



World Health
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CHILDHOOD CANCER

INEQUALITIES IN THE
WHO EUROPEAN REGION





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Abstract

Childhood cancer encompasses a wide and heterogeneous range of rare cancers defined by the age group in which they occur. While significant progress has been made in recent years in improving survival and treatment quality for children with cancer, significant inequalities still exist across the WHO European Region. This report draws together available evidence and information from a wide range of published sources to present the case for an increased focus on addressing inequalities in childhood cancer within the Region. It summarizes literature in four main areas: the childhood cancer continuum; inequalities across countries; inequalities within countries; and childhood cancer as a driver of inequalities. The report makes recommendations on the key steps that are likely to have the greatest impact in reducing inequalities across the Region. It is hoped that these will be of value to decision-makers and politicians from all countries within the Region looking to address existing inequalities in childhood cancer care through targeted improvement activities.

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ISBN: 978-92-890-5761-5

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Cataloguing-in-Publication (CIP) data. CIP data are available at <http://apps.who.int/iris>.

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Corrigendum

Childhood cancer inequalities in the WHO European Region

ISBN: 978-92-890-5761-5

1. In the acknowledgments section, on page vi:
 - in the fourth paragraph (stories and quotes), an **addition** was made: **Galina Novichkova (Dmitry Rogachev National Medical Research Centre of Paediatric Haematology, Oncology and Immunology, Moscow, Russian Federation)**
 - under external reviewers, one person, **Dmitry Stefanov (Dmitry Rogachev National Medical Research Centre of Paediatric Haematology, Oncology and Immunology, Moscow, Russian Federation)**, was **added**.
2. On page 3, Table 1, the Republic of Moldova was **moved** to the **upper-middle income** column from the lower-middle income column.
3. On page 34, in the source attribution of the “Access to child-friendly formulations in the Russian Federation” boxed text, the name **Dmitry Rogachev** was **added** before the National Medical Research Centre of Paediatric Haematology, Oncology and Immunology, Moscow, Russian Federation.

These corrections were incorporated into the electronic file on 14 March 2022.

Corrigendum II

Childhood cancer inequalities in the WHO European Region

ISBN: 978-92-890-5761-5

1. In the contents on page v, the page numbers were **changed** for **acknowledgements, foreword, preface, abbreviations** and **executive summary**.
2. On page 15, the extra b after Poland **deleted**. The title of the Fig. 3 **changed** to "Leukaemia incidence and mortality in males aged 0–19 years in Bulgaria, Poland, Slovakia and Slovenia".
3. On page 21, both columns titles on Table 2 were **changed** to "Age-standardized mortality rate (per 100 000 population)".
4. On page 22, the Fig. 5 map was **updated**.
5. On page 23, Table 3 was **replaced** with new data to include Kazakhstan and Slovenia. Netherlands was **changed** to The Netherlands. Titles of both columns were **changed** to "Mortality-to-incidence ratio".
6. On page 24, the Fig. 6 map **updated**. Table 4 on pages 24 and 25 were **replaced** with new data to include Lithuania, Bulgaria, Latvia, Croatia, Serbia, Poland, Portugal and Slovenia. Netherlands was **changed** to The Netherlands. Titles on both column were **changed** to "Mortality-to-incidence ratio".
7. On pages 25 and 26, the Fig. 7 map was **updated**. Table 5 on page 26 was **replaced** with new data to include Slovenia and updated information on Malta. Netherlands was **changed** to The Netherlands. Titles on both column changed to "Mortality-to-incidence ratio".
8. On page vii the sentence was **inserted**: "Funding for the preparation, development and printing of the report was kindly provided by a grant from the St. Jude Children's Research Hospital, Memphis (TN), United States of America." was replaced by the following one "Funding for the preparation, development and printing of the report was kindly provided by St. Jude Children's Research Hospital, serving as WHO Collaborating Centre for Childhood Cancer, in Memphis (TN), United States of America"

These corrections were incorporated into the electronic file on 3 February 2023.

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Acknowledgements

This report was produced under the lead of Marilyns Corbex (WHO Regional Office for Europe) and with scientific guidance from Friederike Erdmann (Johannes Gutenberg University, Mainz, Germany).

