

# Childhood cancer in the Eastern Mediterranean Region

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Among the six regions of the World Health Organization, the Eastern Mediterranean Region (EMR) has the second highest incidence of childhood cancer (defined as age 0–14) per capita. At the same time, the survival of childhood cancer patients is seen to strongly depend on the gross national income, causing a difference from an average of 20% of survival in low- and middle-income countries to 80% survival in high-income countries.

This shows the big potential to cure more childhood cancer patients in a region like the EMR where low- and middle-income countries are in the majority and thereby, reducing premature noncommunicable disease mortality – part of the Sustainable Development Goals of the United Nations agenda.

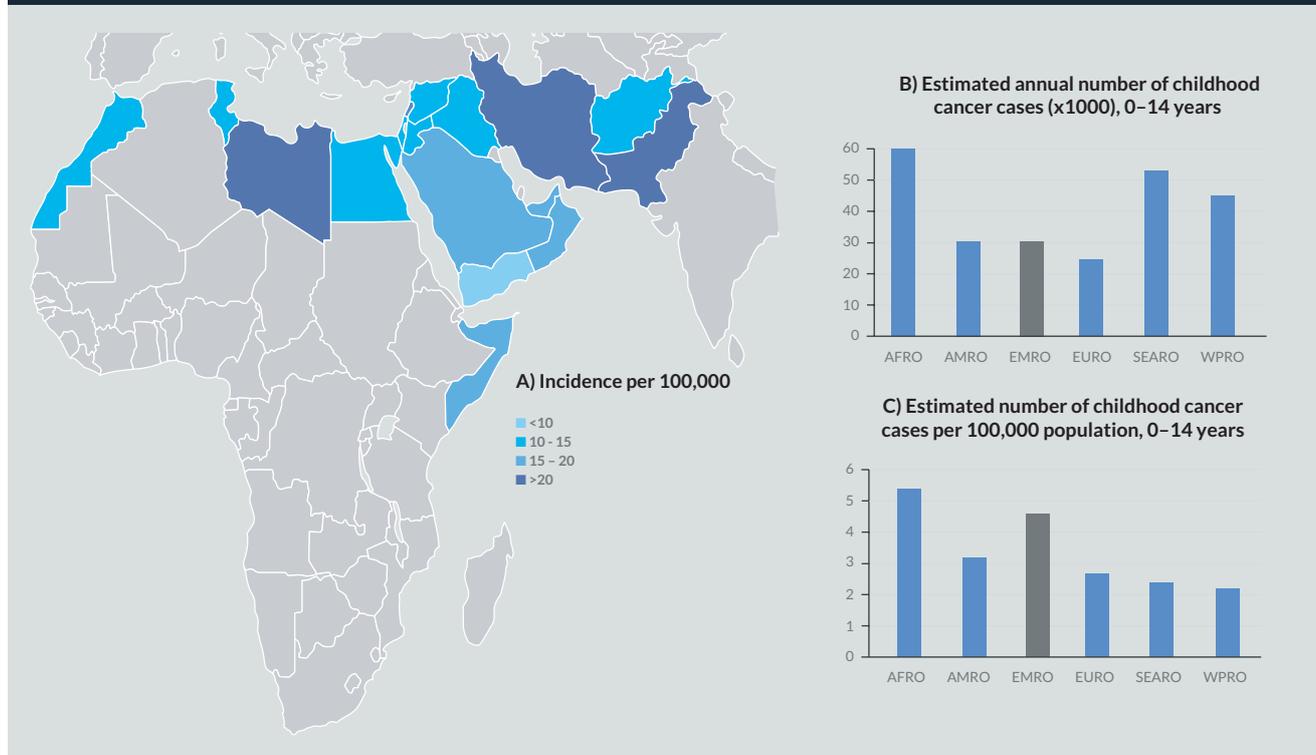
This chapter offers an overview of the current situation with childhood cancer treatment in the EMR from a health system perspective, including the status quo of the region in terms of organization and availability of services, training and research, as well as an examination of regional challenges to overcome.

