
Karaan et al., 2016 2016 0.296 (0.219, 0.373) 40/135
Onyango et al., 2016 2016 0.417 (0.322, 0.513) 43/103
Overall ( I² = 36.5 %, P = 0.09 ) 0.300 (0.264, 0.335) 1233/4338
0.2
0.25
0.3
0.35
0.4
0.45
0.5
Proportion

**Fig 2e**


0.2
0.4
0.6
0.8
1
Prevalence
HP
MP
LP
Subgroups

0.31). Six studies did not report mean birth weights, and hence were excluded from meta-regression analysis

*Publication Bias Results*

Inverted funnel plot was moderately deviated from a well-behaved data with asymmetrical appearance indicating some degree of publication bias (Figure 3a). The Trim-and-fill method estimated 2 missing studies. Begg and Mazumdar rank correlation test confirmed that publication bias did not reach statistical significance – signified by a weak correlation between effect sizes and their variances (Kendall's Tau 0.06, p = 0.35) and a non-significant Egger's regression test (p = 0.32). Standardized residual histograms mildly departed from a normal distribution showing similar findings to the 2 missing studies estimated by Trim-and-fill analysis (Figure 3b).

*Outlier and Small-Study Bias Detection*

Galbraith's plot demonstrated that 20 (83%) of the included studies stayed within 2 standard deviations (SD) from the regression line (Figure 3c) – indicating the remaining 17% were responsible for the moderate amount of publication bias and heterogeneity. Two studies that fell below -2 SD had higher study precision but lower effect size (prevalence) – this indicated mild degree of small-study bias and file drawer problem. Rosenthal's Fail-Safe N test showed that another 6949 studies are needed to nullify the combined summary from our meta-analysis.

*Sensitivity Analysis Results*

Leave-one-out meta-analysis showed that the high ROP prevalence of 89.7% by Ademola et al., 2013 resulted in a substantial influence over the prevalence of 30% (Figure 4a).

*Cumulative Meta-analysis Results*

Cumulative meta-analysis (Figure 4b) showed that the prevalence of ROP has been increasing over the last 2 decades with a prevalence of about 30%. This result suggests that prevention of ROP stayed stagnant in African care settings while survival of preterm neonates improved.

