Strategies to improve diagnosis and access to treatment of retinoblastoma in low-and middle-income countries: a systematic review

Bruna Rabelo[1], Kevin de Alvarenga[2], Karla Emília Rorigues[1], Adeylson Ribeiro[1], and Luiz Lopes[1]

[1]Hospital de Cancer de Barretos
[2]Universidade Federal de Minas Gerais

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Abstract

Retinoblastoma, the most common intraocular tumor in childhood, still faces challenges in diagnosis and treatment, particularly in low- and middle-income countries. Identifying strategies to improve the time to diagnosis and access to treatment is crucial to enhance survival rates and preserve ocular health. We conducted a systematic review to identify interventions that have demonstrated potential in addressing these challenges. We performed a comprehensive search across databases until March 2023. Out of the studies reviewed, twenty-one met the inclusion criteria and were categorized into five main areas: surveillance strategies, genetic counseling, education, public assistance and international partnership. Despite the obstacles faced, the initiatives identified in this review present acts towards improving the time to diagnosis and access to treatment for retinoblastoma. Based on the extracted data, we propose a comprehensive chain of initiatives. We firmly believe that implementing this chain of initiatives can lead to improved clinical outcomes for retinoblastoma patients.

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Bruna Salgado Rabelo[1,2,3], Kevin Augusto Farias de Alvarenga[2,3], Karla Emília de Sá Rodrigues[1], Adeylson Ribeiro[1], Luiz Fernando Lopes[1].

[1] Hospital do Câncer de Barretos, SP, Brazil. [2] Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil.[3] Hospital Felício Rocho, Belo Horizonte, MG, Brazil.[4] Fundação Oncocentro de São Paulo, SP, Brazil.

Corresponding author: Bruna Salgado Rabelo Email: brunasalgadorabelo@gmail.com Telefone: +55 31 991132779 Address: Av. Prof. Alfredo Balena, 110. 30130-100, Santa Efigênia, Belo Horizonte, MG, Brazil

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Abbreviations

Abbreviations	Term
RB	Retinoblastoma
LMICs	Low- and middle-income countries
PSI	Long prediagnostic symptoms interval
BVS	Biblioteca virtual em saúde
MeSH	Medical Subject Headings
WHO	World Health Organizatiom

Keywords: Retinoblastoma, developing countries, diagnosis, health services accessibility.

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Abstract

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INTRODUCTION

Retinoblastoma (RB) is the most common intraocular tumor in children, constituting 10-15% of all cancers diagnosed in the first year of life[1]. It is an aggressive cancer developing rapidly in the retina, before age five years. Epidemiological estimates suggest 7000–8000 children develop RB globally annually with approximately 3000–4000 succumbing to it each year[2].

RB management must prioritize saving lives, although eye salvage and vision preservation are also crucial clinical outcomes. Clinical decisions should be risk-adapted and supported by a multidisciplinary team.

Prevalence and mortality rates vary worldwide, being higher in low- and middle-income countries (LMICs). In Africa and Asia, 40% to 70% of children with RB die, compared with 3% to 5% of children in Europe and North America[3]. Disease extension and prognosis strongly correlates with a long prediagnostic symptoms interval[4–7]. In LMICs, RB diagnosis often occurs at advanced stages due to delayed diagnosis, cost barriers, and a lack of specialized personnel and equipment[8].

An efficient RB screening and diagnostic model could cut healthcare costs, enhance time to diagnosis, and expedite treatment referral[9]. Early diagnosis can increase not only the rate of survival but also very important

vision preservation[2]. Although there are many studies evaluating risk factors for diagnostic delay, few of them report interventions for its reduction. The present study systematically reviewed the literature to identify strategies that can contribute to earlier diagnosis and access to treatment.

METHODS

2.1. Protocol registration

A comprehensive systematic review (PROSPERO CRD42023403511) of the literature, conduced according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines, was performed to map the scope, quality, and efficacy of interventions aiming to improve the time to diagnosis and access to treatment of childhood RB[10].

2.2. Study selection

Pubmed, BVS (*Biblioteca Virtual em Saúde*), Scielo and Scopus searches were concluded in March 2023. The MeSH descriptors used were retinoblastoma; developing countries; diagnosis; health services; and accessibility, and the search strategies adapted to each database. Detailed search strategies are included in Appendix I. All searches, title and abstract screening, full-text evaluation, and data extraction were conducted by two independent authors (B.S.R. and K.A.F.A.). Any disagreements were resolved by discussion until consensus.

Quantitative and qualitative studies employing either interventional or observational approaches to assess the effects of strategies aimed at improving the diagnosis of RB or enhancing access to treatment in LMICs were considered for inclusion. No restrictions were imposed on language or publication date.

We excluded review articles, book excerpts, and studies that did not report intervention results and articles reporting interventions conducted in developed countries (Appendix II).

2.3. Data collection and analysis

Using a data extraction form, relevant data was acquired from each study, including study location and design, population, intervention, comparisons made, and outcomes. Studies were categorized based on the intervention type: surveillance strategies, international partnership, telemedicine, education, public assistance, and genetic counseling. A summary table was assembled to describe the results. The heterogeneity of designs, types of interventions, and outcomes prevented quantitative synthesis.