The report was written by a core writing group consisting of: Susanne Carai (WHO headquarters); Marilyns Corbex (WHO Regional Office for Europe); Helen Crump (Cogency Analysis & Research, London, United Kingdom); Friederike Erdmann (Johannes Gutenberg University, Mainz, Germany); Paola Friedrich (St. Jude Children's Research Hospital, Memphis (TN), United States of America); Anita Kienesberger (Childhood Cancer International); Sandra Luna-Fineman (University of Colorado, United States of America); Yuliya Lyamzina (WHO Regional Office for Europe); Marko Ocokoljic (Childhood Cancer International); Carlos Rodriguez-Galindo (St. Jude Children's Research Hospital, Memphis (TN), United States of America); Roberta Ortiz Sequeira (WHO headquarters); Vitaly Smelov (WHO Regional Office for Europe); Salvatore Vaccarella (International Agency for Research on Cancer); Lin Yang (WHO Regional Office for Europe); and Isabel Yordi Aguirre (WHO Regional Office for Europe).

The work was supported by an advisory group comprising: Theodora Armenkova (Childhood Cancer International); Irina Ban (Childhood Cancer International); Kirsten Isabel Hopkins (International Atomic Energy Agency); Miriam Mikhail-Lette (International Atomic Energy Agency); and Joachim Schüz (International Agency for Research on Cancer).

The following experts provided stories and quotes for the report: Arndt Bokhardt (Heinrich-Heine-University, Dusseldorf, Germany); Sapura Ibragimova (Research Institute of Haematology and Blood Transfusion, Tashkent, Uzbekistan); Dinara Kusainova (Institute of Oncology and Radiology, Kazakhstan); Caroline Maendly (Paediatric and Adolescent Medicine, CHUV Pédiatrie, Lausanne, Switzerland); Yuliya Nogovitsyna ("Tabletochki" nongovernmental organization, Kyiv, Ukraine); Galina Novichkova (Dmitry Rogachev National Medical Research Centre of Paediatric Haematology, Oncology and Immunology, Moscow, Russian Federation); and Elena Ten (Scientific and Production Centre for Preventive Medicine, Ministry of Health, Kyrgyzstan).

External review and comments were provided by: Andres Morales la Madrid (Hospital Sant Joan de Déu Barcelona, Spain); Ivan Kivich and Dmitry Stefanov (Dmitry Rogachev National Medical Research Centre of Paediatric Haematology, Oncology and Immunology, Moscow, Russian Federation); and Olga Kozaeva (European Society for Paediatric Oncology); and Wendy Yared (Association of European Cancer Leagues).

Original figures were produced specifically for this report by: Paola Friedrich (St. Jude Children's Research Hospital, Memphis (TN), United States of America) (Fig. 2); Salvatore Vaccarella (International Agency for Research on Cancer) (Fig. 3); and Elena Ten (Kyrgyz Republic Scientific and Production Centre for Preventive Medicine of the Ministry of the Health of the Kyrgyz Republic) (Fig. 8 and Tables 2 and 3). The maps in Fig. 4–7 were created by Morten Ervik (International Agency for Research on Cancer).

Funding for the preparation, development and printing of the report was kindly provided by St. Jude Children's Research Hospital, serving as WHO Collaborating Centre for Childhood Cancer, in Memphis (TN), United States of America.

Foreword



Despite governments' attempts, health inequalities between and within countries across the WHO European Region remain unacceptably large, with potential negative consequences for social cohesion, economic development and individual outcomes.

Achieving greater equity in health and reducing health inequalities is a key priority for the WHO Regional Office for Europe. Indeed, WHO's European Programme of Work for 2020–2025 identifies guaranteed universal access to quality care without fear of financial hardship, effective protection against health emergencies and thriving healthy communities as priorities that citizens in the Region will legitimately expect their health authorities to deliver.

In the area of cancer, some countries across the Region have made important progress in recent years, expanding access to and advancing innovations in treatment and improving the way that cancer care is provided. Children with cancer, however, still experience differences in terms of rates of undiagnosed cases, access to high-quality diagnostic services and cancer medicines and, ultimately, outcomes, depending on where they live and the circumstances in which they grow up.

A childhood cancer diagnosis can itself be a driver of significant short- and long-term inequalities, both for the survivor and for the wider family. Providing high-quality follow-up care that addresses the social and socioeconomic impacts of a childhood cancer diagnosis, as well as the physical and psychological late effects, can make an enormous difference to health and well-being for these young people and their families.

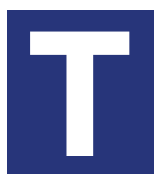
Unfortunately, for many children, most of whom live in low- and middle-income countries, treatment is either unavailable or unaffordable. For this reason, it is extremely important that we work hard to reduce the gaps that still exist in relation to the care and treatment of children with cancer across the Region. As part of the WHO Global Initiative for Childhood Cancer, generously supported by St. Jude Children's Research Hospital, Memphis (TN), United States of America, we have been bringing together stakeholders toward a shared goal of scaling up capacity to save lives and reduce suffering for children with cancer and reducing stark inequalities.

