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Authors	Karim ASSANI, LAURENCE DESJARDINS, Den is Malaise, Irene Kriegel, Fatoumata Sylla, Fous seyni Traore, Pierre Bey

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Title**:**

Improve cure rate of children with retinoblastoma: the AMCC program in sub-Saharan Africa

Authors : Karim Assani[1], Laurence Desjardins[2], Denis Malaise[3], Irene Kriegel[4], Fatoumata Sylla[5], Fousseyni Traore[6], Pierre Bey[7]

Affiliations
[1]Pediatric oncologist, Manager of AMCC retinoblastoma program, Kinshasa, DR Congo : drassanik@gmail.com
[2]Ophthalmic oncologist, president of AMCC, Paris, France: laurence.desjardins@curie.fr
[3]Ocular Oncology Department, Institut Curie, Paris, France, general secretary of AMCC/denis.malaise@curie.fr
[4]Anesthesiologist, member of AMCC, Paris, France: irene.kriegel@gmail.com
[5]Professor of Ophthalmology, IOTA, Bamako, Mali : sylkef70@yahoo.fr
[6]Professor of Pediatrics, University Hospital Gabriel Toure, Bamako, Mal:i drfousseynitraore@gmail.com
[7]Professor of Radiation oncology, Medical director of AMCC, Paris France: pierre.bey@curie.fr@curie.fr

Abstract

Alliance Mondiale Contre le Cancer (AMCC) is a non-profit French association devoted to improving cancer care in poor countries. It is domiciled at Institut Curie (Paris, France), which is the multidisciplinary referent retinoblastoma (RB) centre in France. In sub–Saharan Africa the number of children with RB is high (about 2 000 out of 8 500 worldwide) as 40% of the population is less than 15 years old and the population growth rate is still 2,7 % versus 1,1 for the whole world. Few health facilities were able to treat retinoblastoma in 2010. Diagnosis was often not possible or too late and mortality was high (over 80%) compared to Europe or the USA (mortality less than 5 % since decades).
Since 2011 we have started with the team in Bamako (Mali) a program to develop the care for RB in sub-Saharan Countries. Demonstration was obtained that the situation could improve with some specific support.
Since 2019, a 10-year program (2019-2029) was initiated in sub-Saharan countries including training of ophthalmologists and ocularists, development of multidisciplinary teams (MDTs) with paediatric-oncologists, the supply of complementary ophthalmological equipment to allow conservative management in bilateral cases, support for chemotherapy in some countries, data collections and publications and early diagnosis actions. To-day, halfway through the program's deployment, it is supporting 30 teams in 23 countries: French speaking and some English and Portuguese speaking countries. Efforts will continue over the next 5 years to improve sustainably early diagnosis with the aim of curing at least 60 % of all children with RB in 2030 with preservation of a useful vision for most of the bilateral cases.

Key words: retinoblastoma' sub-Saharan Africa 'early diagnosis' enucleation' chemotherapy'survival rate

Introduction

Retinoblastoma (RB) is a rare intraocular cancer that affects young children from birth and usually before the age of 4. It occurs in approximately one out of 15,000 births. This retinal tumour appears after two mutations of the *RB1* gene which is located on chromosome 13. The disease can be unilateral in 60% of cases and bilateral in 40% of cases. All bilateral and 15% of unilateral RB are due to a pre-existing germline mutation of the *RB1* gene. In 85% of unilateral RB, the two mutations occur in the retinal cells. Bilateral cases are hereditary (transmitted as an autosomal dominant trait with high but incomplete penetrance) and sometimes familial. The children usually have several tumours in each eye (mean 7) in hereditary forms.

The main symptoms are strabismus (which can be an early symptom of a macular tumour) and leukocoria (which usually becomes visible when the intraocular tumour is already large).

If early diagnosis is not made, a rapid growth of the tumour usually leads to high globe pressure, local inflammation and pain, buphthalmos and rapidly exophthalmia with extraocular growth, orbital and optic nerve involvement, which can threaten the child's life.