2.4. Quality appraisal

To evaluate the methodological quality of the studies, the Joanna Briggs Institute's critical appraisal instruments were employed[11, 12]. Both reviewers (B.S.R. and K.A.F.A.) independently assessed the quality of all studies, using a specific form tailored to each study design: cohort, case series, and cross-sectional. Any discrepancies were discussed and resolved through consensus. Four articles were excluded from the analysis: Joseph et. al., 2006, because it is a diagnostic model proposal[13], and Chantada et al., 2016, Howard et al., 2018, and Wilimas et al., 2009 that are public policy studies[14–16]. In total, 17 studies underwent analysis. Concerning the quality of the study, the included articles were categorized as "high", "moderate", and "low " based on the percentage of "yes" answers within the domains: 70% or more, 50-69%, and 0-49%, respectively.

RESULTS

The search yielded 870 records. Thirty-two reports were selected after title/abstract screening and assessment for eligibility, and twenty-one studies included (Fig. 1). Publications were further classified into 5 categories: surveillance strategies[3,17–22], genetic counseling[9,13,23], education[24–27], public assistance[28]and international partnership[8,14–16,29,30]. Table 1 describes the extracted data.

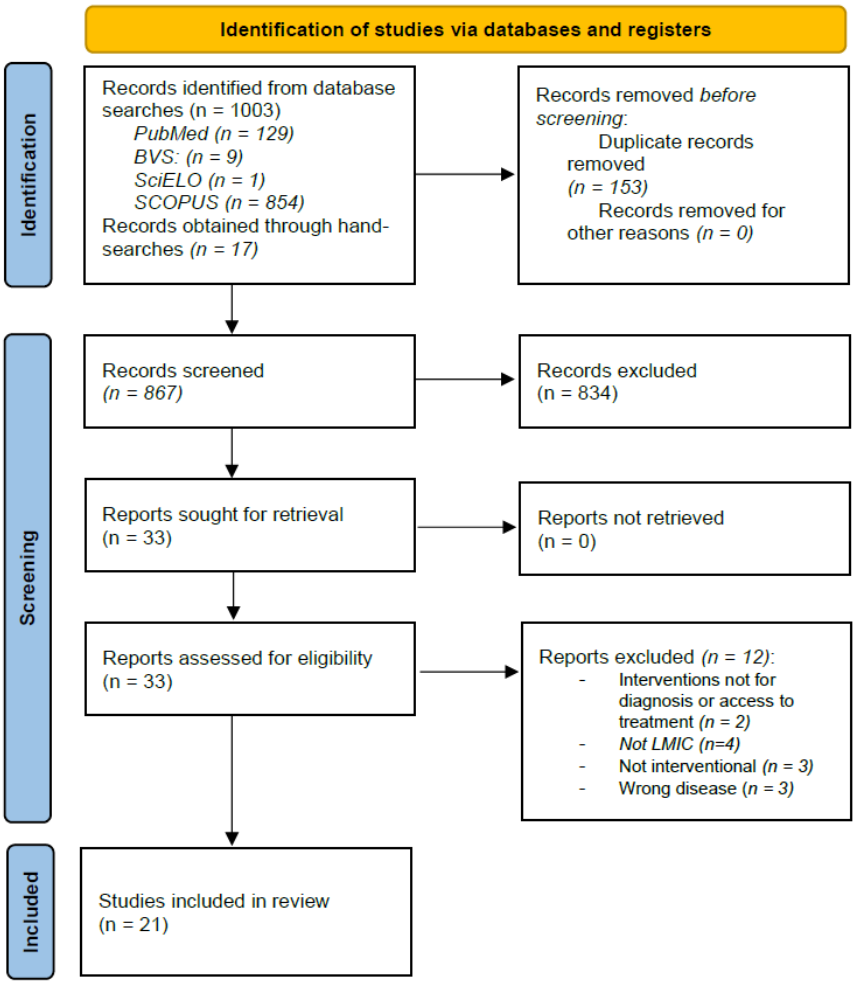

Figure 1. Study selection process flow diagram .

3.1. Public Assistance

Hill et al. in 2016[28]addresses the development of a multidisciplinary and multisectoral strategy embracing health professionals, students, survivors of RB, their families, and members of the government of Kenya. It was structured from annual meetings and resulted in the development of National Retinoblastoma Strategy Guidelines, that counted with facilitated access to government-subsidized health insurance, the creation of a nursing home, centralization of the pathological diagnosis of the disease, and the acquisition of artificial eyes for the children.

3.2. Surveillance strategies

New software technologies like CRADLE® and MDEyeCare® have been developed to detect leukocoria, the main and most early signal of RB[20]. Using this principle, Bernard et al.[3] with their EyeScreen® mobile application, Vargas-Cuentas[21] with RetinoApp® and Khedekar et al[20] with MDEyeCare® demonstrated that mobile apps are promising screening strategies. EyeScreen® application achieves a sensitivity of 87% and specificity of 73% [8]. RetinoApp®, associated with an algorithm that detected leukocoria, correctly identified 93.33% of cases and 95% of controls[21]. MDEyeCare® had good results for advanced intraocular disease, but low sensitivity for initial stages.

