Glaucoma control strategies in Sub-Saharan Africa: a review of the clinical and health economic evidence

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Abstract:

Purpose: A review of the effectiveness, costs and cost-effectiveness of detection and treatment strategies for glaucoma control in Sub-Saharan Africa (SSA) was conducted.

Methods: Detailed searches were performed using the Ovid Medline; Ovid Embase; The Cochrane Library; Web of Science; Scopus; and LILACS databases up to September 2016. The key Medical Subject Heading (MeSH) search terms used included: *glaucoma, diagnosis, treatment, effectiveness, costs, cost-effectiveness and Sub-Saharan Africa*. Effectiveness was measured as the proportion of study participants with an intra-ocular pressure (IOP) less than or equal to 22 mm Hg.

Results: A total of 5,658 records were examined with 48 papers identified. The sensitivity and specificity of portable instruments or smart phone technologies to detect glaucomatous changes ranged from 58.3% to 93.8% and from 82.4% to 96.8%, respectively. The overall effect size for various glaucoma interventions was: 0.39 (95% C.I. 0.27-0.54, I^2=64.85, P=0.036) for laser trabeculoplasty; 0.56 (95% C.I. 0.23-0.84, I^2=85.74, P=0.001) for drainage implant devices; 0.66 (95% C.I. 0.61-0.71, I^2= 0.00, P=0.402) for medical management; and 0.73 (95% C.I. 0.65-0.80, I^2= 93.25, P=0.000) for all other non-drainage tube surgical interventions, including trabeculectomy surgery and the use of anti-metabolites. The mean annual cost of anti-glaucoma drugs across SSA was US$ 394, with a mean direct non-medication cost per year of US$ 54, and a mean surgical cost per year of US$ 283.

Conclusions: While effective glaucoma control interventions exist their widespread use and diffusion across SSA remains challenging principally due to low per capita income levels and high glaucoma treatment costs.

Word Count: 250

Key words: Glaucoma control, Sub-Saharan Africa, effectiveness, costs, cost-effectiveness,

Background:

Magnitude of the problem

Cumulatively the "Glaucomas" constitute a significant global eye and public health challenge with some 64.3 million persons being affected worldwide in 2013, rising to 76 million by 2020 and 111.8 million by 2040, respectively [1]. Geographically, Quigley *et al* showed that Sub-Saharan Africa (SSA) was the most adversely affected region and had the highest ratio of glaucoma to adult population of any region on the globe, the figures being 4.32% of the population in 2010, rising to 4.39% by 2020, respectively [2]. In terms of actual patient numbers, this equates to roughly 6.48 million persons with glaucoma in SSA in 2010 rising to 8.35 million by 2020 [2]. Such a disproportionate burden of glaucoma in SSA is due to a myriad of factors including: a shortage of ophthalmologists - including glaucoma specialists; a lack of knowledge about glaucoma and its treatment; the cost prohibitive nature of treatment; the poor uptake of possible interventions both for screening and detection as well as for medical, surgical treatment and management strategies [3-4]. Similarly, in 2011 Palmer *et a*l, showed that the ratio of ophthalmologists to population across SSA, was a staggering 2.9 per million of population [5]. Additionally, there is the persistent problem of the maldistribution of ophthalmologists throughout many parts of SSA, where an estimated 67% of ophthalmologists reside in capital cities across SSA, when 62% of the population of SSA actually lives in rural areas [5-6]. Further compounding the above is the negative impact of low per capita income levels across SSA which make current expensive treatments cost prohibitive for the vast majority of the population. Additionally, chronic under investments in the public healthcare sector, particularly in eye care services throughout much of SSA limit the effectiveness of such glaucoma control strategies as are currently available.

The high cost of glaucoma care in Sub-Saharan Africa

Eye care services for glaucoma control across SSA are significantly constrained by both high direct and indirect treatment and management costs as well as by low mean Gross National Income (GNI) per capita incomes, which in 2015 amounted to a mean per annum annual income of US$ 1,631 across SSA [7]. This is to be contrasted against the high annual medical and surgical cost of glaucoma care across SSA, eye care which if available, is principally the preserve of a tiny wealthy urban minority. In this regard, Omoti *et al* has calculated that in Nigeria the mean annual medical cost in 2010 for glaucoma was US$ 273.47±174.42 (range, $41.54 to $729.23) while the mean annual cost of surgical treatment for glaucoma was US$ 283.78±202.95 (range, $61.33 to $592.63) [8]. Thus, assuming that such costs structures may be generalized to the rest of SSA, most patients if they could pay, would part with something in the region of 16% to 17% of their annual income solely to treat and manage their glaucoma. Added to these direct eye care costs are the many indirect costs, such as those associated with travel often from rural locations to urban centers for treatment, etc. Not surprisingly, as Adio and Onua have noted, if one adjusts such glaucoma expenditures by income levels, many glaucoma patients across SSA on much lower income levels would actually spend the majority of their monthly income on glaucoma treatments, while those middle-income earners could potentially spend upwards of 50% of their monthly incomes on glaucoma care [9].

Rationale for current research

Viewed in the above context, it is surprising that, to date, no comprehensive review of the optimal detection and treatment strategies for glaucoma control at a population-based level in SSA has been conducted. This is despite the clear urgency of the problem at least as recognized by the global Vision 2020 coalition on blindness prevention and treatment [10]. It is against precisely this backdrop that the current research project was conceived with the aim of establishing the current evidence base surrounding the effectiveness, costs and cost-effectiveness of key glaucoma control strategies at the population-based level across SSA.

Aims:

Given the imperative of assessing the current evidence base related to glaucoma control strategies in SSA, the scope of this comprehensive review was to examine recent published data on the effectiveness, costs, and cost-effectiveness of various modalities for the detection and treatment of glaucoma in SSA. In particular, the key questions to be answered by the review were:

1) What is the effectiveness of various modalities of detecting and treating glaucoma patients in SSA?

2) What are the direct and indirect costs associated with detecting and treating glaucoma patients in SSA? and;

3) What is the cost-effectiveness of various strategies for the detection and treatment of persons with glaucoma in SSA?

Methods:

Study design

We performed detailed searches across six (6) biomedical and science databases to retrieve relevant literature for glaucoma control in SSA. The databases searched were as follows: Ovid Medline (1946 to September 2016), Ovid Embase (1947 to September 2016), The Cochrane Library (to September 2016), Web of Science (1900 to September 2016), Scopus (1823 to September 2016), and LILACS (1982 to June 2016). The key search terms used included: *glaucoma, diagnosis, treatment, effectiveness, costs, cost-effectiveness and Sub-Saharan Africa*. Our search strategy adopted standard Medical Subject Headings (MeSH) terminology conventions such that those terms with synonymous and derivative forms were also captured. Specifically, we used “costs” as a search term and this included all alternative terms including “cost* or econom* or afford* or expens* or expend*, where * denotes any number of possible endings, such as “cost”, “costed”, “costing”, “economic”, “affordable”, “expenses”, “expenditure” or “expenditures”. To this extent, therefore, our literature search strategy cast a very broad and comprehensive net. All the search results were transferred to an EndNote library where duplicate records were removed and 5658 single records remained.

Inclusion and exclusion criteria

Papers were regarded as worthy for inclusion in our review if they met the selection criteria. These inclusion criteria were: 1) The study must have been written in English, as English remains the main language of publication for the majority of high impact ophthalmology journals; 2) the study must have been conducted on adults ≥ 18 years of age with a diagnosis of primary open angle glaucoma (POAG), the principal form of glaucoma seen in SSA; 3) the study must have reported on either the effectiveness, costs, and/or cost-effectiveness of a particular glaucoma detection or treatment strategy; and 4) the study must have been conducted in a SSA country as defined by the United Nations [11]. Conversely, studies were excluded from our review if they met any following conditions: 1) the study was written in a language other than English; 2) the study was conducted on a paediatric population, that is, <18 years of age; 3) the study examined a type of glaucoma other than POAG; 4) the study occurred in an African country outside of SSA; and 5) the study did not specifically mention the effectiveness, costs, and/or cost-effectiveness of the various glaucoma detection and treatment modalities in the title of the retrieved publications.