Childhood cancer is a leading cause of death among children and adolescents, with large disparities in survival rates between and within countries. In high-income countries with strong healthcare systems, survival rates for the most common childhood cancers surpass 80%, while the average survival approximates 20% in resource-limited settings (1, 2). Decreasing this disparity and increasing the global average survival to 60% by 2030 is one of the overarching aims of the Global Initiative for Childhood Cancer (GICC), launched by the World Health Organization (WHO) in partnership with St Jude Children's Research Hospital in 2018. As part of the GICC, six common childhood cancers (acute lymphoblastic leukemia, Burkitt lymphoma, Hodgkin lymphoma, retinoblastoma, Wilms tumour, low-grade glioma) have been identified as tracers for monitoring progress; chosen because they are relatively common across EMR countries as well as highly curable with proven therapies (1, 3). With childhood cancer contributing to premature NCD mortality,

the GICC will not only serve the Sustainable Development Goal (SDG) target 3.4 to reduce premature NCD mortality by one third by 2030, but is also an opportunity to operationalize the 2017 World Health Assembly resolution 70.12 on cancer prevention and control in the context of an integrated approach (4).

The WHO Report on Cancer 2020 with data from the International Agency for Research on Cancer (IARC) estimates 33,808 new cases of childhood cancer in the WHO Eastern Mediterranean Region (EMR) in 2018. It should be noted that this only includes children aged 0–14 years (5). Figure 1A shows the estimated age-standardized incidence rates for cancers in children aged 0–14 years in the EMR countries, as reported by GLOBOCAN in 2018. The EMR had the second to lowest estimated annual number of childhood cancer cases compared to other WHO regions (Figure 1B). However, it has a significantly smaller population, such that the per capita number of annual childhood cancer cases is in fact the second

Figure 1: Estimated annual childhood cancer cases in EMR region. All data are extracted from the IARC GLOBOCAN 2018. A) Incidence of cancer cases in children 0–14 years old, by EMR country. Shades correspond to the range shown in the legend on the right. B) Estimated age-standardized burden of cancers in children aged 0–14 years in the specified WHO regions. C) Number of estimated childhood cancer cases in children aged 0–14 per 100,000 population in the specified WHO regions. WHO regions: AFRO = African; AMRO = the Americas; EMRO = Eastern Mediterranean, EURO = European, SEARO = South-East Asia, and WPRO = Western Pacific



highest compared to other regions, superseded only by the African region (AFRO) (Figure 1C) (6).