Ademola-Popoola, 2017[17]evaluated the use of a cell phone's basic camera's photo and video functions along with a 20D lens after eye dilation. Although images captured through this approach were not as clear as those obtained through fundoscopy, new camera technologies can overcome this limitation.

Another strategy to enhance screening effectiveness relied on a clinical assessment of the risk of harboring germline RB1 mutations. Kaliki et al. (2019)[19]successfully executed this strategy by conducting ophthalmological examinations on parents of children diagnosed with RB. If at least one parent had a spontaneously regressed RB, there is a presumed risk of a sibling having a germline RB1 mutation. Similarly, Yousef et al.[22]devised a calculated risk model based on factors such as family history, the presence of affected family members, and the classification of unilateral or bilateral disease. The study's findings revealed that the calculated risk model resulted in enhanced detection of the disease at earlier stages, thereby providing increased opportunities for ocular salvage.

3.3. International partnership

In the study conducted by Qaddoumi et al.[29], it was observed that the twinning strategy facilitated the provision of high-quality care and early identification of issues that could potentially harm the patients. Furthermore, the training of skilled professionals in developing countries was found to reduce the need for sending professionals abroad for extended periods to enhance their expertise, thereby reducing associated costs. Additionally, it is crucial to support the development of a well-established infrastructure to ensure effective multidisciplinary interventions.

In another study conducted by Wilimas, et al.[16], twinning strategies were implemented in Central America countries in collaboration with St. Jude Children's Research Hospital and the ocular oncology team at the Hamilton Eye Institute (UTHEI). The primary focus of the program was on early diagnosis and specialist referrals, and as the program expanded, there was an increase in ocular salvage[16]. However, the study also highlighted the need for additional resources and inputs to support the program.

Jordan was another country that benefited from the twinning program with the St. Jude Children's Research Hospital. The study conducted by Yousef et al. demonstrated improvements in mortality rates, ocular salvage, and increased autonomy throughout the program, as well as successful decision-making with the implementation of the telemedicine strategy[30].

Another example of an international partnership was between the Children's Cancer Institute and St. Jude Children's Research Hospital, as described in the article by Al Haddad et al[8]. This partnership aimed to address the needs of children with RB in Lebanon. The study observed an annual increase in admissions of patients with RB; however, there was a higher number of diagnoses of patients with locally advanced tumors (stages D and E) and lower rates of ocular salvage for those with early-stage disease (A, B, and C). Most cases of early-stage disease were diagnosed in bilateral RB, with the second eye being more advanced[8].

The My Child Matters program, which supports projects in LMICs, including the African Retinoblastoma Network also demonstrated promising results. The program covers 55 projects in 42 countries and has initiatives related to awareness of early diagnosis and training of professionals in disease management. The program resulted in a reduction of extraocular disease, increased survival, and ocular preservation[15]. The Mali Retinoblastoma Program pioneered the strategies developed, had substantial results, and was extended to the Democratic Republic of Congo, Senegal, Côte d'Ivoire, and Madagascar[15,31].

Finally, it is crucial to highlight a significant 20-year cooperation between Garrahan Hospital in Argentina with Memorial Sloan Kettering Cancer Center in New York, which serves as an exemplary model to be followed. Throughout the stages of this process, it became evident that the primary focus was on empowering the country to develop local capabilities to deliver high-quality patient care. The program, initiated in 1995, initially concentrated on medical education through oncologist visits to New York, alongside the development of a protocol aimed at enhancing ocular preservation and reducing late effects. Subsequently, with financial support, the program facilitated the research and treatment protocol for RB in Latin America, leading to the incorporation of the first center in the region capable of performing intra-arterial chemotherapy. One

notable impact of the program has been the significant improvement in the survival and ocular preservation of patients afflicted with the disease, resulting in a three-year probability of disease-free survival, which rose from 0.84 before program implementation to 0.97[14,32,33].

3.4. Education

In the study conducted by Elfalah et al.[25]educating medical students about RB resulted in significantly improved knowledge about the disease, particularly in terms of its severity and diagnosis, following the intervention[25].

Another example of medical education was developed by Hill et al.[26] in Kenya. They designed a comprehensive and interactive workshop on RB genetics, followed by discussions of patient case studies. The study revealed that participants felt more confident in discussing genetics with patients and improving genetic counseling as a result of this training[26]. This strategy is of great importance in the country, as there is evidence indicating that the second and third children with RB are often diagnosed at an advanced stage of the disease, highlighting a failure in genetic counseling. Therefore, this tool shows promise in expanding the knowledge of healthcare professionals regarding the disease. However, knowledge assessments conducted one year after the workshop showed low scores, suggesting the need for frequent reinforcement of knowledge.

Concerning familiar awareness about the disease, Soliman et al.[34] and Nawaiseh et al[18]demonstrated that increased knowledge of the disease among parents who had a first affected child led to improved care for subsequent children.