Identification and selection of studies

In order to ensure the comprehensiveness of our review, several quality control steps were followed. These included reading the titles and abstracts of all retrieved papers. Initially, this was conducted by a single member of the research team (GN). Papers were excluded after a close review of the abstract only if it could be ascertained that they did not meet the inclusion criteria or if any of the exclusion criteria were satisfied. Subsequently, a full copy of the paper was obtained and reviewed in detail by a further two members of the research team (AFS and AM) to ensure that the study met the inclusion criteria.

Data abstraction and reviewing strategies

Data were extracted from the relevant publications and entered into an Excel based spreadsheet to keep track of all relevant parameters and references. Initial search strategy results were generated in September 2016, however, the initial review occurred over the period from October 2016 to January 2017 (GN, DB, AFS, HB, KD and IM). Between February and April 2017, the detailed extraction of the key data relevant to the review was completed (AFS and AM) and preparation of the final results occurred between May and July 2017 in collaboration with the full research team (AFS, GN, AM, IM, DB, KD and HB). Papers were graded using standardized levels of evidence (1 through 5) specifically developed for conducting systematic reviews in evidence-based medicine [12]. In this regard, Level 1 evidence generally denotes a well-controlled blinded randomized clinical trial, the so-called "Gold standard" in clinical research studies; Level 2 evidence typically refers to cohort or observational studies; Level 3 evidence represents case-control studies; Level 4 evidence corresponds to case-series reports; and Level 5 evidence is characterized as so-called "expert" opinions and is regarded the least rigorous form of all evidence-based reviews [12].

Further, for all articles included for review, several key criteria were abstracted including: (1) the study author; (2) the year of publication; (3) the country of study location; (4) the relevant healthcare setting; (5) the number of eyes involved in the study; (6) the type of intervention evaluated; (7) the effectiveness measure used; (8) the relative effectiveness of the intervention of interest; and (9) the quality of the study conducted in terms of levels of evidence. For articles reporting on costs and cost-effectiveness of various detection and treatment modalities, the additional criteria of the direct and indirect costs along with measures of cost-effectiveness were also abstracted from the articles reviewed.

Quality Assessment and Effect Size Measures

Although not formally measured, assessment of the quality of the papers included for review was performed to ensure that it was carried out in a robust and comprehensive manner. This was accomplished by determining if the papers included for review addressed a central research question related to the current review and whether the findings from the reviewed paper followed logically. In addition, all papers included in the systematic review were independently reviewed by two members of the research team (AFS and AM) to ensure a high degree of internal validity in the key findings and to reduce the potential for bias in the findings from papers, particularly those from nonrandomised observational studies which were included as part of the overall systematic review [12].

Simultaneously, key effect measures from individual papers included in the review were extracted for each of the three key areas, namely, effectiveness measures, cost components, and measures of cost-effectiveness. In the case of effectiveness measures, these were further stratified according to the type of detection or treatment strategy reported on. In the case of papers measuring the effectiveness of treatment strategies for glaucoma in SSA, the primary effectiveness parameter measured was intra-ocular pressure (IOP), specifically an IOP <22 mmHg. Costs and cost-effectiveness measures were reported in relevant currencies and using standardised cost-effectiveness measures, specifically the cost per disability adjusted life year (DALY) averted.

Statistical Analyses

The statistical analysis of pooled data around the effectiveness of various treatment options for glaucoma in SSA was performed in order to determine the heterogeneity, that is, the degree of variation in the findings in study outcomes between various studies reviewed. The effect measures from these aggregated studies were examined to determine the degree of heterogeneity or the "non-combinability" of the pooled results. Heterogeneity was assessed using both Cochran's Q and I^2 statistics. In this regard, the Cochran's Q statistics was calculated as the weighted sum of the squared differences between individual study effects and the pooled effect across various studies, where Q is distributed as a chi-squared statistic with k (number of studies) minus 1 degree of freedom. Thus, when the number of studies is small, Q has a low power as a comprehensive test of heterogeneity, while conversely when the number of studies is large Q tends to have too much power as a test of heterogeneity (13-15). The I^2 statistic was also calculated as it is regarded as an improvement on the Q statistic and measures the proportion of the total variation that occurs within trial heterogeneity and thus the I^2 statistic is independent of the total number of trials involved and can be used to understand the consistency of the findings across meta-analyses of data (15-16). As such, an I^2 value of 0% denotes a complete lack of heterogeneity, while values of 25%, 50% and 75% denote a low, medium and high degree of heterogeneity, respectively. Both the Q and I^2 statistics were calculated using a dedicated statistical software package, Comprehensive Meta-Analysis Version 3 (Biostats Inc. © www.meta-analysis.com) and the overall the significance threshold was set at $P \leq 0.05$ [17]. Lastly, a random effects model was used to analyse the studies included in the review, as the results were likely to vary not just due to sampling errors, but also due to underlying variability in the population of effects as well [17].

Results:

Search strategy yield

As presented in Figure 1, a total of 5658 records were initially examined and on the basis of the strict inclusion and exclusion criteria this was reduced to a total of forty-eight (48) relevant papers being identified for final review. In terms of the time dependence of the research conducted, it is worth noting that as Figure 2 reveals, 85% (n=41) of the studies included for review were conducted since the turn of the current century, with the remaining 15% of studies reviewed (n=7) being conducted prior. Moreover, the majority of the papers included in the review, that is 92% (n=44) reported on either the effectiveness of various glaucoma interventions (n=33), or on glaucoma detection and screening strategies (n=11). Less than a handful of papers (n=4) focused on the costs or cost-effectiveness of glaucoma control strategies in SSA.

Search strategy by level of evidence

Figure 3 reveals the distribution of the reviewed studies according to the level of evidence of the papers using standardized grading criteria for conducting evidence based reviews [12]. As can be seen, the vast majority of the papers reviewed, some 83% (n=40) were graded as Level 3 (case control studies) or as Level 4 (case series studies) in terms of evidence-based criteria. The remaining 17% (n=8) of the papers reviewed were graded as Level 1 (RCT) or Level 2 (Cohort or observational studies). No Level 5 studies which are based solely on expert opinion were available for analysis.

Glaucoma detection strategies

Table 1 presents the findings related to the eleven papers on detection strategies which were reviewed. Only one paper reporting the ascertainment of a family history of glaucoma as a detection strategy for glaucoma in SSA met the Level 2 criteria for evidence-based reviews. Sixty-three percent of papers (n=7) met Level 3 criteria for evidence-based reviews for a range of detection strategies ranging from the use of simple measuring tests of common ocular features (pupil size, anterior chamber depth, etc.) as well as the degree of agreement between various cadres of medical personnel of such ocular features to screen for optic nerve cupping using a direct ophthalmoscope by calculating cup to disc ratios; the relative extent of visual field loss using simple optical kinetic visual field tests, etc. The remaining papers (n=3) were graded at Level 4 for evidence, and report on studies evaluating devices for measuring IOP and imaging the optic nerve via mobile phone technologies, or the relative success of outreach clinics to detect early glaucomatous changes using such relatively simple ocular measuring devices.

It is interesting to note that studies reporting on detection strategies for glaucoma in SSA were nearly equally split between those conducted in primary (n=4) versus tertiary (n=5) eye care settings, with a further two studies conducted in a secondary eye care setting or within the context of a stand-alone eye study. This is relevant as potentially successful strategies for detecting glaucoma should be as community-based as possible in order to detect and refer those most likely to benefit from observation and/or the initiation of treatment interventions. Digital palpation of the eyeball and examination of the pupils in a primary eye care setting had sensitivity values <80% for detecting glaucoma [20] while a simplified visual function test which could be conducted on 90% of patients in primary eye care in SSA showed good performance and correlation to the size of the optic disc cup, a measure of glaucoma injury [26]. Another paper reported no difference in agreement (p=0.98) between the vertical cup to disc ratio obtained via a dilated pupil fundus camera eye examination and a smart phone image capturing system under field conditions [27]. There was also very good agreement in terms of detecting cup to disc ratios using an ophthalmoscope amongst a range of eye care personnel (kappa range 0.75-0.92) in a primary eye care setting [23]. In both a primary and tertiary eye care settings, the sensitivity and specificity of detecting glaucomatous visual field loss using the Oculo-Kinetic Perimetry Glaucoma Sreening Test (OKPGST) was found to be 93.8% and 96.8%, respectively [22]. Other screening tests reported on in a tertiary care setting included the Peripheral Anterior Chamber Depth (PACD) which had a sensitivity of 77.8% and a specificity of 82.4% and the Central Anterior Chamber Depth (CACD) test with a sensitivity of 58.3% and a specificity of

96.1% [21]. Given the wide range of effect sizes measures no statistical analysis was performed to determine the degree of heterogeneity among the papers reported in Table 1.