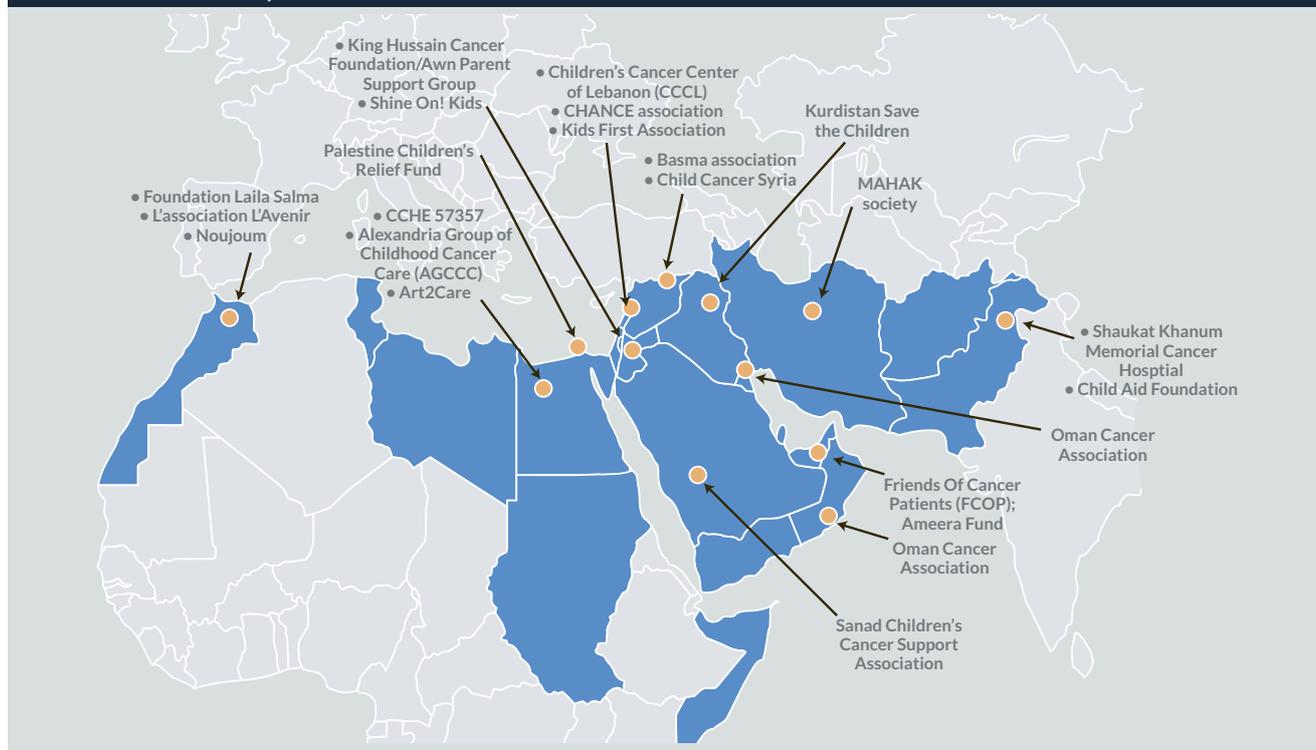
The purpose of this narrative review is to give a comprehensive overview of the situation of childhood cancer in the WHO Eastern Mediterranean region from a health system perspective. In addition, some examples from Turkey are included. We focus on the availability of services, training and research capacities, as well as challenges in the region hampering service delivery and survival outcomes.

### Organization of services

**National cancer control and healthcare plans:** Countries in the EMR are diverse in many aspects: socioeconomic factors, organization of services, level of complexity of healthcare systems, as well as cultural and language differences. Few have formal national cancer control programmes, and childhood cancer being a relatively minor component of the disease burden, frequently follows the general healthcare coverage. In the cancer monitoring progress survey that was carried out by the WHO Regional Office for the Eastern Mediterranean in 2019 (7), only six countries – Kuwait, Morocco, Oman, Sudan, Tunisia, and the United Arab Emirates – reported that childhood cancer was included in their priority benefits package, which typically also includes the required access to essential paediatric cancer medicines as defined by the WHO (8).

The Gulf Cooperation Council (GCC) countries – Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates – all of which fall within the World Bank high-income category, have healthcare systems where financing of paediatric cancer care is provided by the government for all nationals. For non-nationals, however, who comprise a large proportion of the population, healthcare for paediatric cancer in these cases is dependent on insurance plans, or in their absence, not covered at all. For other countries in the region, governmental coverage of healthcare costs for paediatric cancer can vary, with the majority having private and public healthcare sectors of varying service infrastructure, and where governmental healthcare coverage, when applicable, is primarily carried out at the public hospitals. The latter in turn, are frequently under staffed and lacking in adequate resources for effective treatment delivery. In the private healthcare sector, the cost is higher, and essentially unaffordable to the majority of patients. In countries such as Egypt, Jordan and Lebanon, specific childhood cancer charity organizations affiliated with a particular childhood cancer hospital, have filled in the financial gap for a large proportion of patients, helping ensure accessibility to care at well-equipped private sector or university cancer centres (9–11). Nevertheless, the scale of these successful financing interventions is still not sufficient enough to reach all paediatric cancer cases in the respective

Figure 2: Distribution and list of regional childhood cancer civil society organizations, as extracted mostly from the Childhood Cancer International (CCI) website. Note that this list may not be exhaustive



countries, but it has alleviated the cost for a substantial proportion of patients.

**Quality of healthcare services:** In the EMR, there are several well-established cancer centres of excellence where patients can expect to receive high-quality care similar to that available in advanced healthcare systems. Consequently, the care outcome is also comparable. These centres, however, are only able to support a proportion of children with cancer in their respective countries, with the remaining children seeking care in hospitals with less facilities, less well-trained human resources, weaker multidisciplinary services, and less financial support, which are all necessary to successfully deliver standard-of-care paediatric oncology treatments.