Worldwide around 8 500 new cases of RB occur every year and only 15 % of those cases occur in high income countries like the USA or Europe, where RB can be cured in over 95%. In these settings, combinations of several treatment modalities are provided such as enucleation in unilateral RB (with additional chemotherapy when necessary) and with the use of conservative management for bilateral cases[1]. An early diagnosis and the management by an expert multidisciplinary team are mandatory to fulfil such results. Historically, radiation therapy (external beam and plaque brachytherapy) was the first conservative treatment modality. Nowadays, the conservative management includes either 6 courses of intravenous chemotherapy (vincristine, etoposide, carboplatin), intra-arterial chemotherapy by melphalan and/or topotecan and intravitreal chemotherapy in case of persisting vitreous active seeding. All types of chemotherapy are always associated with local ophthalmological treatments started usually at the third chemotherapy cycle, by transpupillary thermotherapy with diode laser, cryotherapy of peripheral small lesions and plaque brachytherapy if needed and if it is accessible. Close follow up is mandatory after the initial treatment when the tumours are considered cured, and chemotherapy is discontinued.

The remaining 85% cases of RB occur in low- and middle-income countries. Most of the low- and lower-middle-income countries are in sub-Saharan Africa where around 2 000 new cases of RB occur every year. For these children, late diagnosis and poor access to trained and equipped

multidisciplinary teams lead to a high rate of death.[2] In these countries, RB is also proportionally more frequent due to the high rate of births[3,4] and the number of new cases per year will approximately be doubled in 2050.[5] Because of the travel burden and poor access to care, it is predictable that some cases are not diagnosed and data show more than half of the cases of RB present with advanced disease and mortality rate is still high [6].

To help bridge the gap of RB outcome between high and low- and lower-middle-income countries, *Alliance Mondiale Contre le Cancer* (AMCC, https://cancer-amcc.org/), a non-profit French association devoted to contribute in improving cancer care in poor countries, decided to support diagnosis and treatment of RB in sub-Saharan Africa where the majority of low and lower-middle income countries are located.

The first AMCC RB program in sub-Saharan Africa started in 2011 in Bamako (Mali)[7], supported by the My Child Matters program of the Sanofi Espoir foundation and the Curie Institute in Paris, which is the referent RB center in France. The aim of the program was to increase survival rate by improving early diagnosis. We started to collaborate with hospitals where there was a paediatric oncologist with access to chemotherapy drugs, thanks to the *Groupe Francophone Africain d'Oncologie Pédiatrique* (GFAOP,https://www.gfaop.org/), a pathologist and an ophthalmologist willing to take care of patients with rRB. The program included training of ophthalmologists for the care of RB (enucleation and conservative management), training of an ocularist for custom ocular prosthesis, support of early diagnosis campaigns, supply of complementary ophthalmologic equipment (surgical boxes, diode laser, indirect ophthalmoscope, cryotherapy device and fundus camera) and support for data collection. The program started in Bamako (Mali) and extended the following years in Antananarivo (Madagascar), Abidjan (Ivory Coast), Dakar (Senegal) and Lubumbashi (Democratic Republic of Congo). With implementation of all the actions in Bamako since 2011 by the RB multidisciplinary team of IOTA (*Institut d'Ophtalmologie Tropicale de l'Afrique*) and Gabriel Touré University hospital, it was demonstrated in 2018 that survival could improve from 50 % to more than 80% for unilateral intraocular RB, with local prosthetic rehabilitation after enucleation in all children and that conservative treatment was possible[8]. The achievement of this first program was considered a success and an additional proof of concept that it is possible to improve care for unilateral and bilateral RB in sub-Saharan Africa.

We can summarise the most important lessons learned from the previous AMCC RB program:

- It is important to structure intervention in a sequence: first of all training and equipment - then geographical and financial accessibility for patients - then improving early diagnosis and referral pathway
- Improving early detection without easy access to trained and equipped multidisciplinary teams seems to be inefficient and may be interpreted as unethical.
- The situation of late presentation of patients with RB in sub-Sahara Africa, mostly treated on palliation, involves more the leadership of the paediatric oncologists and less the ophthalmologists. Improving RB care will change the leadership to be more and more on the ophthalmologists and this should be well understood by the ophthalmologist in charge and welcome well by the entire RB multidisciplinary team. Worldwide, it seems that improvement of RB care is always associated with a strong leadership of a dedicated ophthalmologist into a multidisciplinary team
- There is almost 0% rate of refusal of enucleation while treating only RB extra-orbital disease when, most of the time, enucleation is no more a curative option. Improving early diagnosis should be coupled with strategies to mitigate refusal of enucleation
- Improvement of RB care in sub-Saharan Africa may need time
- It is possible to improve RB survival rate in sub-Saharan Africa with ambitious objectives.

Bringing all together, it was then possible to build a 10-year RB program to extend the support of multidisciplinary teams taking care of patients with RB in many other countries in sub-Saharan Africa with the objective to improve cure rate of RB in line with the WHO GICC objectives to cure 60% of children with cancer in 2030.[9]

Patients and Methods

The AMCC RB program 2019-2029 was built for the multidisciplinary teams (MDTs) treating patients with RB in sub-Saharan Africa. The first step was to integrate in this program the lessons learned from the previous AMCC RB program (2011-2018) developed in the same setting.