In producing this report, we have benefited from the expertise of leading scientists and clinicians working in the field of children's cancer in the European Region, who have worked with us to identify key priorities for reducing inequalities in childhood cancer. The WHO Regional Office for Europe stands ready to support countries in the coming years as part of a concerted effort across the Region to close these gaps for all childhood cancer patients across the continuum.

Nino Berdzuli

Director, Division of Country Health Programmes
WHO Regional Office for Europe

Preface



Today, more than 80% of childhood cancers in high-income countries are cured. Thanks to improved treatment and adequate management, cancer is no longer a death sentence for children and adolescents. This is not true for everybody everywhere, however, and strong inequalities remain across the WHO European Region. These inequalities arise along the whole cancer care continuum, from access, to care, to diagnosis, on to treatment and supportive care.

This report brings together evidence and information from a wide range of sources to explore and present the nature and magnitude of these inequalities. It explores inequality across countries but also within countries and across different population groups. It examines the impact of cancer as a cause of inequalities later in life and how cancer produces inequalities by transforming the future of children and their families.

Evidence sources range from peer-reviewed academic research to advocacy reports, policy papers, and data collected by the WHO Regional Office for Europe team, including specific data generated by our network of collaborators for this report. Where research and data specific to the WHO European Region were available, we have endeavoured to use them, but evidence is in short supply in relation to some aspects of childhood cancer in the Region. In these cases, we have included research drawn from countries outside the Region.

This report does not pretend to be exhaustive. Its aims are to shed light on relatively ignored issues and make the case for an increased focus on childhood cancer inequalities. It represents a first step; more work is needed to fully describe and understand childhood cancer inequalities and improve our ability to tackle them efficiently. Based on the information and evidence presented in this report, propositions are made to help countries of the Region to address childhood cancer inequalities and work on closing the gaps.

Health leaders throughout the Region should not hesitate to set up ambitious targets. Reducing many of the inequalities highlighted in this report is highly feasible, all the more so since it does not require high resource investments. Tremendous progress can be made in a few years, so let's go, there is no time to lose!

Marilys Anne Corbex

Senior Technical Officer, Division of Country Health Programmes
WHO Regional Office for Europe

Abbreviations

ALL	acute lymphoblastic leukaemia
AML	acute myeloid leukaemia
CanCon	(European Commission) Joint Action on Cancer Control
CNS	central nervous system
CT	computed tomography
EMLc	(WHO) Essential Medicines List for children
ERN PaedCan	European Reference Network for Paediatric Oncology
EU	European Union
ExPO-r-Net	European Expert Paediatric Oncology Reference Network for Diagnostics and Treatment
GDP	gross domestic product
HDI	Human Development Index
HIC	high-income countries
IAEA	International Atomic Energy Agency
IARC	International Agency for Research on Cancer
IICC	International Incidence of Childhood Cancer
LMIC	low- and middle-income countries
NHS	National Health Service (United Kingdom (England))
PanCareSurFup	PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies (consortium)
PTSD	post-traumatic stress disorder
SIOPE	European Society for Paediatric Oncology
TNM	tumour, node and metastasis (-based staging systems)
UHC	universal health coverage
UNAPECLE	Union Nationale des Associations de Parents d'Enfants Atteints de Cancer ou de Leucémie [National Union of Associations of Parents of Children with Cancer or Leukaemia] (France)

Executive summary



Childhood cancer encompasses a wide and heterogeneous range of rare cancers defined by the age group in which they occur. Most childhood cancers tend to be fast growing, meaning establishing a diagnosis and treatment plan quickly is important. Additionally, with the exception of retinoblastoma, no effective screening tools are available and little is known about how to decrease the risk of developing sporadic cancers in the first two decades of life.

Different types of cancer tend to affect children at different ages, with some more common in young children and others more common in adolescents. Survival has been increasing since the 1980s, but significant disparities endure both between and within countries.

Inequalities across countries

Inequalities can be observed in childhood cancer incidence, mortality and survival rates across countries. Incidence rates vary by region. There is a general pattern of greatest incidence in the countries with the highest positions in the Human Development Index (HDI). In countries with lower HDI scores, however, childhood cancer makes up a higher proportion of all cancers. It is believed that most (if not all) of the variations in incidence rates are due to underdiagnosis and underreporting.