The assessment of quality care delivery is difficult in most EMR countries, due to the limited cancer registry data, which precludes accurate determination of the burden of childhood cancer within the population. Accordingly, no data exists regarding indicators for quality provision and effectiveness of the available cancer care. Cancer registries, when they do exist, are either hospital-based, or are limited in scope and lack outcome and survival data. The information that is available is mostly derived from single hospital-based registries and reports the outcome on only a subset of patients, making national generalization difficult and fraught with biases. The lack of such data registries also limits the ability to conduct quality and performance monitoring of treatment delivery and patient outcome nationally (12).

**Professional societies and organizations:** In recent years, the EMR has witnessed an increase in educational, awareness and lobbying efforts focusing on paediatric cancer care. International medical professional organizations such as regional branches of the International Society of Paediatric Oncology (SIOP), the Paediatric Oncology East & Mediterranean (POEM) collaborative group, Groupe Franco-Africain d'Oncologie Pédiatrique (GFAOP), and the Eastern Mediterranean Bone Marrow Transplantation Group (EMBT), have been active in enhancing communication, collaboration, and educational activities among paediatric oncology healthcare professionals across the region. Multinational organizations such as the Union for International Cancer Control (UICC) and Childhood Cancer International (CCI) have also been including increasing numbers of regional NGOs (Figure 2) to lobby for more effective paediatric cancer care.

### Paediatric oncology – a multidisciplinary and collaboration model

The complexity of effective treatment regimens for childhood cancer makes a multidisciplinary approach necessary. This includes not only provision of the various clinical disciplines needed for diagnosis, treatment and supportive care, but also the training of healthcare professionals and investing in research infrastructure. This multidisciplinary model is one of the main drivers behind the success witnessed in

paediatric cancer survival during the last 50 years and sets the framework for further development (13). The modalities used in the treatment of paediatric cancers are mainly surgery, chemotherapy including biological agents, and radiotherapy. A number of relevant healthcare specialities (Box 1) are essential for effective treatment in paediatric oncology, and platforms for multidisciplinary exchange (Box 2) are needed to enhance treatment planning and appropriate delivery, and to ensure continuing education and maintenance of expertise (14). Clear referral networks and connections between primary and secondary care centres on the one hand and tertiary care centres that are equipped with well-coordinated multidisciplinary elements, on the other hand, are necessary to enable early diagnosis, good quality of care, and reasonable outcomes.

There are several good examples of institutions in the EMR that combine the disciplines and specialties required for the multidisciplinary care of paediatric patients with cancer. These include well-established cancer hospitals in Egypt, Jordan, Lebanon, and Saudi Arabia, among others. However, the number of comprehensive paediatric cancer centres in the EMR is still limited and unable to serve the breadth of patients in need. There is also a paucity of databases or reports addressing the region's availability of multidisciplinary care, research and training. Therefore, the multidisciplinary model must be a priority within the national cancer control strategies and plans.

The feasibility of implementation of a multidisciplinary model for paediatric oncology care across the nation, and its impact on childhood cancer outcomes, is demonstrated by the experience of Turkey. Paediatric oncology in Turkey started as a discipline in the late 1960s and early 1970s and finally became a specialty in 1983, merging with paediatric haematology in 2011. After the 2000s, more specialists became available across Turkey, but still some centres remain without specialists. The centres which do not have all the required specialities in-house, overcome this by collaborating with other comprehensive centres. Currently, multidisciplinary teams are available in all major cities. As a result of such efforts, the overall 5-year survival of children with cancer in Turkey is currently estimated around 70% (15). In comparison, while the survival at national level is not available for the early years of the establishment of the paediatric oncology speciality, an institutional study on 5-year survival carried out at Hacettepe University during the 1970s showed a 23.6% survival rate (16).