The program was launched in June 2019, when AMCC was able to secure funding from a Swiss foundation for the first 5 years (2019 to 2024).

The objectives of the program were to empower sub-Sahara African MDTs with necessary training, ophthalmological equipment, supply for anticancer drugs for French-speaking countries, early diagnosis activities, advocacy and support for data collection and publication of

papers while promoting experience sharing within the continent. All these objectives couldn't be fulfilled by AMCC alone. It was mandatory to establish fruitful collaborations during the deployment of the program to mutualize energies and avoid competition with other stakeholders working in the same field.

These actions were structured as follows:

- Training of ophthalmologists for examination under general anaesthesia (EUA), enucleation, and conservative management of RB and of ocular prosthetists was provided. A short-term training program (less than 2 months) was designed by training institutions and preferred because of the lack of health professionals in their countries and their ongoing responsibilities. Training was done preferably in a sub-Saharan Africa setting (Bamako, Accra or Nairobi) and/or training in a high income setting such as Paris (Curie Institute) or Barcelona (Hospital Sant Joan de Déu).
- Every two weeks, an on-line RB tumour board led by expert ophthalmologists was organised. An additional hands-on training at the site of the trainee was to be provided by an African or high-income country ophthalmologist expert at the time there is a patient who needs eye salvage procedures.
- Ophthalmological equipment for EUA, enucleation, and conservative management as well as ocular prosthesis equipment and consumables were to be donated by the program according to local needs and capabilities: surgical boxes for enucleation, indirect ophthalmoscope, diode laser with helmet or operating microscope, cryotherapy machine and fundus camera. Because of the high cost of both ophthalmological equipment and training for eye salvage, they were eligible to be supported by the program only if the expected bilateral cases was above 5 per year in the catchment area of the multidisciplinary team with no possible options available in a reasonable distance for patients to be referred.
- Early diagnosis activities were to be initiated, developed and implemented by local teams with the support of the ministry of health. The local team should apply for financial support by AMCC and be supported partly or totally if all the necessary financial and implementation requirements are met.
- In many countries in sub-Saharan Africa, families are the one to pay the RB treatment costs for their child. Advocacy was to be done by the local team at different levels to improve access to care for children with RB. AMCC helped the advocacy efforts in signing partnerships with hospitals where the multidisciplinary teams were working.

- All RB multidisciplinary teams were to be supported by AMCC for their efforts of data collection and publications. AMCC encouraged local initiatives to improve quality data collection as per local policies. Oral presentations and posters on RB were encouraged as well as publications of papers on RB. AMCC was ready to contribute financially for publications related fees.
- Experience sharing was considered as a cornerstone of improving RB care within Africa and could contribute to connecting RB specialists in French, English or Portuguese sub-Saharan Africa. This could be done through virtual or in person meetings during scientific gatherings such as congress, symposium or others.

A detailed program logical framework was established at the beginning of the program and divided the first 5 years for logistical aspects (training, equipment, initiation of early diagnosis, conservative management, improving data collection and publications) more dedicated for the multidisciplinary teams and the last 5 years for the phase of increasing early diagnosis and publications with more visible impact on patient's outcomes.