In Honduras, the integration of an RB education program into a nationwide vaccination campaign resulted in a reduction in the occurrence of extraocular disease[27]. Similar findings were observed in the study of Antonelli et al.[24] in Brazil, where campaigns involved publishing articles in non-medical magazines, placing billboards at strategic locations in the city, providing guidance to medical professionals through courses offered at medical schools, and publishing findings in a medical journal to raise awareness of the disease, resulted in a reduction of referral time and, consequently, an increase in the number of detected intraocular tumors.

3.5. Genetic counseling

Joseph et al., 2004, compared the costs of genetic testing and a clinical strategy based on familiar risk assessment. Significant cost savings of 3.5 times for the proband and 6.1 times for the family were observed[9].

Thirumalairaj et al.[23]observed in their study that the genetic analysis of RB is hindered in developing countries due to the extensive size of the gene and the presence of multiple dispersed exons. This results in time-consuming and costly procedures, as demonstrated by the comprehensive DNA sequencing model developed by Joseph et al. in 2006[13], which leads to an average delay of 84 days in obtaining results and subsequent management, particularly in India. Consequently, Thirumalairaj's study emphasizes the need for alternative approaches that can offer faster and more efficient outcomes. The strategy they developed is based on prioritizing analysis based on the local frequencies of mutations reported in the literature and genetic databases[23].

3.6. Other studies and initiatives

Despite not meeting our inclusion criteria (see Appendix II), we came across other relevant studies that warrant mention. One, the 'One World, One Vision' symposium in January 2007, presented a global perspective on RB assistance disparities, showcasing successful case studies. The symposium catalyzed advancements in the field and aimed to explore country-specific RB programs [35]. The 'Grupo Mexicano de Retinoblastoma' (RtbMex), established in January 2003, educated health professionals, provided national RB guidelines, and conducted early diagnosis campaigns [36]. The CureAll framework, supported by the WHO Global Initiative

for Childhood Cancer, aims to improve children's cancer outcomes globally, prioritizing childhood cancer through regional, national, and global action plans. The initial focus is on six main childhood cancer types, including RB, to assess care landscapes and identify areas for improvement, with the goal of achieving a minimum 60% survival rate worldwide and reducing overall suffering [37].

3.7. Assessment of the risk of bias of the included studies.

Qaddoumi, 2008[29], the only cohort study, was considered as of moderate quality. The most significant issue identified was related to the identification and strategies for addressing confounding factors. Participants were not clearly free from the outcome at the beginning of the study, and it was unclear whether strategies were employed to manage follow-up losses. Among the twelve cross-sectional studies evaluated, most demonstrated moderate to high methodological quality[3,9,17,20,21,23,25,27,28,30]. The primary issues identified pertained to insufficient detail in the study sample and a failure to identify strategies for managing confounding factors. Four case series studies were assessed, with the majority exhibiting high methodological quality (3 out of 4 studies)[18,19,22]. The main problem identified was a lack of clarity regarding the consecutive inclusion of participants (See Appendix III).

DISCUSSION

In the current systematic review, we aimed to find and evaluate strategies to improve access to diagnosis and treatment in LMICs. Retinoblastoma is a tumor which diagnosis and treatment require a multidisciplinary team that includes an ophthalmologist, oncologist, pathologist, and specialized geneticist[38,39]. Nationally coordinated strategies are important to build this integration and a chain of care. Public policies need to be guided by experts' knowledge and require governmental funds and when possible, it is important to establish cooperation with high-income countries.

International partnerships can bring the quality of care from high-income countries closer to children around the world[8,30,36,40,41]. This has been achieved through cooperative programs known as twinning, which involve partnerships between a developing country and a mentoring institution from a developed country. This collaboration has become possible due to the advancement of communication technology on a global scale.

Telemedicine serves as an alternative for extending services to regions lacking specialists by integrating virtual education, mentoring, and case discussions. It also provides an opportunity for professionals to enhance their skills and receive training in their home country.

Concerning strategies of diagnosis, typically, an ophthalmologist can diagnose RB using indirect ophthalmoscopy with a dilated pupil[38]. However, in resource-limited areas, accessing an ophthalmoscope can be challenging, along with other restrictions such as the need for sedation and technical expertise for diagnosis. Beyond screening, smartphones are being tested for fundus examination. Since they are more accessible, portable, and compatible with teleconsultation, they can be a cost-effective strategy compared to traditional ophthalmoscopy. Promising results have been reported in the current literature, as also reviewed elsewhere[42]. It is essential to emphasize that healthcare professionals using these devices should receive proper instructions for use and interpretation. Furthermore, expanding the use of the applications for screening to family members or individuals without medical training can increase the chances of early diagnosis, but at the same time, may increase testing anxiety and false positive rates. New studies are needed to evaluate this possibility before implementation.

In our review, we did not find studies on the screening benefits in the general population of LMICs, possibly due to the rarity of the disease and the scarcity of ophthalmology services. Additionally, there is a lack of secure access to anesthesia and genetic testing in these regions[43]. However, it is important to emphasize the relevance of routine ocular health evaluation early in childhood for the diagnosis of other conditions, which can also provide an opportunity for the diagnosis of RB [44].