Effectiveness of Glaucoma Interventions

As can be seen from Table 2, four broad glaucoma intervention strategies were identified during the review including: i) medical management (n=2); ii) drainage implant surgical intervention (n=3); iii) laser treatment (n=4); and iv) all other non-drainage tube surgical interventions, including trabeculectomy surgery and the use of anti-metabolites (n=24). In the case of the medical management of glaucoma in SSA, the pooled effect size was found to be 0.66 (95% C.I. 0.61-0.71, Q=0.70, I^2= 0.00, P=0.402) although this was based on only two studies and is unlikely to be representative in nature. Analysis of the pooled effect size for surgically implantable glaucoma drainage devices revealed a mean effect size of 0.56 (95% C.I. 0.23-0.84, Q=14.02, I^2=85.74, P=0.001) indicating high degree of heterogeneity, albeit on a relatively small number of papers reviewed. With regards, to laser interventions for controlling glaucoma, principally laser trabeculoplasty, the mean effect size was found to be 0.39 (95% C.I. 0.27-0.54, Q=8.54, I^2=64.85, P=0.036) again denoting a moderate degree of heterogeneity across the papers reviewed. Most striking, perhaps, in terms of effectiveness of intervention strategies for glaucoma control, were those papers reporting on surgical interventions, including trabeculectomy surgery with the use of anti-metabolities which had a combined pooled effect size 0.73 (95% C.I. 0.65-0.80, Q=340.54, I^2= 93.25, P=0.000) again yielding a high degree of heterogeneity across the studies reviewed. Figure 4 graphically presents the effect sizes from each of the papers (n=24) reporting on the surgical intervention strategies for controlling glaucoma among the papers reviewed.

Cost of Glaucoma

Table 3 details the breakdown of those papers reporting on the costs of glaucoma care in SSA. As can be seen, the mean annual cost of anti-glaucoma drugs across SSA was US$ 394 (n=3). Similarly, the mean direct non-medication costs per year incurred by glaucoma patients in SSA was estimated to be US$ 54 (n=1), while the mean surgical costs per year were US $ 283 (n=1). With respect to indirect costs, particularly those directly related to seeking treatment for glaucoma, including patient transportation to and from eye care professionals, lodging costs, the cost of food and sundries, the mean aggregated indirect costs per year incurred by persons with glaucoma and seeking care for their glaucoma amounted to 872 USD (n=2). The authors of these studies did not, however, differentiate indirect costs in detail, though it is likely that the lion's share was associated with travel and transportation from rural areas to urban centres offering glaucoma care and a smaller proportion being spent on local housing and sustenance, including food and sundries. Lost productivity costs due to reduced or underemployment due to time lost from work due to glaucoma and seeking care were not captured in either of these two papers.

Cost-Effectiveness

In Table 4, the sole paper reporting on the cost-effectiveness of various strategies to control glaucoma in Ghana is presented. It is important to note that the paper was entirely based upon a computer simulation model for the entire population of Ghana and did not include actual measures of ocular health status. Nevertheless, this study did explore a range of strategies including: i) incident case identification; ii) syndromic self-referral by patients with mild visual impairment; and iii) universal glaucoma screening for the entire population of Ghana at ages 45, 55, 65, 75 and 85 [63]. The cost per DALY averted for each of these three options was found to be: i) 6,896 USD; ii) 3,947 USD and iii) 13,504 USD, respectively [63]. A further treatment strategy of providing one-time laser surgery resulted in a cost per DALY averted of: i) 1,771 USD; ii) 1,407 USD and iii) 9,808 USD, respectively [63].

Discussion:

Caliber of the Evidence

Overall, our literature search found that a preponderance of the evidence on the outcome of various strategies for screening and treating or controlling glaucoma were of poor to average quality with only a total of four RCTs (Level 1 evidence) studies being reported. The remaining studies reviewed consisted of Level 2 (n=4), Level 3 (n=22) and Level 4 evidence (n=18) studies across a range of detection and intervention strategies. Papers included for review had sample sizes ranging from 12 eyes [37] to 484 eyes [18] and up to 864 patients [20]. Papers reporting on detection of glaucomatous changes showed generally good sensitivity and specificity, as well as good observer agreement across a range of eye care professional for detecting key glaucomatous features using simple instruments and or smart phone technologies.

Screening and detections strategies

A number of papers reviewed reported high sensitivity and specificity values for detecting glaucomatous changes and a high degree of agreement across a range of eye care professional for detecting key glaucomatous features using simple instruments and or smart phone technologies in SSA. Such portable screening technologies may be particularly helpful in screening for glaucoma in remote rural locations across SSA. In this regard, for example, Thomas et al recently showed that tele-glaucoma screening in a sparsely populated rural Canadian context is highly cost-effective, principally owing to the high patient travel costs associated with accessing ophthalmologists and additional waiting room costs [64]. In particular, the authors of this Canadian study demonstrated that tele-glaucoma screening saved CDN $27, 460 for each additional quality adjusted life year (QALY) gained, well below the CDN $ 40,000 cost per QALY threshold, and that over the long term, tele-glaucoma screening prevented 24% cases of glaucoma blindness after 30 years [64]. While the finding that such tele-glaucoma screening techniques are promising and have been deemed to be cost-effective in Canada, more research is needed to determine if such tele-glaucoma technologies could be sufficiently adapted to SSA to be deemed to be equally cost-effective, such as perhaps via the use of low-cost mobile phones with retinal images sent to regional reading centres across SSA for grading.

In urban areas across SSA, recent data from India suggests that traditional in person eye examinations for glaucoma screening may be equally cost-effective, particularly if conducted in the 40-69 years age group and if implemented in the urban areas [65]. In practice, therefore, it is likely that the optimal glaucoma screening strategy for SSA and other low-income regions is likely to consist of a combination of tele-glaucoma solutions deployed in rural locations and traditional in person eye examinations in high density population urban centers across SSA and other regions where the burden imposed by glaucoma is particularly onerous [66].

<u>Effectiveness of glaucoma interventions</u>

Having detected and referred a glaucomatous patient for treatment, a number of effective medical and surgical interventions have been evaluated in SSA and represent a range of currently available treatment options. The reported effect size from the papers reviewed for medical therapies in SSA was found to be 0.66 (95% C.I. 0.61-0.71). This figure closely corresponds to data from a recent meta-analysis for anti-glaucoma drugs for the medical management of glaucoma which found that among all trials comparing any topical anti-glaucoma drops versus placebo or untreated subjects there was clear evidence of a positive treatment effect on visual field protection (odds ratio 0.62, 95% C.I. 0.47 to 0.81) [67]. The use of anti-glaucoma medications, while expensive, represents the first line treatment option throughout most high-income economies. Across SSA, however, as already discussed, anti-glaucoma medications are often very expensive and too cost prohibitive to be widely used, except by the wealthy urban elites. Other surgical control options might offer greater promise in this regard in the long-term control of glaucoma across SSA.

In terms of laser trabeculoplasty among studies conducted in SSA, this was found to have an effect size of 0.39 (95% C.I. 0.27-0.54) while drainage implant devices had an effect size of 0.56 (95% C.I. 0.23-0.84) for studies conducted in SSA. When compared to the international literature, the data suggests that fifty percent (50%) of diode laser treatment eyes and 58% of argon laser treated eyes were successful in maintaining an IOP <21 mm Hg after 5 years [68] Similarly, a number of studies have shown that if laser trabeculoplasty (LTP) was given as the initial treatment, up to half of the patients did not require medical treatment for up to 1–2 years afterwards [69-70]. Thus, the pooled effect size for laser trabeculoplasty from our review was roughly in line with that reported in the international literature. In the case of drainage implants, the international data point to a relative survival of a functioning drainage device in 71% of eyes operated on for high IOP at 5 years [71]. Interestingly, in a randomized clinical trial comparing tube shunt surgery with trabeculectomy, it was found that the cumulative probability of failure during 5 years of follow-up was 29.8% in the tube group and 46.9% in the trabeculectomy group (P =0.002; hazard ratio = 2.15; 95% confidence interval = 1.30 to 3.56) [72]. Overall, our review found the effect size of all glaucoma surgical interventions, including the use of anti-metabolities yielded an effect size of 0.73 (95% C.I. 0.65-0.80). This is in keeping with success rates derived from other studies on the long-term outcome of glaucoma surgery in terms of IOP. A Scandinavian study, for instance, found that according to the Kaplan-Meier survival curve, success rates defined as an IOP <21 mm Hg were 82% at 1 year, 70% at 2 years, 64% at 3 years and 52% at 4 years, respectively [73].