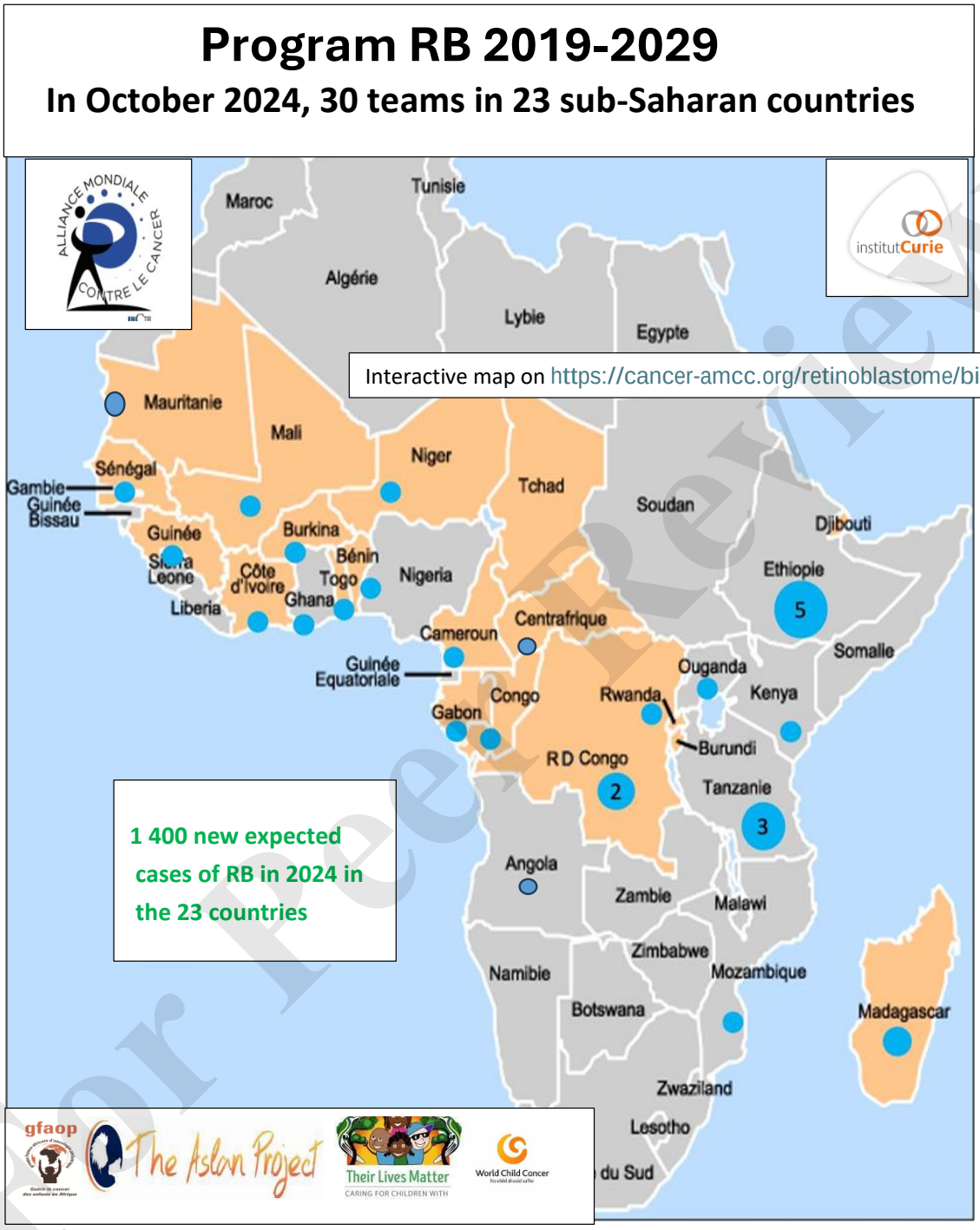
The expected outcomes of all these actions are an establishment of sustainable quality treatment provision for all patients with RB in sub-Saharan Africa and improvement of RB survival rate even for bilateral RB with preservation of useful vision in 2029.

The AMCC team recruited a full-time manager for this program in June 2019. The program was led by the AMCC team with the support of an international steering committee, meeting once a year, and a sub-Saharan operational committee, meeting regularly with the management team. These two committees had an advisory role to the management team. Financial and technical audits were carried out before the end of the first 5 years of the program and generated recommendations for the next 5 years.

Results

From June 2019 to June 2024, the program was deployed in 23 sub–Saharan African countries including French (15), English (6) and Portuguese (2) speaking countries representing 30 multidisciplinary teams (Fig.1 below).. The total number of expected RB cases in these 23 countries according to the population is to-day about 1 400 each year, half of them in French-speaking countries.

Fig.1



Training of ophthalmologists

In each country the identification of a RB multidisciplinary team was the first essential step. In all these teams, chemotherapy was routinely delivered for patients with RB, mostly under the supervision of paediatric oncologists. The multidisciplinary teams had to figure out ophthalmologists willing to embrace leadership into the MDT for him or her to be trained for RB care and another health professional to be trained as an ocular prosthetist.

For the total of 30 multidisciplinary teams, 5 teams had already ophthalmologists trained and practicing conservative management of RB while 21 teams needed initial training or complementary training. Four teams were not eligible to be trained through AMCC on conservative management of RB. A total of 11 out of 21 MDTs was trained in Bamako (IOTA and Gabriel Touré hospitals) and/or received complementary training in France (Curie Institute) or in Barcelona (Sant Joan de Déu Hospital). All trainees met the training objectives. Among the 10 MDTs who didn't receive training, 7 MDTs joined the program lastly and 3 others had some logistical issues.