Childhood cancers are rare, with 200 adults being diagnosed for every child diagnosed. Childhood cancers can have very different biology, classification, staging, treatment and prognosis from adult cancers. Significant gaps exist in the data relating to survival, but disparities in survival rates between high-income countries (HIC) and low-income countries for childhood cancer are wider than for most adult cancers. Childhood cancers are not preventable, so the use of standardized therapeutic protocols, precise and timely diagnosis and access to first-line diagnostics, contemporary therapies and supportive care currently are the best options for reducing childhood cancer mortality. In some eastern European and central Asian countries, guidelines recommending annual medical check-ups for children (so-called children dispensarization), which rely on extensive use of laboratory and instrumental diagnostic methods such as ultrasound of the abdomen, thyroid and kidneys, lead to overdiagnosis and overtreatment and represent inefficient use of resources.

The picture on diagnosis is very different across the parts of the WHO European Region. For instance, an estimated 3% of childhood cancers went undiagnosed in western European countries in 2015, with higher proportions in southern and eastern Europe and central Asian countries. Lack of universal access to

high-quality laboratory, imaging and pathology services can lead to incorrect diagnosis, incorrect staging and (in turn) inappropriate diagnosis and/or staging and clinical management, ultimately leading to poorer patient outcomes. Improved professional information on presenting symptoms, public information and collaboration among primary and referral providers would support earlier detection of childhood cancers.

Cancer patients and their families can face high financial costs in health systems where a copayment is expected as part of the cost of treatment, but even health systems in HIC with social health insurance or national health service-type schemes sometimes cannot afford the high prices of some cancer medications. The configuration of health-care services can also affect patients' and parents' ability to access appropriate care, with centralization in specialist centres and collaboration between paediatric and oncology teams viewed as important for improving care quality. Out-of-pocket costs indirectly related to therapy (such as drugs for side-effects of chemotherapy, nutritional supplements to maintain weight during chemotherapy, transportation, lodging and loss of employment) can affect families very significantly.



3% OF CHILDHOOD CANCERS
WENT UNDIAGNOSED IN
WESTERN EUROPEAN COUNTRIES



Staging can be challenging in childhood cancer. Specific childhood cancer staging guidelines that should be implemented widely in childhood cancer registries across the Region have recently been developed for this purpose. At present, differences in access to essential diagnostics and medical devices mean some countries within the Region face greater challenges regarding diagnosis and staging.

Inequalities within countries

Within individual countries, inequalities across groups can be seen in relation to cancer detection and outcomes. This finding is true in both HIC and low- and middle-income countries (LMIC). In HIC, boys with cancer tend to have poorer outcomes than girls. Data from LMIC suggest that girls are registered less frequently than boys, with indications that girls are being underdiagnosed.

Children of families with higher socioeconomic status experience higher survival rates than children from families with lower socioeconomic status. Geography plays a significant role in inequalities, with centralized services requiring patients to travel long distances for care; this is more challenging for less affluent families, but dispersed services sometimes can lack sufficient expert staff, leading to a lower standard of care being provided.

There are relatively few data sources available regarding childhood cancer in migrant and seldom-reached groups, but children of international migrants tend to use primary care and oral health services less than non-migrants and use emergency rooms and are hospitalized more frequently

“On childhood cancer, we are now actively supporting 50 countries, providing medicines in conflict settings like Yemen and the Syrian Arab Republic, almost doubling the health workforce in some countries, supporting the construction of new cancer centres and the development of legislation to guarantee access to care for children with cancer throughout their lifetime. The gaps of child survival, especially from cancer, in high-income countries and low-income countries is huge. In low-income countries less than 25% of kids survive, in high-income countries with technology more than 80% survive. So, the whole programme is to narrow the gap.”

Tedros Adhanom Ghebreyesus,
WHO Director-General

Childhood cancer as a driver of inequalities

A childhood cancer diagnosis can lead to significant short- and long-term inequalities in the life of a child. Somatic effects vary depending on the patient's age, sex, cancer type and treatment, but can include secondary cancers, cardiovascular late effects and chronic conditions, decreased height, problems with adaptive functioning, neurocognitive dysfunction, lung problems and fertility issues.

Childhood cancer patients sometimes are not sufficiently well informed about their treatment history on reaching adulthood, which can affect their ability to benefit from adequate follow-up care. Transition between children's and adults' services is known to be a critical point for childhood cancer survivors and it can be challenging to find the right time to initiate the transition process and determine where to transition the patient.