In the context of SSA, while non-drainage glaucoma surgical interventions, such as trabeculectomy surgery were shown to have the greatest effect size of 0.73, they require a high degree of training to attain high quality outcomes. Anti-glaucoma medications come a close second with an effect size of 0.66, however, as has been noted, at present they are cost prohibitive for most people with glaucoma in SSA. Next are the use of drainage implant devices and laser trabeculoplasty with an effect size of 0.56 and 0.39, respectively. It is probable too that as surgical skills and capacity are increased, the success rates for such surgical options for controlling glaucoma in SSA could be further improved upon. Such an approach is, however, dependent on the creation and maintenance of high calibre surgical training centres and on the provision of affordable domestic or imported drainage implant devices across SSA, both not inconsequential essential conditions. Indeed, in reviewing these options, it is clear that efforts to increase glaucoma surgical capacity and access to low cost generic anti-glaucoma medications are two desirable glaucoma control strategies likely to yield significant results across SSA. In particular, increasing glaucoma surgical capacity may also have the additional benefit of increasing the overall capacity to perform both drainage implant and laser trabeculectomy surgery.

Cost of glaucoma care

Despite being listed as essential medications on the WHO Model List of Essential Medicines, anti-glaucoma medications such as acetazolamide, latanoprost, pilocarpine and timolol remain cost prohibitive for many patients with glaucoma in SSA [74]. The high cost of anti-glaucoma medications and glaucoma surgery is not unique to SSA and many other low-income countries also face these same economic barriers. In India for example, it has been calculated that expenditures on anti-glaucoma medications ranged from 0.3% among high income earners to 123% of glaucoma patient's gross monthly income among those on the lowest income levels [75]. It was also found that the total cost, including travel, lodging costs and lost wages of patients as well as accompanying persons ranged from 1.6% among high income earners to 137% of the monthly income among low income earners in India [75]. Moreover, in the same study an overwhelming 92% of patients were not covered by any insurance plan/government reimbursement for their glaucoma treatment [75]. The situation is much the same in Mexico City where it was reported that the monthly economic burden of treating and managing their glaucoma was greatest in the lowest income group (61.5% of monthly income) and lowest among those on the highest income levels (7.9% of monthly income) [76]. In this respect, a recent study in the United States concluded that: "Although a small part of the total cost of glaucoma care, non-medical 'out-of-pocket' costs constitute a substantial non-covered medical expense to most patients in the United States" [77]. The paper further suggests that non-medical or 'out-of-pocket' patient expenditures may have a greater effect on patient adherence to office appointments than the direct medical costs [77]. The authors emphasise that clinicians should consider these additional 'out-of-pocket'expenses when determining the frequency of follow-up care for glaucoma patients [77].

A possible solution, perhaps, to combating the high costs of anti-glaucoma medications and surgeries across SSA may lie in developing low cost generic anti-glaucoma medications and devices within SSA or to import these from elsewhere, such as from excellent low-cost alternatives now being manufactured in India (e.g. The AuroLab Aqueous Drainage Implant (AADI) with a retail price of US$ 60) [78]. Such low-cost drainage implants could be further bolstered by providing glaucoma patients with favourable financing options to spread out the large upfront cost of glaucoma surgery over time. Finally, surgical training costs could be reduced by developing regional surgical training programmes based in strategic locations across SSA in order to improve the overall quality and quantity of glaucoma surgery available across SSA.

<u>Cost-effectiveness of glaucoma care</u>

As noted above, the sole study reporting on the cost-effectiveness of glaucoma control strategies for SSA, found that the overall cost-effectiveness of screening for glaucoma was US $ 6,896 per DALY averted, with additional cost for a one-time laser treatment US $ 1,771 per DALY averted [63]. To put these figures into context, it is generally asserted that those interventions which cost less than three times the average per capita annual Gross Domestic Product (GDP) in a given country are deemed to be cost-effective, while those interventions which cost less than a particular country's per capita annual GDP are considered to be highly cost-effective [63]. In reality, of course, there are a myriad of health interventions all competing for adoption and implementation subject to funding constraints. Calculating the relative cost-effective of various interventions using the cost per DALY approach is, therefore, closely tied to the prevailing budgetary constraints operating within any given country. Thus, assuming that the per capita GDP for Ghana in 2011 was US$ 1,575, it is likely that laser surgery for glaucoma is highly cost-effective, while screening for glaucoma is not at all cost effective [79]. Caution, however, should be exercised in extrapolating this limited computer simulation across the whole of SSA and more real-world data would help immensely in confirming or invalidating such findings. This is in sharp contradistinction to glaucoma control strategies from a substantial number of publications from outside of SSA which have showed that screening as well as medical and surgical interventions are generally cost-effective particularly given the often large personal and societal costs associated with vision loss and blindness due to glaucoma [80-81]. The difficulty in comparing our findings to those from studies outside of SSA is, of course, that the healthcare systems of high income economies have completely different healthcare and social care costs as well as completely different eye care infrastructure systems in place than most of SSA.

Study Limitations

A key limitation of the present study is the fact that most studies included for review were relatively poor grade in terms of rigorousness, with only four papers being well controlled randomized clinical trials (Level 1 evidence) and a further four papers being either cohort or observational studies (Level 2 evidence). In addition, relatively few of the studies were conducted in a primary eye care setting (n=5). Both these factors necessarily impose severe limitations on the generalizability of the current review. Nevertheless, they do serve to highlight the deficiencies in the current evidence-base which attends the whole area of how best to manage and control glaucoma across SSA and in a cost-effective manner. In addition, the review found a greater number of papers which reported on the effectiveness of various glaucoma detection and treatment interventions, and relatively few papers which reported on the costs, or cost-effectiveness of glaucoma control strategies across SSA. Both cost and cost-effectiveness data while available was of extremely limited value and future studies should be geared towards redressing this lack of high quality health economic data comparing various glaucoma control strategies across SSA.