Another component of the training of ophthalmologists is the regular webinar, which have been demonstrated to be useful for retinoblastoma care.[10] Sharing experience while discussing challenging cases was the main format of these meetings registered on RB-NET platform. These meetings were implemented in November 2020 and improved its structure in May 2021 organised every 2 weeks with regular reminders 2 days before and minutes distributed after each meeting. From May 2021 to May 2024, a total of 77 meetings were organised. The mean number of participants was 8 in 2021 but moved to 10 in 2022 and to 11 in 2023 and 2024. The mean number of cases discussed was 2.25 cases/webinar from 2022 to 2024 and the mean number of multidisciplinary teams represented was 4.3/webinar during the same period. In 95% of time, only French speaking multidisciplinary teams were represented. English and Portuguese speaking multidisciplinary teams were less represented (Uganda Cancer institute, Kabgayi hospital and Maputo Central Hospital) as most of these countries have already established similar platform for challenging cases discussions with experts from USA, England, India and Israel.[11]

For practical training, it was understood that launching conservative treatment for the first time remains difficult in the context of sub-Saharan Africa. So when there was a need of conservative treatment of RB for a case presented in the web conference and the local team was not comfortable enough with the procedure, an expert ophthalmologist had to travel for a few days for this onsite hands-on training. This expert ophthalmologist could be from experienced centres in Africa or from France if African experts couldn't be available themselves on time. A

total of 4 missions of this type were organised: in Lubumbashi (DRC), in Kinshasa (DRC), in Maputo (Mozambique) and in Lomé (Togo). These missions allowed conservative treatments to begin in the DRC both at Kinshasa and at Lubumbashi. In Maputo there were some logistical issues and the mission in Lomé was postponed. These missions also helped to strengthen links between teams, discuss or optimise treatment protocols, anticipate or prepare for other local treatments (intravitreal chemotherapy injections). Once the mission was completed, conservative treatments could be continued by local teams, and clinical response to treatment could be discussed during web conferences.

- **Training ocular prosthetists.**

For the ocular prosthetists training, 6 teams already had the services in their settings but one team had to interrupt the services because the ocular prosthetist had another position. So a total of 25 MDTs were in need of ocular prosthetists training. During the 5 years of the program, a total of 11 people received training out of 25, either in Paris, Bamako or Accra.

Taking advantage of some scientific gathering like SAFO Congress (*Société Africaine Francophone d'Ophtalmologie)* or SIOP Africa Congress, AMCC organised 4 workshops (Sally in Senegal, SIOP Africa at Kampala Uganda, SAFO Congress at Kinshasa in DRC and at Abidjan in (Ivory Coast) for ocular prosthetists for French speaking teams and English speaking teams. Both theoretical discussions format and exchange experience and practising tips in the ocular prosthesis lab format was organised. The mean attendance was 10 ocularists per workshop representing 19 MDTs (10 french speaking and 9 english speaking countries).

- **Other approaches and other training opportunities.**

Although ophthalmologists and ocular prosthetists were supposed to be trained in the frame of this program, the remaining team members of the MDTs benefited also on some experience sharing and training opportunities.

For example, during the SIOP Africa congress in Uganda 2022, paediatric oncologists and pathologists were invited to practical discussions of how each can contribute improving RB Care.[12]

And for pathologists, the pathology centre CRDCE (*Centre de Référence pour le Diagnostic des Cancers de l'Enfant*) in Dakar (Pr Cherif Dial) was able to accept trainers. Only one pathologist benefited from this training.

A multidisciplinary 3 days' workshop (ophthalmologist, pathologist, paediatric oncologist, ocular prosthetist) was first organised in Ethiopia for the benefit of the 5 multidisciplinary teams in collaboration with the expert team of Sheba hospital and Kenyata National hospital. Because of last minute logistics challenges, the workshop needed to be held at a reduced format.

Repeated and regular examination under anaesthesia for RB was to be introduced in some settings where anaesthesiologists were not solicited for that before. Anaesthesia requires sharing the operating field between the ophthalmologist and anaesthesiologist working as a team, the anaesthesiologist understanding and adapting to the ophthalmologist's needs, understanding and getting to know the children and parents (importance of fasting rules, history and psychological aspects). Non-specialized practice increases the risk, hence the importance of appropriate structure and organisation and maintenance of skills.[13–15] Understanding the potential needs, AMCC tried to contribute as much as possible to help multidisciplinary teams who expressed to be more in need. A total of 2 centres benefitted to the collaboration of an expert anaesthesiologist for one-week onsite training and donation of small but very useful routine consumables.