There are several ways to enhance the diagnosis and access to treatment for RB through education, whether

by guiding the general population or individuals at higher risk regarding the signs and symptoms of the disease or by offering guidance to healthcare professionals. Medical education interventions play a fundamental role because, in numerous countries, newly trained doctors play a pivotal role in healthcare facilities, and the general practitioner will likely be the first healthcare professional to evaluate a child with suspected RB[45]. For this reason, a clinician's ability to identify RB when first assessing a child and to make a timely referral needs to be trained[24]. Thus, it is important to improve teaching strategies, adding information about the disease and its warning signs to the medical curriculum. There is evidence that frequent reinforcement of knowledge is necessary, since important concepts may be lost over time. Continued medical education can be achieved by promoting periodic educational workshops[26].

Furthermore, increasing family awareness about the disease also plays a fundamental role. By being well-informed about the disease and its potential risks, parents can take proactive measures to ensure the well-being of their children and seek appropriate medical attention at the earliest possible stage[18].

Studies that identified education strategies for the general population's awareness of the disease have yielded positive results in reducing extraocular disease upon diagnosis[24,27], indicating that this approach has the potential to be implemented in countries where late diagnosis is prevalent.

In patients at higher risk of the disease due to positive family history, there are two ways to conduct screening: through genetic counseling and by using risk models calculated based on clinical assessment. Genetic counseling is important for the control and management of RB, identifying individuals at increased risk, and guiding screening and education for healthy lifestyles. RB is primarily caused by biallelic inactivation of the RB1 gene in a precursor retinal cell, followed by progressive mutations in other specific genes. Only a small number of relatives will carry the mutation. However, every child born to a parent with a germline RB1 mutation has a 50% chance of inheriting the mutation[22].

In most LMICs, widespread access to genetic testing for RB is limited due to the absence of advanced technology capable of detecting RB1 mutations. Consequently, researchers have suggested calculated risk models to identify patients at a high risk of RB1 mutations, who could benefit from targeted screening programs[19,22]. However, findings from this review indicated that genetic testing incurred lower costs when compared to calculated risk models. This can be explained, because the latter approach often led to unnecessary and expensive repetitive ophthalmological examinations. Those unnecessary exams also cause heightened concerns among family members, and increase the risk of complications related to anesthesia[9].

Therefore, implementing a genetic screening model would not only enable more accurate and cost-effective care for patients with a higher susceptibility to cancer but also aid family decision-making regarding future pregnancies.

4.1. Improvement opportunities

Despite facing numerous challenges, the initiatives identified in this review highlight important acts that may improve the time to diagnosis and access to treatment. By implementing these acts collectively, we have the potential to not only preserve the lives of children but also enhance their overall quality of life by avoiding treatment late effects; and preserving functionality and facial aesthetics. Drawing upon the extracted data, we propose a comprehensive chain of initiatives (Fig. 2) that we believe can yield improved clinical outcomes for patients with RB.

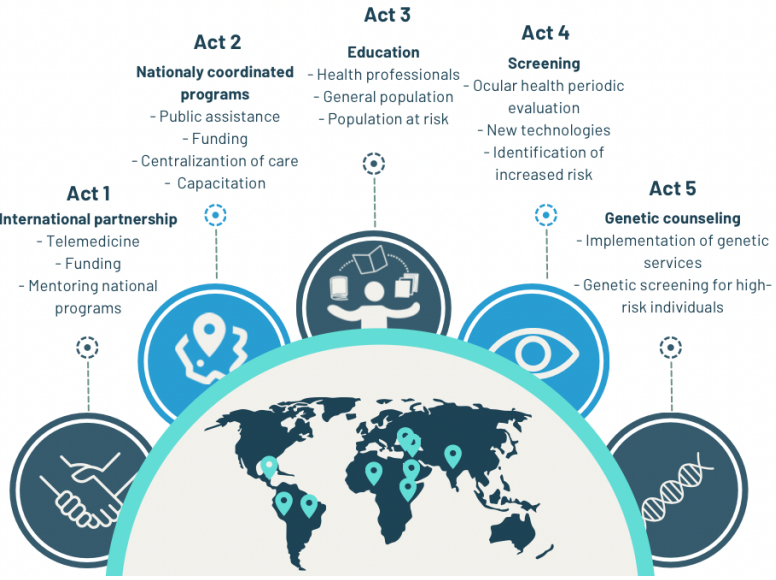

Figure 2: Improvement opportunities - a proposed chain of initiatives based on the review of studies in the countries pointed in the map (Jordan, India, Kenya, Lebanon, Brazil, Nigeria, Honduras, Ethiopia, Peru) and multinational studies. *Act 1: International Partnership* : Establishing partnerships with the teleconsultation of specialists, mentoring programs, and financial aid to support the development of local programs. *Act 2: Nationally Coordinated Programs:* Implementing nationally coordinated programs for public assistance, including centralization of care, financial aid from local governments, and educational initiatives. *Act 3: Education and Awareness:* Develop educational tools for the medical community and general population to increase awareness of the disease, particularly targeting populations at higher risk. *Act 4: Screening Programs:*Implementing screening programs focused on populations at higher risk, while also incorporating periodic ocular health evaluation for all children. Future considerations include the integration of smartphone applications and algorithms to enhance screening accuracy. *Act 5: Genetic Services:* Establishing cost-effective genetic screening services to support early detection and diagnosis.