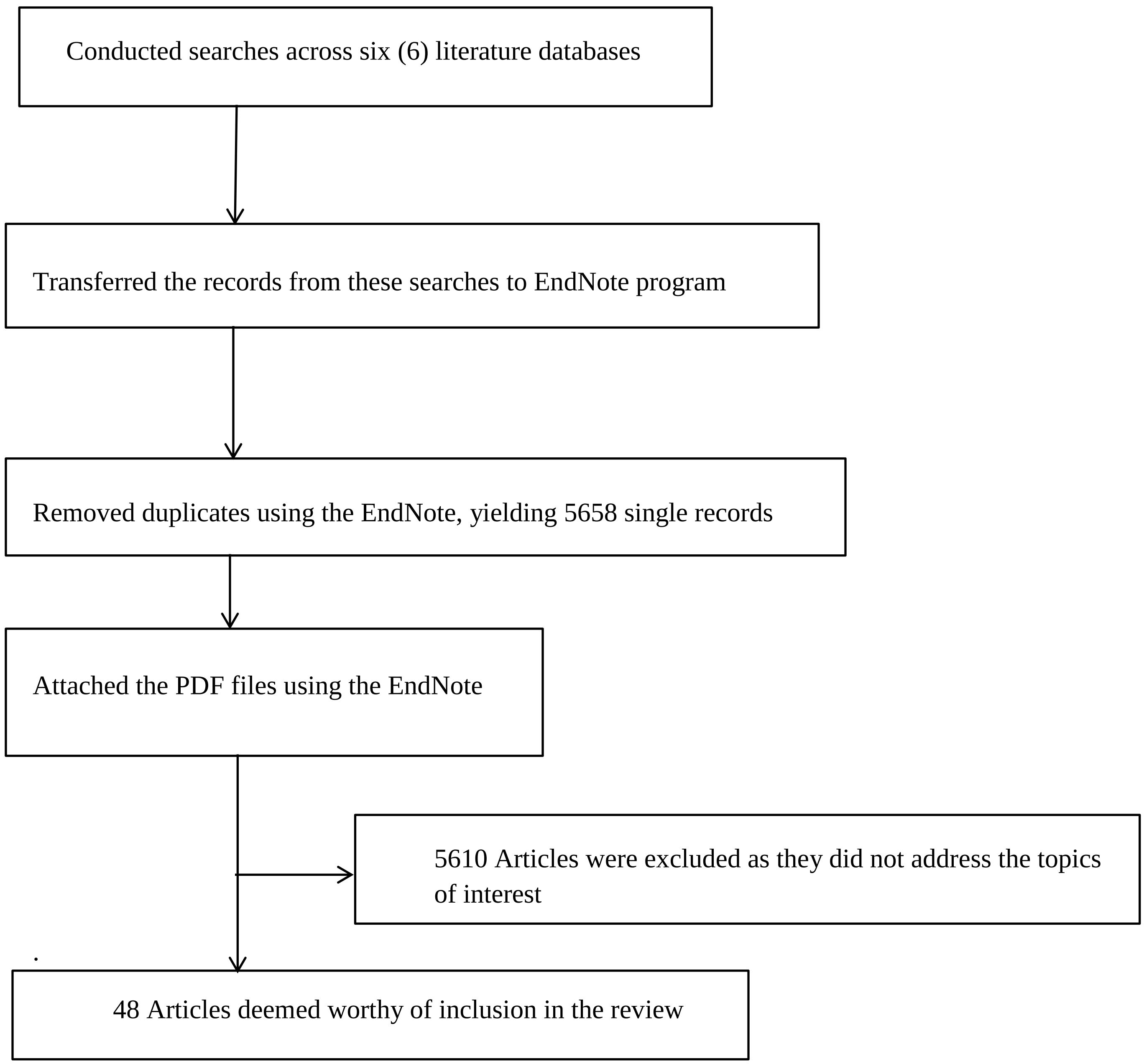
Recommendations and future research

Although a limited number of studies have demonstrated the effectiveness of glaucoma detection and treatment interventions in a SSA context, to date no real-world comprehensive cost-effectiveness analyses have been undertaken. Rather, cost-effective computer simulation modelling from Ghana has suggested that treating glaucoma is more likely to be cost-effective than instituting population-based screening measures. What this single modelling study fails to take into account is the high direct and indirect costs associated with glaucoma treatment across SSA, particularly relative to low per capital income levels. It is imperative, therefore, that much needed research to collect real-world health economics data on different glaucoma control strategies are also accompanied by policies aimed at reducing the costs of glaucoma treatment across SSA.

It is tantalizing, perhaps, to speculate about what sort of optimal glaucoma control policies might be advanced to effectively tackle glaucoma across SSA. Certainly, greater specialized glaucoma surgical training programmes could train more glaucoma surgeons and SSA governments could impose wage and price controls on glaucoma treatments and medications to make treatment more affordable, or greater public-sector investments in eye health could be made, but all options come at a cost. In fact, most ophthalmologists currently working across SSA work in the private sector and it will be imperative to ensure that there is "buy in" from the existing if largely private eye care infrastructure across SSA. The real challenges ahead lie not in not knowing what to do to control glaucoma from a technical perspective, but rather, as is often the case, in translating the evidence into practice given the prevailing political, economic, clinical, professional and other constraints operating across SSA. In the final analysis, only if SSA governments and ophthalmologists are truly willing to invest in expanding the public eye care sector, will a more robust and sustainable long-term way forwards be found to improve overall glaucoma control efforts across SSA.

Figures:

Figure 1: Literature search Yield



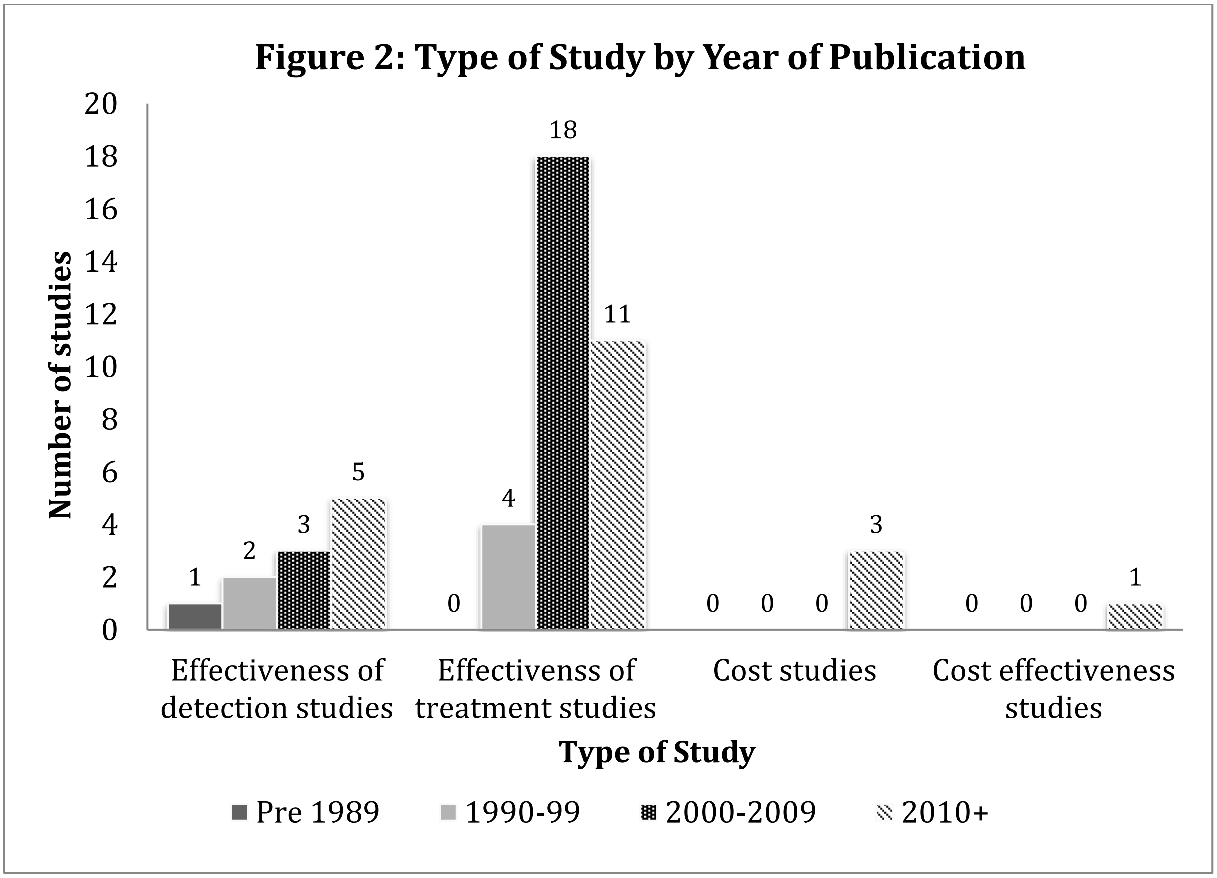


Figure 2: Type of Study by Year of Publication
Number of studies
20
18
16
14
12
10
8
6
4
2
0
1
2
3
5
0
4
18
11
0
0
0
3
0
0
0
1
Effectiveness of detection studies
Effectivenss of treatment studies
Cost studies
Cost effectiveness studies
Type of Study
Pre 1989
1990-99
2000-2009
2010+