- **Ophthalmological and ocular prosthetists equipment.**

For the total number of 30 MDTs, 8 had already equipment for eye salvage and 7 had already equipment for ocular prosthesis. So only 18 were eligible to have conservative management equipment, and 23 to have ocular prosthetists equipment based on the criteria adopted for the program. From 2019 to 2024, 14 new MDTs received donation of the eye salvage equipment and 7 received donation of ocular prosthesis equipment. From the 8 MDTs who already had eye salvage equipment, 6 MDTs received additional equipment because what they had was not sufficient (3 MDTs) or not well functional or adapted for RB (3 MDTs). The total number of Diode Laser with Helmet and cryotherapy machine donated was 14 and 12 respectively, while only 7 fundus cameras and 3 operating microscopes were donated. The number of surgical boxes and indirect ophthalmoscopes donated was respectively 14 and 15.

Providing equipment came with challenges like shipping from high-income settings to sub-Saharan Africa where custom fees were not always easily cleared and the support of beneficiary hospitals or ministry of health of the countries were sometimes scarce. Another potential challenge is maintenance of those equipment.

Anti-cancer drugs for RB were provided to the teams in French-speaking countries through a partnership with GFAOP and the support of Foundation Valentin Haüy in Paris (https://www.fondationvalentinhauy.fr/).

- **Early diagnosis of RB**

The program was launched a few months before the covid-19 pandemic that lasted for more than a year. It was not possible to develop early diagnosis activities for RB during that time.

From 2021, all the MDTs were encouraged to initiate early diagnosis activities. Only 18 MDTs (9 English-speaking and 9 French-speaking) in 12 countries (4 English-speaking and 8 French-speaking) were able to initiate early diagnosis activities with AMCC support. Most of the time the MDTs were combining training of health professionals (frontline health workers) on early signs of RB and awareness in the general population. From these 18 MDTs, 8 teams had the support of a local organisation (e.g. local NGO) to help plan and/or implement early diagnosis actions. Subsequently, activities seemed to be implemented with less difficulties and more efficiently compared to the 10 others MDTs who had to plan and implement these activities on their own. From the 4th year of the program, it was suggested to MDT to use the potential of social media in disseminating information in benefit of RB awareness. Short videos of 30 seconds (it was called "30 sec challenge videos") where recorded by MDTs members and other health professionals (ophthalmologists) in their mother tongue or English or French while showing pictures of leukocoria and strabismus with a call to action when they were seen into the child's eye. Within a short time, 10 MDTs adopted the idea and more than 1 000 videos were recorded. With the help of "Know the Glow" (https://knowtheglow.org/), some of them were disseminated in social media during RB week in 2024 in 5 countries. The campaign reached nearly 800,000 people in just seven days and the videos were viewed by over 600,000 people.

- **Advocacy for RB**

Improving access to treatment was also seen as an important enabler of different RB MDT's actions. For the total of 30 MDTs, the enucleation cost alone was distributed from 0 (free of charge) to more than 600 USD that should be paid by the family. Knowing that in the majority of these countries, 60% of the population live with less than 3.65 USD per day (Source: World Bank Poverty and Inequality Platform (2024)) and the health expenditures are estimated to be less than 50 US dollars per capita per year[16,17]. It was clear that actions should be taken to overcome such barriers. Only 3 MDTs applied free of charge enucleation for RB but yet families need to pay for initial investigations and metastatic workup (e.g. CT scan or MRI). For the remaining MDTs, families are the one to pay totally or partly the enucleation cost and other costs including CT scan or MRI, EUAs and other tests like pathology.

Not later than 6 months after the launch of this RB program, the covid-19 pandemic brought unprecedented challenges and it lasted for more than 12 months. Travelling for patients was

stopped even within the same country and the economic impact was described to be significant in sub-Saharan Africa. Soon after, an important international crisis (conflict in Ukraine) came to worsen the economic impact.

From all the program actions (like training, provision of equipment, early diagnosis) emerged ethical and operational questions about the need to continue their implementation and their efficiency in such a context.

All advocacy actions succeeded to reduce the costs of enucleation and AMCC was able to secure additional funding dedicated for vulnerable families of children with presumed curable RB. A total of 9 multidisciplinary teams utilised the funding for more than 66 patients. In addition, 12 children with RB in RDC (6 in Kinshasa and 6 in Lubumbashi) have benefited from the support of the For Hope association (https://www.forhopeassociation.org/) during the year 2023, through a partnership with GFAOP.