As paediatric cancer is a relatively rare disease, national and international collaborations are imperative for continuing clinical advancement and the sharing of expertise, as well as the successful addressing of research questions. Most

#### Box 1: Main disciplines and services necessary for paediatric cancer care

- Paediatric haematology/oncology
- Surgical sub-specialties and anaesthesiology:
  - Paediatric surgery
  - Neurosurgery
  - Orthopaedic surgery
  - Ophthalmologic surgery
- Imaging
  - Radiology; paediatric radiology, neuroradiology, interventional radiology
  - Nuclear medicine
- Pathology, molecular biology/genetics
- Radiotherapy
- Oncology nursing
- Paediatric sub-specialties: infectious diseases, intensive care, cardiology, nephrology, gastroenterology, neurology, immunology, endocrinology, pulmonology, etc)
- Palliative care, psychosocial support, social services and supportive care
- Stem cell transplantation
- Supporting units: pharmacy, blood banks, nutrition, respiratory therapy, social services, data management

#### Box 2: Collaborative and multidisciplinary platforms for paediatric cancer units

- Tumour boards and other multidisciplinary educational and research meetings
- Inter-departmental programmes and relationships within the institution
- Multi-institutional collaborations
- National pediatric oncology/hematology societies
- Regional cooperative groups and societies (POEM, GFAOP, etc)
- Major international groups (SIOP, COG, BFM, etc)

paediatric oncology professionals in the EMR are actively engaged within the major relevant international medical societies, such as the International Society of Paediatric Oncology (SIOP). Through initiatives such as the SIOP - Global Health Network, much work is underway to attempt to address the inequity of access to appropriate care for children with cancer in developing countries (17), including suggestions for adapted best approaches of care in resource-limited settings (18–21). Initiatives with international cancer centres, for example in the form of twinning programmes, have also helped in programme building and bridging the survival gap (22).

National societies and regional collaborations have become major portals among the paediatric oncology community to bring together different disciplines to share knowledge and expertise. They also have great potential to act as platforms to address the main barriers affecting paediatric cancer care in the region, such as the lack of human capacity, financial support, support for research and training, and political will and prioritization (12). The Moroccan Society of Hematology and Pediatric Oncology produces various national guidelines (acute lymphoblastic leukemia, Hodgkin's disease, retinoblastoma, medulloblastoma and pain management, organized three continental meetings and conducted several clinical research programmes and also contributed

significantly to education and advocacy for children with cancer in the country

(23, 24). The Middle East Childhood Cancer Alliance (MECCA) was established in 2000 (25), and worked on data collection in acute lymphoblastic leukemia (26). More recently, the Paediatric Oncology East and Mediterranean (POEM) Group, established in 2013, now comprises hundreds of members from 28 regional countries, providing a platform for collaboration, capacity building initiatives, training and education, and collaborative research initiatives across the region (27, 28, 29). In North Africa, paediatric oncology units in 2000 formed the French African Paediatric Oncology Group (GFAOP), which has initiated prospective adapted regimens for the five most frequent and curable childhood cancers (Burkitt lymphoma, Wilms tumours, retinoblastoma, Hodgkin disease and acute lymphoblastic leukemia) (30) and created the African School of Paediatric Oncology (31). Such collaborative groups are expected to have a major role in prioritizing and coordinating projects and efforts that have the potential to drive paediatric oncology care, research, and policy in the region.

### Availability of services

While the required diagnostic tools (e.g., imaging modalities, immunohistochemistry, flow-cytometry, and cytogenetics) are largely available in the major cancer centres, the capacity for conducting a comprehensive diagnosis may be lacking in different centres even within the same country, leading to a considerable subnational variety (32). During recent years, expanded facilities have been developed in most of the EMR countries, either within the public domain or supported by charitable organizations. This has increased the capacity and quality of childhood cancer care, with many more children being correctly diagnosed and treated. In many countries, however, these centres are concentrated in major cities, which require travel and often relocation for families seeking care (32–34). The establishment of similar centres, or the creation of satellite units, in smaller cities and towns is beginning to happen in some countries, such as Egypt and Pakistan, and is expected to result in a much-needed improvement in local access to care (12).