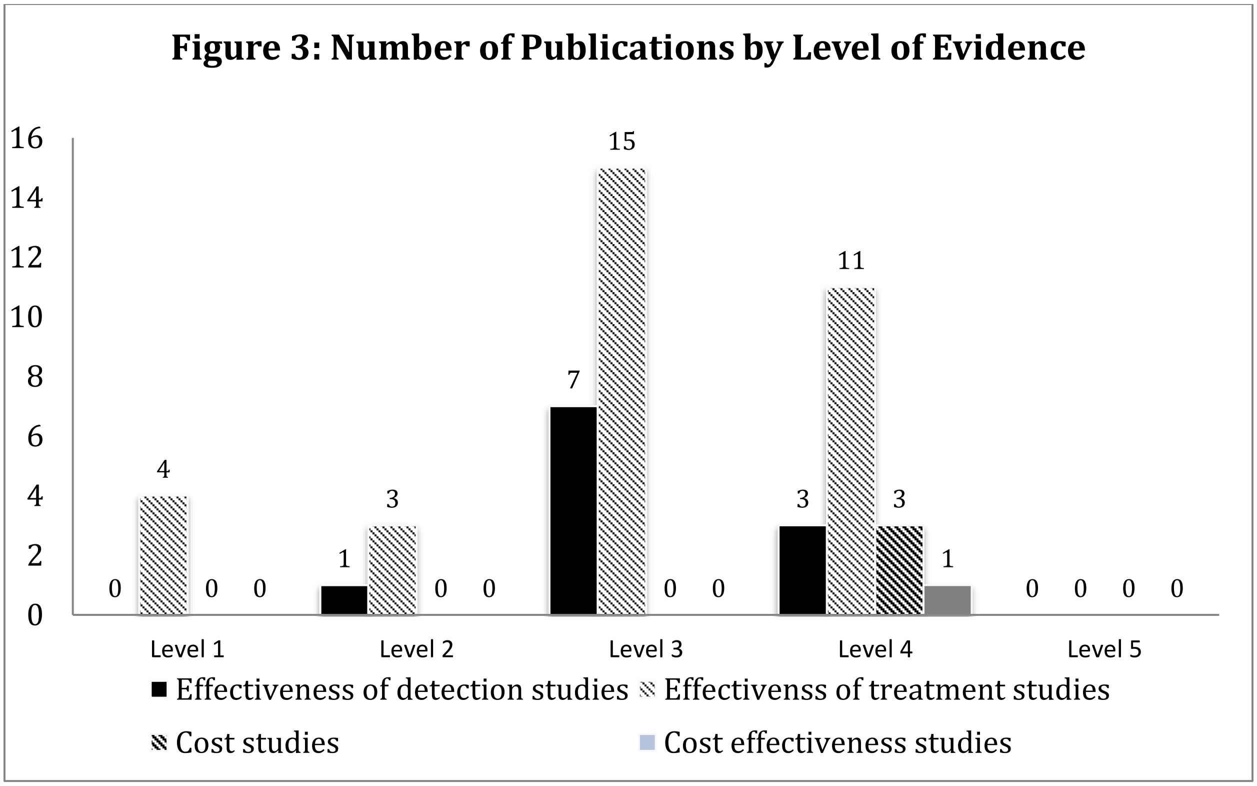


Figure 3: Number of Publications by Level of Evidence
16
14
12
10
8
6
4
2
0
0
4
0
0
1
3
0
0
7
15
0
0
3
11
3
1
0
0
0
0
Level 1
Level 2
Level 3
Level 4
Level 5
Effectiveness of detection studies
Effectivenss of treatment studies
Cost studies
Cost effectiveness studies

Figure 4. Effect Size of Surgical Interventions for Glaucoma in SSA

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
Kirwan et al 2006	0.701	0.627	0.766	5.001	0.000
Yorston et al 2001	0.299	0.233	0.375	-4.880	0.000
Egbert et al 1993	0.667	0.376	0.869	1.132	0.258
Mwanza et al 2001	0.818	0.493	0.954	1.924	0.054
Mielke et al, 2006	0.222	0.086	0.465	-2.210	0.027
Girma et al 2006	0.387	0.235	0.565	-1.246	0.213
Anand et al, 2001	0.852	0.784	0.902	7.408	0.000
Ashaye et al, 2009	0.783	0.662	0.870	4.101	0.000
Dahan et al, 2000	0.500	0.396	0.604	0.000	1.000
Grieshaber MC et al, 2010	0.783	0.662	0.870	4.101	0.000
Kim et al, 2008	0.567	0.388	0.729	0.728	0.467
Agbeja-Baiyeroju et al, 2001	0.550	0.502	0.596	2.063	0.039
Alemu 1997	0.789	0.750	0.824	11.678	0.000
Bekibele 2001	0.732	0.602	0.832	3.332	0.001
Lawan 2007	0.972	0.894	0.993	4.937	0.000
Verry et al 1990	0.839	0.799	0.872	12.084	0.000
Stegmann et al 1999	0.832	0.776	0.876	8.746	0.000
Olawoye et al 2013	0.830	0.695	0.913	4.081	0.000
Mielke et al, 2003	0.645	0.532	0.744	2.487	0.013
Adegbehingbe et al, 2007	0.611	0.495	0.716	1.870	0.062
Anand et al 2012	0.881	0.771	0.942	4.981	0.000
Quigley et al 2000	0.889	0.648	0.972	2.773	0.006
Kabiru et al 2005	0.898	0.840	0.937	8.249	0.000
Bowman et al 2010	0.854	0.769	0.912	6.113	0.000
	0.702	0.683	0.720	19.278	0.000

Statistics for each study

Event rate and 95% CI

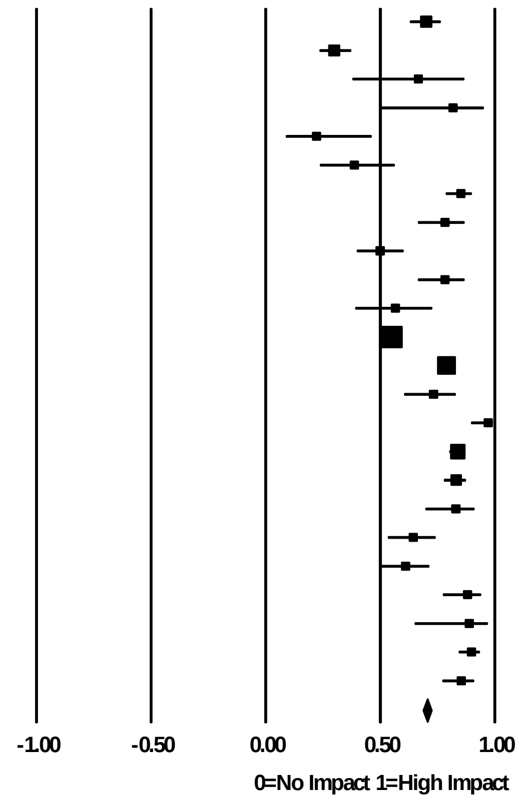


Table 1: Effectiveness of Detection Strategies for Glaucoma in Sub-Saharan Africa (n=11)

Author	Country	Setting	Number of Participants (Eyes)	Detection Strategy Evaluated	Effectiveness Measure Used	Effectiveness of Intervention	Level of Evidence
Munachonga et al 2007 [18]	Tanzania	Tertiary eye care	484	Ascertainment of first degree relative history	Provision of free eye exam to FDR	OR=1.87 for attending eye exam if offered free of charge, but low yield. Free eye exams insufficient incentive for an eye exam	2
Dean et al 2012 [19]	Malawi	Primary health care	294 persons screened by nurse and 147 referred to ophthalmic clinical officer; 56 referred to ophthalmologist	Pin hole visual acuity of >6/18 and cup to disc ratio of >0.7 using direct ophthalmoscope	Percent correctly referred for definitive ascertainment of glaucoma status	Only two (0.68%) patients out of the original 294 were found to have glaucoma by ophthalmologists. Poor performance.	3
Kok et al 1998 [20]	Nigeria	Primary health care	864 patients	Combination of pupil exam, palpation, and excavation as screening tools for glaucoma	IOP	None were found to be effective replacements (sensitivity's all <80% even for IOP >30mmHg). Poor performance overall.	3
Ashaye 2003 [21]	Nigeria	Tertiary care	240 glaucoma cases 250 controls	Peripheral Anterior Chamber Depth (PACD) and Central Anterior Chamber Depth (CACD)	Open or closed angles	PACD for PACG and POAG: Sn=77.8%; Sp=82.4% CACD Primary glaucoma Sn=58.3%; Sp=96.1% Overall good performance	3
Mahmoud et al 2008 [22]	Nigeria	Tertiary eye care	65 glaucomatous eyes 62 control eyes	Oculo-kinetic perimetry glaucoma screening test (OKPGST) versus KOWA AP 125 automatic central visual field plotter	Visual field defects	Performance: Sn=93.8% Sp=96.8% Performed very well in both clinic and rural outreach setting	3
Foster et al 1989 [23]	Ghana	Primary eye care	100 eyes	Direct ophthalmoscopy by either an Ophthalmologists, General Practitioner or Ophthalmic Nurse	Inter-observer agreement on: C/D ratio, colour, symmetry and diagnosis	Kappa Values (Reference was an ophthalmologist) For C/D ratios: Ophthalmologist (0.92); GP (074); Ophthalmic nurse (0.75) For Diagnosis of Glaucoma: Ophthalmologist (0.81); GP (075); Ophthalmic nurse (0.77)	3