All patients in need as per the assessment and request of the MDT received the support.

Another important advocacy may be done by the parents themselves. AMCC encouraged all the MDTs to help parents to organise themselves as association or local NGO that can be devoted to help RB care in their settings. Parents association of 2 MDT were invited to be part of the ISOO Africa congress in 2023. This could have given the opportunity to these younger associations to network and develop collaborations with very experienced parents' associations like Retinostop in France (https://retinostop.org/) or other similar associations who attended the same congress.

- **Data collection and publications:**

The total of 30 RB MDTs were able to collect the number of new cases of RB treated with their initial staging and outcomes. But for more detailed data like intraocular staging, the optic nerve length removed during the enucleation, detailed pathology risk factors, not all MDTs had those data available. To contribute to improving this aspect, a set of variables on RB to be collected was suggested to all the RB MDTs. This could help facilitate future multicentre studies at regional level. A total of 7 MDTs had already an established well organised data collection tool with GFAOP, and AMCC supported the action according to the need expressed by the MDT. This support could be the provision of a computer or to contribute for the part time incentive of a data manager for a limited period. The remaining MDTs who didn't have such organised data collection tools were encouraged to have one and AMCC engaged in the partnership agreement to support the action.

From 2019 to 2024, congress presentations and posters on RB in Africa were supported by AMCC who invited members of 27 MDTs to attend 6 international congresses where RB were among the major themes. A total of 5 international congresses were held in Africa (SAFO congress 2022 et 2023, SIOP Africa 2022 and 2024, ISOO Congress 2023) and 1 international congress held out of Africa (ISOO Congress 2022). During these scientific gatherings, MDT members had the opportunity to make oral presentations or to present posters, to network with colleagues from around the region and beyond, to be encouraged for publications and to be part of research opportunities through collaborations.

There was no publication on RB that utilised the AMCC support for publication related fees during the first 5 years of the program, but two research projects were supported: a project on RB genetics and a multicentre cross sectional study on related causes of late presentation of RB in Africa. These two projects will be published in the near future.

- **Experience sharing and networking for RB**

During these 5 years, AMCC was involved in 9 scientific gathering (3 virtual: 2 London global cancer week and 1 AMCC virtual workshop, and 6 in person: 2 SAFO, 2 SIOP Africa, 1 AMCC Saly, 1 ISOO Africa) in order to allow MDT to share their experience and network with other RB specialist.

AMCC had also the opportunity to share experience and learn from different organisations working in sub-Saharan Africa: GFAOP, gfaop.org, for French speaking countries but also with Their Lives Matter or Tumaïni la Maïsha (TLM, in Tanzania, tumainilamaisha.org), World Child Cancer (WCC in Ghana and Cameroon, worldchildcancer.org) and ASLAN project (in Ethiopia, aslanproject.org) for English speaking countries. We had also some kind of collaboration with African ophthalmologic associations like SAFO (African Francophone Society of Ophthalmology, safo-net.org/) and COECSA (The College of Central, Eastern and Southern Africa, coecsa.org), and with St Jude Children's Research Hospital (Memphis, USA, stjude.org), SIOP (International Society of Paediatric Oncology, siop-online.org) Africa, the Eye Cancer Foundation (USA, eyecancercure.com) and Know The Glow (USA, knowtheglow.org). The experience was shared in different areas such as early diagnosis, equipment, training, research.

- **Monitoring and evaluation of the program:**

During the period, the steering committee gave insightful advice and the operational committee monitored the program.

A third party assessment of the technical aspects of the program was conducted by another RB expert who understands challenges in sub-Saharan Africa and formulated some recommendations to the program management.

A financial audit was conducted at the end of the fourth year of the program and certified the accuracy of the accounting.

Discussion

Despite the high number of cases of RB in Africa, about one third of the world number, there are little reliable data on precise incidence and outcomes of RB particularly in sub-Saharan Africa, due to a lack of exhaustive childhood cancer registries.

Many publications[18–20] report on local retrospective data describing the state of affairs of children with RB in sub-Saharan Africa revealing the scale of the challenges.

Variations of age-standardised rate on the world population (ASR-world) of RB in Africa were reported in 2017 from 2,9 per million children less than 15 for Guinea up to 27,2 in Malawi[20].