Early diagnosis, timely referral, and appropriate intensity of treatment and management of side effects, are essential prerequisites for improved childhood cancer outcome. With few exceptions, EMR countries lack a clear referral system for paediatric oncology care. In many of the high-income countries, such as those that constitute the GCC, there is significant investment in health and development of primary care systems that can facilitate early referrals, but this has at yet not matured (35). As such, in most of the EMR, children

with cancer may be treated at any public or private hospital, as determined by their treating physician and the hospital's financial considerations, rather than a specific guidance regarding acuity of care or intensity of therapy, or the presence of needed multidisciplinary and nursing expertise. The assessment of local resource needs (workforce, beds, imaging, and treatment modalities) versus their availability, therefore, becomes difficult, as paediatric cancer patients are staggered across hospitals of various tiers, contributing to a variable outcome that is not accurately captured. Referral responsibility is often relegated to individual physicians and to the patients' families. Delayed, inappropriate, and missed referrals result in higher stages at presentation, advanced comorbidities, and even failures in diagnosis (36). In Pakistan, for example, it is believed that diagnosis is made in only half the number of children estimated to develop cancer within the population (32).

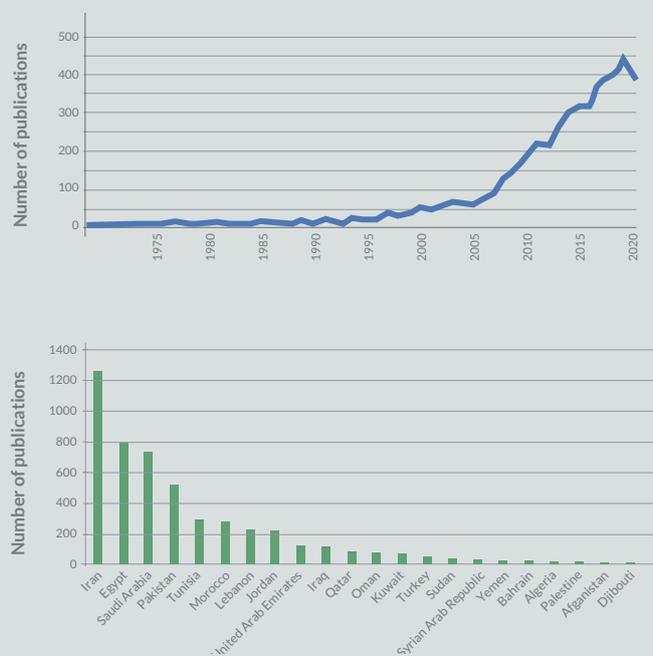
National paediatric cancer treatment guidelines have started to be initiated in some countries but are still lacking in most. When they do exist, their implementation is difficult to assess. Similarly, national guidelines for palliative care are still lacking in most EMR countries, while some hospitals are working to introduce palliative care to paediatric patients as a continuous service, through efforts driven primarily by NGOs (37–39).

Importantly, the supply of cancer chemotherapeutic drugs, particularly those used for childhood cancers, has been inconsistent and inadequate, in line with worldwide concerns (40–42). While high-income countries are also affected, low- and middle-income countries are disproportionately impacted, including within the EMR (43–45). The availability and utilization of supportive care medications, including opioids, also remains a problem in many developing countries and specifically in the EMR (46, 47).

### Training

The availability of multiple-accredited institutions of higher education, medical schools, nursing schools, and regional medical training programmes, continues to contribute to the improvement in available expertise and human resources in the EMR. Many well-reputed institutions of higher education and cancer centres in the EMR offer long-, and/or short-, term training opportunities for physicians and nurses. However, because the EMR comprises Arabic-based, English- and American-based, and French-based systems of education, some differences exist in training and certification details and requirements across the region. The Francophone countries, for example, do not have board-certified sub-specialization. Instead, clinicians that undergo paediatric oncology training recognized by a university will receive a formal diploma and

**Figure 3: Scientific publications identified via SCOPUS search engine, published between 1 January 1951 and 30 September 2020. A) Number of publications per year, over the period 1 January 1970 – 30 September 2020. B) Number of publications by country of author affiliations. Additional author affiliations on the same publications from outside the EMR were excluded from this graph**