Kiage et al 2013 [24]	Kenya	Secondary care	309 patients	Tele-glaucoma assessment by glaucoma specialist versus gold-standard clinical examination	Frequency doubling Vertical Cup to Disc Ratio (VCDR)	KappaValues (Reference was an ophthalmologist): Tele-glaucoma: 0.55 Only moderate ability to detect glaucoma, mainly due to poor photographs	3
Onochie et al 2016 [25]	Nigeria	Tertiary eye care	75 patients	Tono-pen versus Goldmann applanation tonometry (GAT)	IOP mmHg measurement	Tono-pen tended to yield higher IOP values than GAT (p-value 0.005) but was better tolerated by patients than GAT	3
Quigley et al 1993[26]	Tanzania	Primary eye care	120 patients	Tono-pen tonometer, direct ophthalmoscope, laptop visual field and scotopic sensitivity testing	IOP measures, Cup to disc ratio, Visual fields on laptop computer	Visual function tests could be conducted on 90% of patients and were correlated with the size of the optic disc cup, a measure of glaucoma injury. Good performance.	4
Giardini et al 2014 [27]	Kenya	Eye study	300 patients recruited from ongoing eye study	Dilated eye exam of the fundus using a Smart Phone camera	Agreement between Vertical Cup to Disc Ratio using Fundus Camera and Smart Phone	Excellent agreement in VCDR between fundus camera and Smart phone (p=0.98 for no difference in agreement between the two)	4
Olawoye et al 2013 [28]	Nigeria	Tertiary eye care	653 patients	Comparison of outreach versus other referral sources	Severity of glaucoma damage	Patients from outreach sources experienced more mild to moderate glaucoma and thus more likely to benefit from early intervention for glaucoma vision loss and blindness	4

Table 2: Effectiveness of Treatment Strategies for Glaucoma in Sub-Saharan Africa (Assumes a random effects model, n=33)

Author	Country	Setting	Number of Eyes	Intervention Evaluated	Effectiveness Measure Used	Effectiveness of Intervention	Level of Evidence
Medical Treatment Strategies (n=2)							
Koffuor et al 2012 [29]	Ghana	National Health Insurance Scheme (NHIS)	Review of 141 patients being treated for glaucoma using both mono and combination anti-glaucoma medications	Efficacy of the National Health Insurance Scheme listed anti-glaucoma drugs in the management of primary open-angle glaucoma in Ghana	IOP reduction	Combination therapies involving Latanoprost and listed anti-glaucoma drugs reduced IOP significantly than combination therapies involving NHIS-listed drugs only ($p \leq 0.01$). 63% reduction in IOP < 21 mm Hg after eight visits to ophthalmologist	3
Tamrat et al 2015 [30]	Ethiopia	Tertiary eye care	200 patients	Adherence to topical anti-glaucoma medications	Non-adherence to glaucoma therapy (NAGT)	135 (68%) were deemed to be NAGT	4
Pooled effect size			***341 patients***			***0.66 (95% C.I. 0.61-0.71)***	***Q= 0.70 I^2= 0.00***
Laser Treatment Strategies (n=4)							
Egbert et al, 2001 [31]	Ghana	Tertiary eye care	79 eyes completing follow-up	Diode Laser trans-scleral cyclophotocoagulation (TSCPC)	IOP reduction	38 eyes (48%) had IOP <22 mmHg at 3 months	2
Schwering et al 2013 [32]	Malawi	Tertiary eye care	Review of 47 eyes treated with TSCPC and 18 eyes completing full follow-up	Transscleral cyclophotocoagulation (TSCPC)	IOP reduction	After a single treatment session, IOP decreased by 25 % in 88 % (21 of 24) after 2 weeks, however, this decreased to 50 % (nine of 18) of patients after 3 months.	3
Babalola, 2015 [33]	Nigeria	Tertiary eye care	Review of 30 eyes	Laser trabeculosplasty	IOP reduction	5 out of 30 or 17% decrease in IOP post op	4
Mavrakanas et al 2013[34]	Tanzania	Tertiary eye care	49 eyes	Diode laser transscleral cyclophotocoagulation for the treatment of glaucoma	IOP reduction	Postoperative IOP was significantly lower ($P < 0.01$). At the first postoperative visit, 21/49 (43%) patients had an IOP of ≤ 21 mm Hg	4
Pooled effect size			***176***			***0.39 (95% C.I. 0.27-0.54)***	***Q= 8.54 I^2= 64.85***

Surgical Treatment with Valve Implants (n=3)							
Giorgis 2012 [35]	Ethiopia	Tertiary eye care	13 eyes reviewed	Ahmed Tube Shunt Implants for refractory adult glaucoma cases	IOP reduction	77% (n=10) had IOP <22 mmHg post-operatively	3
Woodcock et al 2008 [36]	South Africa	Tertiary eye care	157 eyes reviewed	Molteno implants	IOP reduction	Complete success defined as an IOP of 6-22 mmHg with no additional treatment was achieved in 30% (n=47) of eyes or	3
Gessesse, 2015 [37]	Ethiopia	Tertiary eye care	Review of 12 eyes	Ahmed valve implantation	IOP reduction	67% (n=8) < 22mmHg 6 months post op	4
Pooled effect size			***182***			***0.56 (95% C.I. 0.23-0.84)***	***Q=14.02 I^2= 85.74***
Surgical Treatment Strategies (Including the use of Anti-metabolites) (n=24)							
Kirwan et al 2006 [38]	South Africa	Tertiary eye care	320 people 156 no radiation 164 β radiation	Trabeculectomy plus β-radiation	IOP reduction	Percent failing treatment at 12 months defined as IOP > 21 mmHg: 30% in placebo arm versus 5% in treatment (β-radiation) Success Rate: 70%	1
Yorston et al 2001 [39]	Kenya & Tanzania	Tertiary eye care	68 eyes 32 FU 36 Controls	5-fluorouracil (5-FU with trabeculectomy surgery	IOP reduction	At 24 months 5-FU had greater success in IOP reduction (<22 mmHg) 89% to 71% in the placebo group	1
Egbert et al 1993 [40]	Ghana	Tertiary eye care	55 eyes 24 eyes in 5-FU group 31 eyes in control	Intra-operative 5-FU	IOP reduction	Twenty of 24 eyes in 5-FU group (83%) and 12 of 31 eyes in control group (39%) had post-operative IOP ≤ 20 mmHg without medical therapy (p=0.01)	1
Mwanza et al 2001 [41]	Congo	Tertiary eye care	22 eyes 11 eyes MMC 11 eyes no MMC	Intraoperative application of mitomycin-C during trabeculectomy	IOP reduction	At 20 months success defined as an IOP ≤21 mmHg without anti-glaucoma medications was 81.8% and 63.6% respectively in eyes treated with and without MMC	1
Mielke et al, 2006 [42]	Nigeria	Tertiary eye care	39 eyes 21 control group 18 Intervention	Deep sclerectomy (DC) and DC plus MMC	IOP reduction	24% for DU with MMC and 13% without MMC <18 mmHg at 1year, but low power of study and not statistically significant	2