On the contrary, incidence and outcomes are homogeneous in high-income countries, where exhaustive registries have existed for decades. It is the situation in France (66 million inhabitants with 17% less than 15 years), with the French National Registry of Childhood Cancer, which has been exhaustive for more than 20 years. The last report[21] indicates a mean incidence of 50 new RB cases per year, representing 4,3 new cases per million children less than 15 years, 804 cases between 2000 and 2015, 96% diagnosed before the age of 4, survival at 10 years: 99,1% (the highest among all cancers in children which show a mean cure rate of 80,8% at 10 years).

Outcomes (survival and globe salvage) in sub-Saharan Africa, including many Low-Income Countries, are lower than in other parts of the world. There is a direct relationship between outcomes and national income level[21] and with socioeconomic and health-care factors as reported by this meta-analysis[22] with survival range from around 50% and salvage globe from 6% for LIC up to survival of 98% and salvage globe 70% for HIC.

The Global Retinoblastoma Study Group published in 2024[6] the results of a 3-year prospective observational study on survival and globe salvage in a total of 958 patients (27% bilateral) treated in 66 centres from 41 African countries. 93% came from L and LMICs. The overall survival of the declared cases with 10% abandonment was 62,7% at 4 years, which seems

relatively high. But, as it is reported, the estimation of new cases of RB during 2017 in the 41 countries was estimated to be 2 370, indicating that only 40% of the estimated incident cases were reported in the study, and it can be assumed that most unreported cases did not reach a treatment centre and that most of them died undiagnosed or untreated.

This study, and others[23,24] identifies the reasons of this situation and perfectly illustrates the ways to improve it in sub-Saharan Africa: increase the number of competent and well-equipped multidisciplinary teams, increase the number of children able to reach such a team, reduce treatment abandonments by reducing costs borne by families.

Different strategies have been suggested to reverse this deleterious situation[25,26].

The RB 2019-2029 program coordinated by the AMCC is, to our knowledge, the only one to be deployed in a transnational regional framework, in sub-Saharan Africa, based on the estimated incidence in each country and with a global approach supporting multidisciplinary teams from early diagnosis to rehabilitation after treatment, facilitating access to treatments including conservative treatments for bilateral cases. Previous programs to improve the care for childhood cancer in Africa have concentrated their efforts on onco-paediatricians training and access to chemotherapy drugs. The particularity of our program is that while insisting on working within multidisciplinary teams, we have directed our efforts toward training ophthalmologists and ocularists and providing them the necessary ophthalmological equipment and by supporting early diagnosis plans. When only advanced cases arrive in hospitals, children with RB are treated by onco-paediatricians who provide chemotherapy if possible but often palliative care and pain medication. When intraocular retinoblastomas are diagnosed, the role of the ophthalmologist becomes essential for diagnosis and to provide enucleation and when possible conservative management in bilateral cases. Ophthalmologists treating retinoblastoma in Africa must face difficult problems (socio economic problems, enucleation refusal, treatment abandonment or follow up problems). They must be patient, organised, inventive, empathic and hard workers.

Our program followed previous AMCC programs since 2011 in Mali[18] and 4 other countries. The demonstration, proof of concept, was given in Mali in 2018[8] demonstrating that, after selective support (training, equipment, access to drugs, awareness campaigns), more than 80% of cases of unilateral intraocular RB could be put into remission and that conservative treatment was possible, but with still about 50% of cases arriving too late to be treated.

The AMCC RB Program 2019-29 seems to be the only comprehensive program of concrete actions aimed at sustainably improving the situation of children with RB, simultaneously in

more than 20 countries in sub-Saharan Africa. This program provides financial support for practical training of ophthalmologists, anaesthesiologists and ocularists, for

supplementation of ophthalmologic equipment to allow enucleations, prostheses and conservative treatments in bilateral cases, access to essential anticancer drugs in French speaking countries, and is also supporting national plans for early diagnosis and the collection of reliable data for evaluation and publications.

Of course, with such an approach, the results of this long-term program will appear gradually, at different speeds depending on the teams and on the involvement of the authorities of each country in facilitating access to care for children and their families.

Perspective

The second part of the program, 2025 to 2029, will support 5 actions:

1. Increase awareness of early diagnosis of RB

2. Increase efficiency by facilitating children's access to skills through the collaboration of university teams with "Secondary Centers"

3. Continue on-site support for teams that require it

4. Help with the regular publication of results

5.Increase advocacy and collaboration with ophthalmology societies.

The final objective is that at the end of the second 5-year period of the program, in 2030, in the majority of countries the care of children with RB will have become a completely autonomous national cause, within an African network.

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Legend of the figure

map of centres supported by AMCC treating retinoblastoma in Africa

Can be found as an interactive map on AMCC web site: https://cancer-amcc.org/