**Fig 3a:** Publication bias assessment plots.

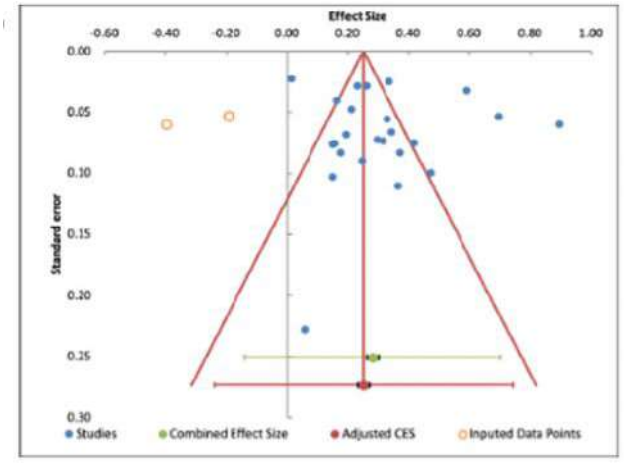



**Fig 3b**

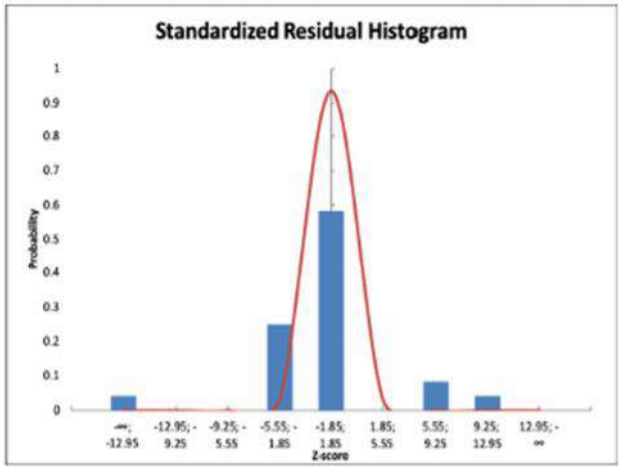



Fig 3c

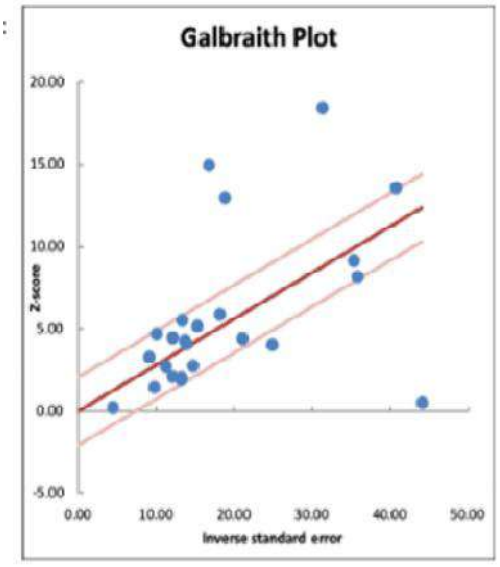


**Fig 4:** Sensitivity analysis and cumulative meta-analysis.

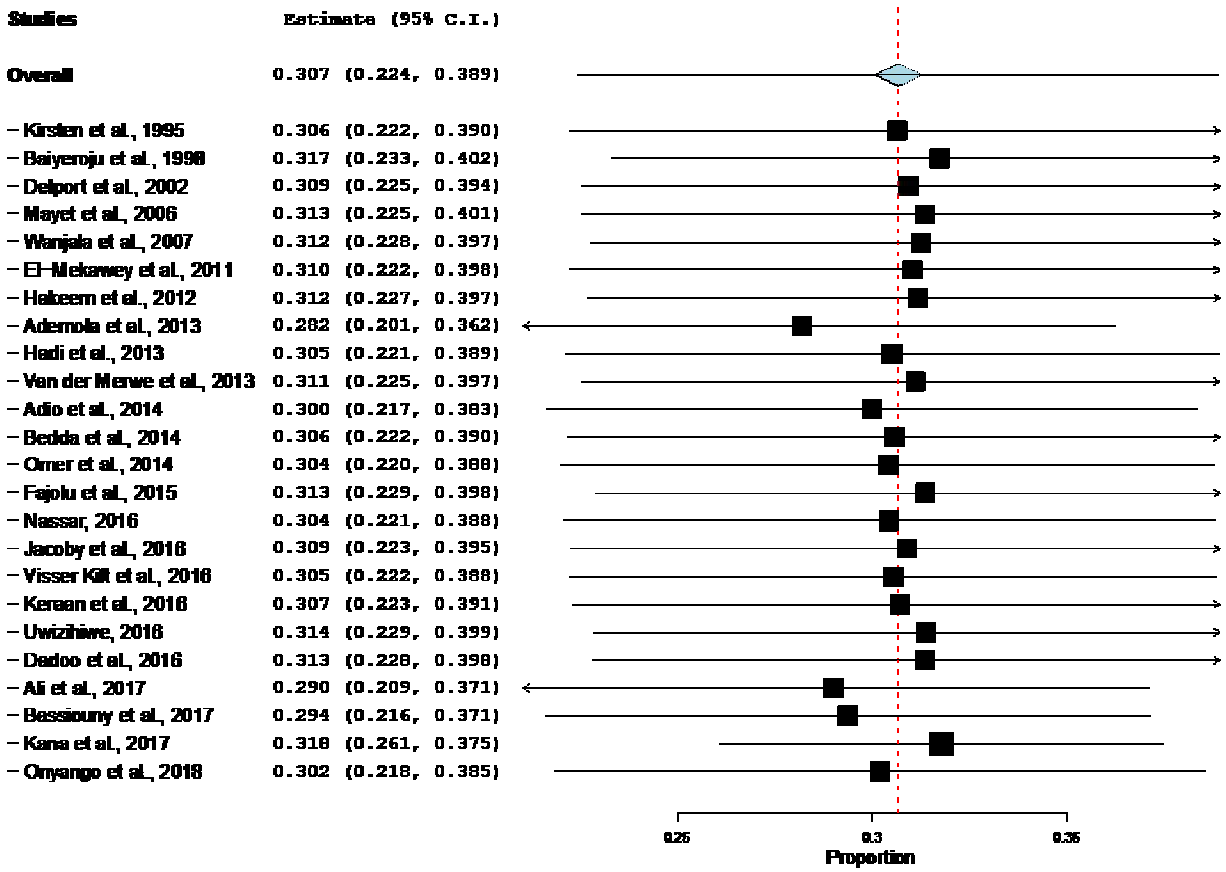
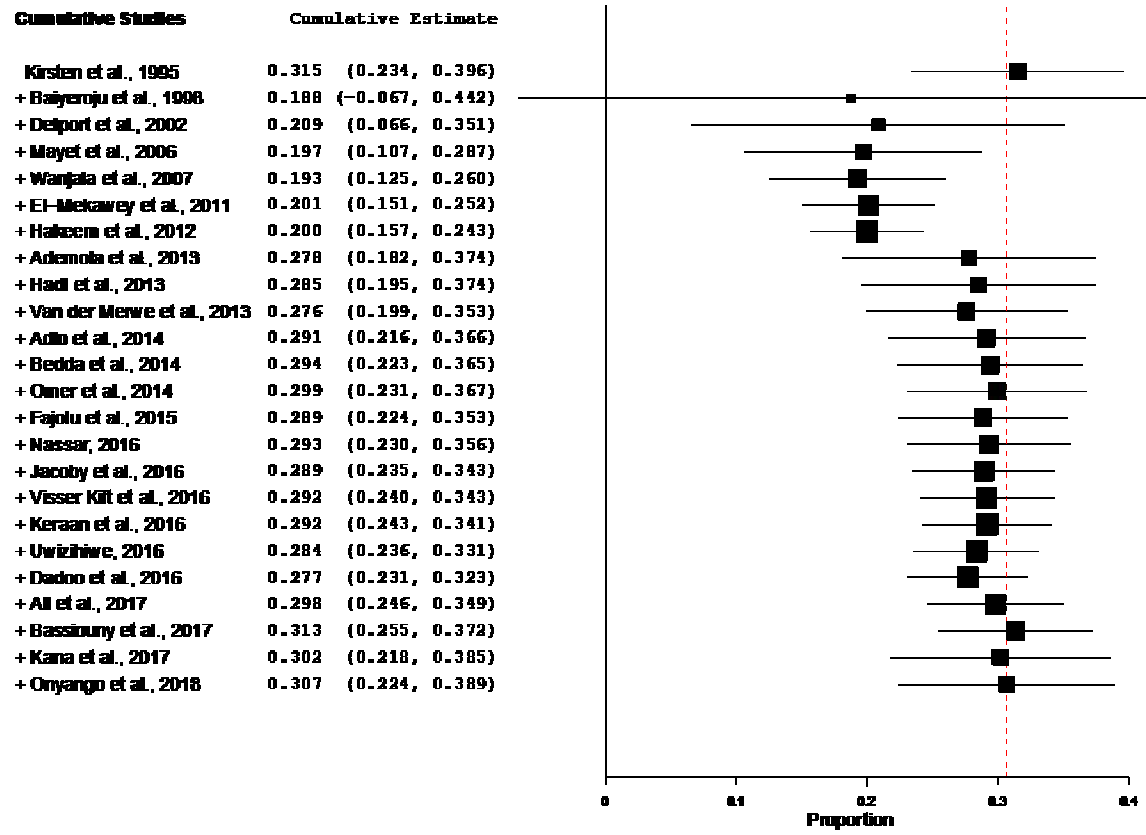



**Fig 4b**



Prisma check list

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| *Title* | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | Page 1 |
| *Abstract* | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | Page 2 |
| *Introduction* | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | Page 4-5 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | Page 5 |
| *Methods* | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | Page 8 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | Page 6-7 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | Page 6 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Page 6 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | Page 6-7 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | Page 7 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | Not applicable |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | Page 8 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | Page 8 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | Page 7 |

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | Page 7 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | Page 7 |
| *Results* | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | Page 8 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Page 8 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Page 8 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Forest plots attached |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | Page 10-11 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | Page 11 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | Page 11-12 |
| *Discussion* | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | Page 12-14 |
| Limitations | 25 | Discuss limitations at study and outcomelevel (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | Page 14 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | Page 12-14 |
| *Funding* | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | Not applicable |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097
For more information, visit:www.prisma-statement.org.