4.2. Limitations and other challenges

Heterogeneity in study types and interventions prevented quantitative analysis. No clinical trials on the subject were found. However, this review emphasizes relevant interventions from observational studies, suggesting their potential evaluation in experimental settings to improve outcome confidence. However, numerous other barriers to early diagnosis and treatment access, such as medical care abandonment, diagnostic errors, referral delays, geographic distance from health facilities, and challenges related to treatment toxicity were not addressed here.

CONCLUSION

Most LMICs lack adequate diagnosis and treatment programs specifically tailored for RB. It is crucial to identify the specific deficiencies and gaps in care within each country to implement the suggested acts in a customized manner. This study provides indirect evidence of interventions that may contribute to improving survival rates and preserving vision in patients with RB, but these findings should be corroborated through appropriately designed studies.

TABLE 1 - Summary of included studies.

Author, year Country	**Type of Study**	**Population**	**Intervention**	**Results**
Public assistance				
Hill, 2016 Kenya	Cross-sectional study.	Mean of ˜ 60 delegates per meeting.	A nationally coordinated multidisciplinary (health workers, academics, retinoblastoma survivors and families, members of government) drawing input and expertise of professionals to optimize the cure of children with retinoblastoma. The program was based on the following principles: (1) Set the agenda together; (2) Interact with stakeholders; (3) Clarify responsibilities; (4) Account to beneficiaries; (5) Promote mutual learning; (6) Enhance capacities; (7) Share data and networks; (8) Disseminate results; (9) Pool profits and merits; (10) Apply results; (11) Secure outcomes.	The program fulfilled 9/11 of its objectives, with the last two (applying results and securing outcomes) in progress. They produced consensus national guidelines for care and supported capacity-building initiatives to facilitate their implementation. Outcomes of children with retinoblastoma will be evaluated in the long term.
Surveillance				
Ademola-Popoola, 2017 Nigeria	Cross-sectional study.	12 (2 RB cases).	Retinal imaging from a smartphone compared to traditional fundoscopy.	In cases of retinoblastoma with a highly reflective tumor mass, the images were not as clear as with a traditional fundus camera.

Bernard, 2022 Ethiopia	Cross-sectional study.	1200 individuals screened.	The EyeScreen® software, a smartphone application designed for use with Android® devices, as an effective, easy-to-perform, community-based screening tool.	Photographs obtained with inexpensive Android smartphones running the EyeScreen® application were used to train an ImageNet (ResNet®) machine learning model and to measure the performance of the app. Eighty percent of the images were used in training the model, and 20% were reserved for testing. The model showed a sensitivity of 87% and a specificity of 73%.
Kaliki, 2019 India	Prospective nonrandomized observational/ interventional case series.	262 parents and 23 siblings of 131 patients.	Routine ophthalmic examination of families (parents and siblings) in a setting of the absence of genetic testing.	Spontaneously regressed RB in 8% of parents and active RB in 2% of siblings indicate that routine fundus screening of siblings allows for early detection of RB in otherwise asymptomatic children and detection of spontaneously regressed RB in parents may act as a surrogate marker for germline RB1 mutation.

Khedekar, 2019 India	Cross-sectional study.	34 eyes of 23 RB patients and 4 controls.	Two iPhone® apps (MDEyeCare® and CRADLE®) with modifications for early detection of RB without anesthesia or pharmacological dilatation of the pupil.	The modified MDEyeCare® app could detect the leukocoria in the early stages of RB (50% of Group B, 83% of Group C, but none of Group A). In the late stages (Group D and E), 100% of tumors were detected. The CRADLE® app failed to provide adequate leukocoria detection except for four late-stage RB eyes.
Vargas-Cuentas, 2019 Peru	Cross-sectional study.	35 participants: 15 RB cases 20 controls.	The use of a mobile app (Retino App®) associated with an algorithm for imaging processing for the detection of RB.	The system correctly identified 93.33% of the cases and 95% of the controls.