SCOPUS search methodology: The below terms related to paediatric oncology topics, within title, abstract, or keywords, in any language, and different spellings were included: Age term (pediatric, infant, child, adolescent, teen, youth, or young) AND oncology term (oncology, cancer, tumor, lymphoma, sarcoma, leukemia, rhabdo-myosarcoma, osteosarcoma, fibrosarcoma, neoplasm, carcinoma, malignancy/ies, wilms tumor, nephroblastoma, retinoblastoma, retinal glioma, eye cancer, neuroblastoma, esthesioneuroblastoma, ganglioneuroblastoma, ganglioneuroma, or neuroepithelioma) AND country affiliation (Afghanistan, Bahrain, Djibouti, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Pakistan, Palestine/Ghaza/West Bank, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, United Arab Emirates, Yemen, Middle East, Near East, East Mediterranean, West Mediterranean, MENA, EMRO, Arab, Levant, East Africa, North Africa, West Africa, Maghreb, Mashriq, Sahara).

are eligible to practice. Importantly, an Arab Board certification has been developed for paediatric haematology-oncology as a subspecialty since 2017, with specifications regarding training programme eligibility criteria, graduation examination requirements, and criteria for the acknowledgement of the degree. However, its implementation is still lagging. Some countries, such as Saudi Arabia and Pakistan, have established country-specific board examinations for paediatric haematology-oncology, that are mandatory for those planning to practice as consultants. Activation of such certifications across the region will be useful to formalize standards of training and allow graduates to pursue academic and clinical positions across the Arab countries. To date, most of the subspecialty training programmes bestow a university-specific certificate acknowledged within the country, and equivalency certificates would be required for those seeking employment in other regional countries. There remains a necessity for structured needs assessment, to ensure that current and future

graduates apply their experience in areas where they are most needed and where they can substantially impact their environment and continue to advance their careers.

As for short-term training, most of the major cancer centres and university hospitals offer a subspecialty, as well as nursing, pharmacy, and other service observerships or hands-on clerkships, with national and international accreditation. However, these have historically been under utilized, likely due to logistic constraints and the lack of a strategic plan for training, by hospitals at which the potential beneficiaries are employed. Initiatives such as the African School of Paediatric Oncology (Ecole Africaine d'Oncologie Pediatrique, EAOP), which was established by the Francophone African Group of Paediatric Oncology GFAOP (48), is an example of efforts at providing short-term intensive courses for nurses, nurse educators, paediatric surgeons, as well as formal diploma in paediatric oncology (31). The availability of this and several similar training programmes in the region, have the potential to enhance the numbers of skilled paediatric oncology healthcare professionals in the EMR.

## Research

Childhood cancer research is indispensable for progress in determining disease burden, promoting delivery of services, and improving survival outcomes (49). In the EMR, regional data availability and analysis remains patchy, limiting knowledge regarding local and regional disease patterns and gaps (1). Thus, strategic planning for cancer control should include promoting and investing in research infrastructure including data registries, health informatics, well-trained researchers, research laboratories, regulatory oversight, and specimen biobanking.

The EMR already boasts a number a renowned and internationally accredited universities and research programmes within major cancer centres. These have already contributed significantly to the understanding of cancer patterns and childhood cancer characteristics and outcomes in their respective countries. A literature search for scientific publications in paediatric oncology, from the EMR region over the period 1 January 1951 to 30 September 2020, identified 4,645 manuscripts, with 70% of those published after 2010 (Figure 3).

Indeed, multiple universities and cancer centres in the region have the required infrastructure for clinical and epidemiologic research, as well as translational and basic

research capabilities, such as clinical research institutes, institutional review boards, biostatistics expertise, basic laboratory space and core research facilities. A few centres have also successfully initiated prospective paediatric tumour biorepositories with annotated clinical data. These will be instrumental for genomic and biology research into the genetic determinants of disease in the regional paediatric patient populations. However, funding sources for research remain very limited in the region, and in many cases are severely restricted either in funding amounts, or in the eligibility of investigators based on national (and not regional) residence.