## Discussion

This review set out to elucidate the prevalence and risk factors associated with retinopathy of prematurity in Africa. The studies reviewed cut across six countries in Africa. The prevalence of ROP in this review varied from 1.2% in a South Africa, to 86.9% in Nigeria. A recently published systematic review on retinopathy of prematurity in Africa also identified studies carried out in these six African countries[43]. However, studies that reported high or medium prevalence were more in number when compared with those that reported low prevalence of ROP which shows that generally, the trend is towards an increasing prevalence. This increasing prevalence of ROP in Africa could be attributed to improvement in maternal and neonatal medical technology and care with resultant increased survival of preterm babies[44].

The high number of medium prevalence studies shows that although there is some improvement in neonatal patient care in Sub-Saharan Africa, more effort is required to ensure reduction in prevalence of ROP. In developing countries, less expert neonatal care, widespread unavailability of oxygen-air blenders and a lack of oxygen saturation monitors and little or no advanced training for neonatologists, ophthalmologists and neonatal nurses, continues to be a reason for the medium to high prevalence of ROP in these countries[45]. The most common risk factors identified in this review were birth weight and gestational age. Neonates who had lower birth weight of less than 1500grams were more likely to have ROP. Similarly, another review of 42 studies including 18,000 premature infants carried out in Iran, reported low birth weight as a risk factor for ROP and it was more likely to occur in babies of much lower gestational ages[46].

Low birth weight and low gestational age have been identified as the two strongest risk factors for ROP[2]hence, the American Academy of Pediatrics guideline states that, infants with a birth weight ≤ 1500 grams or gestational age of ≤ 30 weeks and selected infants with a birth weight between 1500 and2000 grams or gestational age of more than 30weeks with an unstable clinical course, should be screened for ROP[47], yet this is not a common practice in many neonatal units across Africa. It is therefore necessary to prioritize screening among this group of babies when planning for the intervention considering our resource-limited setting and the limited number of available trained personnel who are also burdened by other duties[11]. Timely screening is

very essential for early detection and treatment, and for improved outcomes.

Other risk factors identified in this review include female gender, supplemental oxygen, sepsis, blood transfusion, ventilation and severe apnoea. Babies who received supplemental oxygen were more likely to develop ROP[13 26]. It is more common for many centers to use unblended oxygen[48 49].The use of supplemental oxygen is a known risk factor for ROP[2].In premature infants, the retina is only partially vascularized. High oxygen level leads to down-regulation of vascular endothelial proliferation and survival factors such as vascular endothelial growth factor (VEGF), leading to incomplete retinal vascular formation which characterizes the primary stage of ROP[45].The review carried out in Iran also identified similar risk factors, except for gender which was not identified as an associated factor[50].

The heterogeneity in prevalence of ROP was found to be high ($I^2$=87.5%) and is in keeping with previous studies both in Sub-Saharan Africa and globally[46]. This heterogeneity could result from differences in sample size, or differences in the gestational age and birth weight.

There were few limitations in this study which included an arbitrary selection of cut-offs for LP, MP, HP by authors' judging from the distribution of the prevalence data; it was not tested. Also, there was a high heterogeneity overall in the studies however, the between-study prevalence of 29% in MP subgroup was not significant. The MP combined prevalence was found to be similar to the overall combined prevalence of 30%.

## Conclusion

The current prevalence of ROP in Africa is 30%. The risk factors identified in this review include very low gestational age and low birth weight, Others include female gender, supplemental oxygen, sepsis, blood transfusion, ventilation and severe apnoea. The trend is towards an increasing prevalence possibly related to better survival of preterm babies.

**Authors' contributions**

OBE: Study conceptualization and design, systematic search of literature, data extraction, analysis and interpretation of results, manuscript drafting and approval of the final manuscript for publication.

EE: Study design, data extraction, manuscript drafting and approval of the final manuscript for publication.

ICA: Study design, data extraction, manuscript drafting and approval of the final manuscript for publication.

INO: Study design, data extraction, manuscript drafting and approval of the final manuscript for publication.

YW: Study design, analysis and interpretation of results, meta-analysis, manuscript drafting and approval of the final manuscript for publication.

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