Yousef, 2020 Jordan	Retrospective, clinical case series.	32 families, 76 children. 34 presented signs of RB; 42 were enrolled in the screening program.	Screening routine with examination under anesthesia and non-sedated exams. The frequency of evaluations was scheduled based on a clinical assessment of pre-test risk for relatives to carry the mutant RB1 allele, in the absence of genetic testing.	Out of the 76 children enrolled, 46 children were diagnosed with Rb (12 by screening and 34 had signs of Rb). Patients diagnosed by screening were younger (mean: 2.4 months vs 15.8 months), had significantly earlier tumor stage at diagnosis (p = .0001), had higher eye salvage rate (p = .0001), less need for systemic chemotherapy (p = .022), and better visual outcome (p = .0017). None of the eyes were group D or E, enucleated or irradiated. Six patients were cured without chemotherapy, and the visual acuity was 0.5 or better in 55% of eyes.
International partnership				

Al-Haddad, 2019 Lebanon	Retrospective case series.	40 (after) and 20 (before) RB cases.	The formalization of a multidisciplinary RB program (monthly meetings, centralization of care, clinical nurse) with associated financial support.	Reduced enucleation after the institution of the program (5% after versus 13% before); increased number of diagnostics (52 after versus 20 before); increased reception of patients from neighboring countries. However, even within a multidisciplinary setting, most patients with retinoblastoma still presented with advanced intraocular disease, and eye salvage rates were poor for patients with Group D and E tumors.
Chantada, 2016 Argentina	Public policy study.	(mean/year) 1987-1994: 18. 1995-2002: 35. 2003-2008: 30. 2009-2015: 36 2016-2020: 40 (estimated).	20-year cooperation between Garrahan Hospital in Argentina with Memorial Sloan Kettering Cancer Center in New York. The program initially concentrated on medical education and facilitated the research and treatment protocol for retinoblastoma in Latin America, incorporation of the first center capable of performing intra-arterial chemotherapy.	Improvement in the survival and ocular preservation of patients (3y probability of disease-free survival from 0.84 to 0.97), centralization of care, and participation in clinical studies and publications of the group.

Howard, 2018 ***10 index countries*** *(Venezuela, Honduras, Ukraine, Egypt, Morocco, Senegal, Tanzania, Philippines, Vietnam, Bangladesh). 32 additional countries.*	Public policy study.	201 RB cases.	The My Child Matters program supported diverse projects. Among them, the African Retinoblastoma Network, which had as its goals to raise awareness about retinoblastoma and childhood cancers with public campaigns to promote early diagnosis; to train oncologists and ophthalmologists to manage retinoblastoma; to create infrastructure and expertise for vision conservation in children diagnosed at early stages; to provide ocular prostheses, rehabilitation, and psychosocial support to patients with advanced disease.	Decrease in patients presenting with extraocular disease from 17 (65%) of 26 in 2011 to 19 (42%) of 45 in 2016; 1-year survival for patients with the unilateral intraocular disease increased from 3 (43%) of 7 in 2011 to 10 (71%) of 14 in 2016; 1-year survival for patients with bilateral intraocular disease increased from 0 (0%) of 2 in 2011 to 5 (42%) of 12 in 2016; eye preservation for patients increased from 0 (0%) of 4 in 2011 to 5 (21%) of 24 in 2016.

Qaddoumi, 2008 Jordan	Prospective cohort.	36 patients, 58 eyes.	A collaborative RB program was established with the International Outreach Program at St. Jude Children's Research Hospital in Memphis, Tennessee. Mentoring included Internet consultations, videoconferences, and exchange visits.	Twinning has positively impacted survival and ocular salvage in Jordan. Thirty-three children with retinoblastoma (20 bilateral) were treated. A total of 66 consultations with 29 patients were analyzed. New cases were compared to previously treated cases. The success of the program was evident in bilateral cases, with low enucleation (25%) and irradiation rates (17%).
Wilimas, 2009 ***Central America*** *(Guatemala, Honduras, El Salvador)*	Public policy study.	196 (after) and 167 (before).	A RB program focused on developing early diagnosis strategies, treatment protocols suited to local conditions, building local networks of oncologists and ophthalmologists, training local healthcare providers, using the modern donated equipment for diagnosis and treatment, and teleconsultation to further education and share expertise.	Patients abandoning/refusing treatment decreased in Guatemala from 21% to 11% and in Honduras from 35% to 19%.

Yousef, 2020b Jordan	Cross-sectional study.	478 patients 813 eyes.	Implementing a telemedicine-based program with St. Jude Children's Research Hospital compared to before implementation.	After the program implementation, the mortality rate decreased from 38% to 5% ($P < 0.0001$), and the overall eye salvage rate increased from 4% to 61% (98% for group A, 93% for group B, 81% for group C, and 48% for group D; $P < 0.0001$). Initially, all cases were discussed via telemedicine, but as knowledge transfer increased, the proportion of cases that required discussion decreased to less than 3% 10 years later. Similarly, treatment changes based on consultations decreased from 70% to 7% after 10 years. Both survival and eye salvage rates were comparable at the early and later stages of implementing the twinning program.
Education				

Al-Nawaiseh, 2017 Jordan	Retrospective, clinical case series.	Seventy six eyes of 44 consecutive familial RB.	Screening for RB and raising awareness in non-probands versus probands.	The eye salvage rate was significantly higher in the non-probands than in the probands in this series (p = 0 002). Patients diagnosed by screening (38%) had excellent visual outcomes, and both eyes were saved. The authors concluded that awareness of families of the possibility of retinoblastoma and adequate screening led to a significantly higher rate of eye salvage in patients with familial retinoblastoma.
Antoneli, 2004 Brazil	Cross-sectional study.	105 patients (before the educational program) and 152 (after).	Educational campaigns: articles in non-medical magazines and billboards placed at strategic points in the city. The medical population received training through courses and publications in a medical journal.	Patients who were referred within a period of less than 6 months had a higher frequency of intraocular disease when compared to patients with a referral time longer than six months (75% vs. 25% p< .001). There was no statistically significant difference for extraocular tumors. The mean referral time was 7.5 months (SD 7.79) before the educational program versus 5.3 months (SD 6.84) after the intervention.