### Regional challenges

The lack of accurate and accessible data regarding childhood cancer incidence and outcome is one of the major challenges in identifying and implementing needed changes to improve care. There is a clear need for national registries for childhood cancer across the region, that can capture all relevant data effectively and accurately.

Significant collaborative efforts and civil society actors in the region are contributing to the regional childhood cancer agenda, while paediatric oncology diagnostic and treatment interventions remain poorly reflected in national benefit packages. Few countries in the region, regardless of their socioeconomic status, have developed comprehensive and formal national cancer control programmes that include childhood cancer, and thus the management of these complex cancers, which require specialized and multidisciplinary care, all too often fall into general health care coverage – leading to delayed diagnosis and suboptimal care. Socioeconomic factors and geographic constraints still act as barriers to care, even in countries where multidisciplinary childhood cancer centres exist. Several studies have shown a clear correlation between socioeconomic status and treatment outcomes, indicating that childhood cancer survival could be improved if financial and logistic constraints and information dissemination is better addressed to help improve uptake of services (34).

Development of referral networks based on levels of care, and introduction of accreditation processes for such levels, are needed to ensure that paediatric cancer patients are treated in settings that afford them the best chances for cure and would identify the areas where investment is needed in specific therapeutic modalities at each referral centre based on tier and patient numbers. National prioritization of essential medications is critical to ensure uninterrupted treatment and successful outcomes. This is particularly important in the case of paediatric oncology where a set of specific medications are used, which affects their prioritization due to the demand and supply forces typical for uncommon diseases. In addition, strengthening the primary healthcare systems would be

expected to decrease the current high rates of delayed diagnosis, which are known to contribute to poorer outcomes.

Political instability and prolonged wars in several countries in the region, most notably in Syria, Iraq, Libya, and Yemen, have decimated the healthcare infrastructure and resulted in an exodus of healthcare workers, which has affected paediatric oncology as well as other disciplines. Paediatric oncology units in these countries have been struggling to maintain quality care for children with cancer, with some successes in specific twinning initiatives (12), though much remains to be done with rebuilding in the midst of continuing political instability. These conflicts have also increased the burden of care on neighbouring countries, such as Lebanon, Jordan, Turkey, and others, due to increases in refugee numbers and traveling patients seeking medical care (50–52). These patients have little or no healthcare coverage, and while their management poses an ethical and moral imperative on host countries including public and private hospitals, it creates a major financial and resource utilization burden that has not been adequately addressed to date and that should be treated as an international responsibility.

### The way forward

The current WHO GICC provides the regional paediatric oncology community with a unique opportunity to elevate the priority of childhood cancer as part of national cancer prevention and control agendas, while creating a regional platform to improve advocacy and clinical practice by joining forces of existing regional collaborative efforts. The potential decrease in childhood cancer mortality planned through the GICC would be a substantial contribution to the achievement of SDG target 3.4 to reduce premature NCD mortality by 2030. This gives the paediatric oncology community an opportunity and a strengthened voice when engaging with national policymakers, highlighting the importance of including childhood cancers as part of national benefit packages and the wider cancer agenda. By bringing together the WHO public health approach and access to national level stakeholders, with the global oncology expertise of St Jude Children's Research Hospital, regional centres of excellence, global leaders in paediatric oncology clinical care, and regional paediatric oncology societies, the initiative will capitalize on global and regional resolutions, the UHC agenda and the SDGs, to achieve national level scale up of ongoing childhood cancer efforts in the region.

Some of the key priorities for countries in the region to enable such change under the GICC umbrella will be (a) leverage of regional collaborations to bring together key stakeholders and centres in support of regional implementation of the GICC, (b) strengthened advocacy efforts to ensure the inclusion of

paediatric oncology care as part of UHC benefit packages, (c) establishment of childhood cancer registries to foster research and evidence-informed policy, and (d) strengthen health system components necessary for improved paediatric oncology services including e.g., access to essential medicines, improved diagnostic and treatment service delivery, and planning and provision of relevant training and capacity-building opportunities to meet the regional paediatric oncology workforce needs. ■

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