Girma et al 2006 [43]	Ethiopia	Tertiary eye care	31 cases 29 controls	Mitomycin C in Trabeculectomy	IOP reduction	No statistically significant difference in IOP, however, cases had higher rate of complications post-operatively 12 versus 2.	2
Anand et al, 2001 [44]	Nigeria	Tertiary eye care	142 eyes in a retrospective review	Trabeculectomy	IOP reduction	85% of eye had IOP <22 mmHg at 1 year post op	3
Ashaye et al, 2009 [45]	Nigeria	Tertiary eye care	60 eyes reviewed	Trabeculectomy	IOP reduction	79% eyes has IOP <21 mmHg at 1 year post op	3
Dahan et al, 2000 [46]	South Africa	Tertiary eye care	86 eyes reviewed in total	Trabeculectomy	IOP reduction	50% decrease in IOP < 21 mm Hg post op at 6 months	3
Grieshaber MC et al, 2010 [47]	South Africa	Tertiary eye care	Review of 60 eyes	360 degree viscodilation & canaloplasty	IOP reduction	78% in IOP <21 mmHg at 36 months	3
Kim et al, 2008 [48]	Ghana	Tertiary eye care	Review of 68 30 on MMC 38 on 5-FU	MMC versus 5-FU	IOP reduction	MMC superior to 5-FU (55% to 24% IOP <21mmHg) at 6.5 years	3
Agbeja-Baiyeroju et al, 2001 [49]	Nigeria	Tertiary eye care	Review of operations on 433 eyes over a 10 year period	Trabeculectomy surgery	IOP reduction	55% operated eyes had IOP <21 mmHg by surgery alone	3
Alemu 1997 [50]	Ethiopia	Tertiary eye care	Review of 470 eyes	Trabeculectomy surgery	IOP reduction	79% of operated eyes had IOP < 20 mmHg	3
Bekibele 2001 [51]	Nigeria	Tertiary eye care	56 eyes reviewed	Trabeculectomy surgery	IOP reduction	74% had IOP <21 mmHg from surgery alone and this increased to 96% with anti-glaucoma medication post-operatively	3
Lawan 2007 [52]	Nigeria	Tertiary eye care	71 eyes reviewed	Trabeculectomy surgery outcomes	IOP reduction	97% of eyes had IOP <20mmHg post-operatively	3
Verry et al 1990 [53]	Ghana	Tertiary eye care	Retrospective review of 397 patients	Surgical intervention for glaucoma	IOP reduction	Of the patients treated surgically 84% of those seen at six months had an lOP below 22 mmHg. .	3
Stegmann et al 1999 [54]	South Africa	Tertiary eye care	Prospective study of 214 eyes	Viscocanalostomy for open-angle glaucoma	IOP reduction	IOP <22 mmHg in 83% of eyes IOP <22 mmHg in 89% of eyes if beta blocker added	3
Olawoye et al 2013 [55]	Nigeria	Tertiary eye care	Review of 47 eyes	Outcome of trabeculectomy with adjunctive 5-Fluorouracil (5-FU)	IOP reduction	At 12 months post-operatively 83% of eyes had a complete success defined as an IOP of ≤18 mmHg with no additional anti-glaucoma medications	4

Mielke et al, 2003 [56]	Nigeria	Tertiary eye care	Review of 154 eyes 76 5-FU 78 Control	5-FU versus controls	IOP reduction	64% <14 mmHg in 5FU versus controls at 18 months	4
Adegbehingbe et al, 2007 [57]	Nigeria	Tertiary eye care	Review of 72 eyes	Trabeculectomy	IOP reduction	61.8% < 20 mmHg at 1 year post-op	4
Anand et al 2012 [58]	Nigeria	Tertiary eye care	132 eyes 73 eyes 5-FU 59 eyes MMC	Efficacy and safety of intraoperative 5-fluorouracil (5-FU) or mitomycin C (MMC) in primary trabeculectomy	IOP reduction	88% in MMC group had 1 year IOP < 19 mmHg Postoperative IOPs were significantly lower (P<0.05) in the MMC group at all follow up visits except between 30-35 months (P=0.07)	4
Quigley et al 2000 [59]	Tanzania	Primary care rural Tanzania	Review of 18 patients from a survey	Surgical intervention (iridectomy, trabeculectomy, or combined cataract extraction/lens implant/ trabeculectomy)	IOP reduction	89% (16 out of 18) eyes undergoing trabeculectormy achieving a reduction > 25%.	4
Kabiru et al 2005 [60]	Tanzania	Tertiary eye care	Review of 157 eyes	Audit of trabeculectomy surgery	IOP reduction	90% (141/157) had intraocular pressure of ≤ 21 mm Hg.	4
Bowman et al 2010 [61]	Tanzania	Tertiary ye care	Out of 163 patients identified, 107 attended for follow-up. Data on 96 patients was available for follow-up IOP measurement and on 107 patients for Visual Acuity (VA) assessment	Combined cataract and trabeculectomy surgery for advanced glaucoma	IOP reduction Visual Acuity	IOP: Fifty-nine (62%) patients had follow-up IOPs of 6–15 mm Hg 82 (85%) had follow-up IOPs of 6–20 mm Hg. VA: 75 of 107 (70%) patients had an improved post-operative visual acuity	4
Pooled effect size			***2,937***			***0.73 (95% C.I. 0.65-0.80)***	***Q= 340.54*** ***I^2= 93.25***

Table 3: Costs Associated with the Detection and Treatment of Glaucoma in Sub-Saharan Africa (n=3)

Author	Country	Setting	Number of Participants	Intervention Evaluated	Direct Costs	Indirect Costs	Level of Evidence
Adio et al 2012 [9]	Nigeria	Tertiary eye care	120 patients	Economic burden of glaucoma	Cost of glaucoma drugs averaged US $ 40/ month or US $ 480 per year	Travel, labs, companion costs US $ 105/month or US$ 1,260 per year	4
Ocansey et al 2016 [62]	Ghana	Tertiary eye care	891 patients, but only 84 adhered to all visits	Cost of medical management	Direct medication costs were US $ 36,097 per year among the 84 who adhered to all visits (US $ 429 per patient per year) and Direct non-medication costs (surgery & tests costs) were US$ 4,523 per year or US$ 54 per patient per year. This yields a total direct cost of US $ 483 per patient per year.	Travel costs for 84 patients who adhered to all visits for glaucoma management amounted to US $ 484 per year	4
Omoti et al 2010 [8]	Nigeria	Tertiary eye care	108 patients	Cost of medical and surgical treatment for glaucoma	Cost of medical treatment: US$ 273per patient per year; Cost of surgical treatment: US$ 283 per patient per year	Not given	4
Mean Costs					Mean Drug Costs per year: US$ 394 (n=3) Mean Direct non-Medication costs per year: US$ 54 (n=1) Mean Surgical Costs Per Year: US $ 283 (n=1)	Mean Indirect Costs per year: US$ 872 (n=2)	

Table 4: Cost-Effectiveness of Various Detection and Treatment Modalities for Glaucoma in Sub-Saharan Africa (n=1)

Author	**Country**	**Setting**	**Number of Participants**	**Intervention Evaluated**	**Cost-Effectiveness Calculations**	**Level of Evidence**
Wittenborn et al 2011 [63]	Ghana	Country wide	Entire population modelled	Computer modelling of case-finding and treatment scenarios, including a US guideline-level care and one-time laser surgery to treat glaucoma	<u>Cost per DALY averted*:</u> <u>Scenarios</u> A) Diagnosis on incidence Guideline care: US $ 6,896 per DALY Laser only: US $ 1,771 per DALY B) Syndromic referral Guideline care: US$ 3,947 Laser only: US $ 1,407 C) Universal Screening Guideline care US$ 13,504 Laser only US$ 9,808	4

*Cost Per Disability Adjusted Life Year (DALY) averted

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Disclosures

At the time of this research both AFS and AM were employees of MedMetrics Inc.

Contributions

AFS: Overall design, development and implementation of the entire research project, including review and comment on literature search strategies, extraction of data from the literature, reporting of findings, data analysis and preparation of manuscript

GN: Data searches, data extraction, collection and refinement of search results and review of papers. Input into manuscript preparation.

DB: Designing and carrying out literature search strategies. Managed the retrieved search results including removing duplicate records and finding from PDF files. Input into manuscript preparation.

IEM: Review and comment on literature search strategies, development and refinement of search results and involvement in manuscript preparation and revision.

HB: Review and comment on the literature searches results, as well as input into the manuscript.

KD: Review and comment on the literature searches results, as well as input into the manuscript.

AM: Data searches, data extraction, collection and refinement of search results and review of papers, aggregation of data and reporting of findings as well as input into manuscript preparation.

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