Elfalah, 2022 Jordan	Cross-sectional study.	289 medical students.	Implementing modifications on teaching curriculum of medical students on ophthalmology rotation that focuses on the red flags of RB.	Most participants considered leukocoria an abnormal sign. Medical students of the control group had significantly lower knowledge about the diagnosis of RB (p = .0001), while the intervention group scored higher in tests about critical questions, such as knowing that RB is a fatal disease (p = .041) that needs urgent treatment (p = .042). Only 2% of students adopted the “watch and wait” strategy in the intervention group, compared to 12% in the control group. Proficiency score in the test ([?] 90%) was achieved by 8% of students in the intervention group versus 2% in the control group. In the intervention group 27% of students, compared to 65% of students in the control group, failed to obtain a sufficiency score ([?]70%) in the questionnaire.

Hill, 2015 Kenya	Cross-sectional study.	38 health workers.	A workshop for RB genetics education. Attendees: ophthalmologists, pathologists, oncologists, ophthalmic clinical officers, and nurses.	Knowledge increased significantly post-workshop, driven by increased knowledge of RB causative genetics. One-year post-workshop, participant knowledge had returned to baseline, indicating that knowledge retention requires more frequent reinforcement. Participants reported feeling more confident discussing genetics with patients and had integrated more genetic counseling into patient interactions.
Leander, 2007 Honduras	Cross-sectional study.	23 patients diagnosed after the campaign 59 patients (before).	RB education program linked to a national vaccination campaign in Honduras. Posters and flyers accessible to poorly educated readers, to convey the severity of RB, and to provide contact information.	Extraocular disease at diagnosis was 73% before versus 35% after the campaign (p = .002). Leukocoria was the presenting symptom in 54% of patients before versus 83% after the campaign (p = .02). The median age at diagnosis and the median time between the first sign or symptom and diagnosis were 3.8 (p = .26) and 1.7 (p = .6) months after the campaign.
Genetic counseling				

Joseph, 2004 India	Cross-sectional study.	25 patients.	Presymptomatic genetic screening (RB1) compared to the clinical screening of RB proband and relatives.	The cost of genetic testing and clinical examination for a proband was $US152.27 and 535.60, respectively, while for the nuclear family, it was $US174.51 and $US1071.20, respectively.
Joseph, 2006 India	Diagnostic model proposal.	-	An efficient diagnostic model with a logical and practical flow of various genetics tests (karyotyping, loss of heterozygosity analysis, molecular deletion, linkage analysis (familial cases), mutation screening of - CGA exons first and then non-CGA exons, methylation screening of RB1 and essential promoter regions screening in a laboratory) to reduce the overall health care costs.	In the proposed model, LOH analysis costs around US$ 9.72 (5.3%), RB1 gene mutational screening US$ 146.46 (79.88%), methylation analysis US$ 3.67 (2.0%), and cytogenetic analysis US$ 22.37 (12.8%). Assuming the patient did not exit until the last step in the genetic testing algorithm and did the entire spectrum of the tests with some of them being carried out simultaneously, about 84 days are required to exit from the diagnostic model.

Thirumalairaj, 2015 India	Cross-sectional study.	21 patients (13 bilateral and 8 unilateral RB).	Rapid genetic screening strategy by prioritizing the order of exons to be analyzed, based on the frequency of nonsense mutations, deletions, and duplications reported in the RB1-Leiden Open Variation Database and published literature on Indian patients.	Mutations were identified in 76% of patients in half the usual time and one-third of the cost.

Conflicts of Interest

The authors declare no competing interests.

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Legends:

Figure 1 : Study selection process flow diagram.

Figure 2: Improvement opportunities - a proposed chain of initiatives based on the review of studies in the countries pointed in the map (Jordan, India, Kenya, Lebanon, Brazil, Nigeria, Honduras, Ethiopia, Peru)

and multinational studies. *Act 1: International Partnership* : Establishing partnerships with the teleconsultation of specialists, mentoring programs, and financial aid to support the development of local programs. *Act 2: Nationally Coordinated Programs:* Implementing nationally coordinated programs for public assistance, including centralization of care, financial aid from local governments, and educational initiatives. *Act 3: Education and Awareness:* Develop educational tools for the medical community and general population to increase awareness of the disease, particularly targeting populations at higher risk. *Act 4: Screening Programs:*Implementing screening programs focused on populations at higher risk, while also incorporating periodic ocular health evaluation for all children. Future considerations include the integration of smartphone applications and algorithms to enhance screening accuracy. *Act 5: Genetic Services:* Establishing cost-effective genetic screening services to support early detection and diagnosis.

Table 1 : Summary of included studies.