A substantial proportion of childhood cancer survivors experience post-traumatic stress, with females being more likely to report symptoms than males. Research suggests survivors of childhood cancer can have worse health-related quality of life and mental late effects than the general population, both in childhood and adulthood.

Children with cancer may experience a wide range of developmental vulnerabilities in their physical health and well-being and have lower academic achievement than peers without cancer, in some cases being less likely to pass educational milestones. Childhood cancer survivors have also been found to face greater difficulty in affording necessary health care and meeting high out-of-pocket medical expenses, as well as challenges in obtaining medical insurance and having more frequent reliance on government insurance.

When a child is diagnosed with cancer, the immediate family can face financial difficulties, experience poorer quality of life in terms of their own physical and mental health and well-being and encounter challenges in their social relationships. These effects can also extend to grandparents.

While eradicating these differences completely will require long-term effort, some steps can be taken now. Undertaking some or all of the steps set out in this report will improve the current position of childhood cancer patients. It will also help to ensure that children in all WHO European Region countries who develop cancer will be able to experience better and more equitable outcomes in the future.

“Every paediatric patient with cancer deserves the opportunity to receive a potentially curative treatment and be offered the best possible quality of life.”

Andrés Morales La Madrid,
Head of the Paediatric Oncology Department,
Hospital Sant Joan de Déu Barcelona, Spain

1

Introduction





Childhood cancers are very different from adult cancers. Most adult cancers are carcinomas, whereas paediatric cancers comprise a variety of entities. They come from immature structures, harbour fewer genetic abnormalities and occur in different parts of the body (such as blood (leukaemia), the brain and nervous system (neuroblastoma), and bone and soft tissues (sarcoma)).

Recent decades have seen a dramatic improvement globally in survival from childhood cancer. Improvement has also been observed in the 53 countries of the WHO European Region, with more than eight in 10 childhood cancer patients in several European countries now surviving the disease.

This story of improvement, however, obscures significant differences between countries in the Region in terms of the number of children diagnosed with cancer, outcomes, experiences of care and survivorship. These differences can often be observed within countries when research is undertaken to compare the experiences of childhood cancer patients from different socioeconomic backgrounds, genders and ages. They can also be seen when factors such as living in a remote area are taken into account.

The differences are known as inequalities. Reducing inequalities so that countries, socioeconomic groups and specific populations with poorer outcomes can achieve survival rates and care similar to those with the best outcomes is a main objective of the work of the WHO Regional Office for Europe.

This report summarizes literature in four main areas: the childhood cancer continuum; inequalities across countries; inequalities within countries; and childhood cancer as a driver of inequalities. Where possible, studies from the 53 countries of the WHO European Region are used. These countries span from Iceland in the west to Kyrgyzstan in the east. Thirty-four of these are high-income countries (HIC), with 14 upper-middle income countries and five lower-middle income countries (LMIC) (Table 1).



8/10 OF CHILDHOOD CANCER
PATIENTS IN **SEVERAL**
EUROPEAN COUNTRIES ARE NOW SURVIVING



Table 1. Countries in the WHO European Region by income level

High-income		Upper-middle income	Lower-middle income
Andorra	Latvia	Albania	Kyrgyzstan
Austria	Lithuania	Armenia	Tajikistan
Belgium	Luxembourg	Azerbaijan	Ukraine
Croatia	Malta	Belarus	Uzbekistan
Cyprus	Monaco	Bosnia and Herzegovina	
Czechia	Netherlands	Bulgaria	
Denmark	Norway	Georgia	
Estonia	Poland	Kazakhstan	
Finland	Portugal	Montenegro	
France	Romania	North Macedonia	
Germany	San Marino	Republic of Moldova	
Greece	Slovakia	Russian Federation	
Hungary	Slovenia	Serbia	
Iceland	Spain	Turkey	
Ireland	Sweden	Turkmenistan	
Israel	Switzerland		
Italy	United Kingdom		

The report proposes policy options on the key steps that are likely to have the greatest impact in reducing inequalities across the Region. These recommendations represent positions that it is hoped all countries in the Region will aspire to achieve with regard to childhood cancer, although it is recognized that the Region's countries will begin this work from different starting points and with different contextual factors to take into account. The recommendations nevertheless will be of value to decision-makers and politicians from all countries of the Region looking to target inequalities in childhood cancer care.

The text is interspersed with quotations and country stories highlighting issues faced by children with cancer and their families.

2

The childhood cancer continuum



KEY POINTS

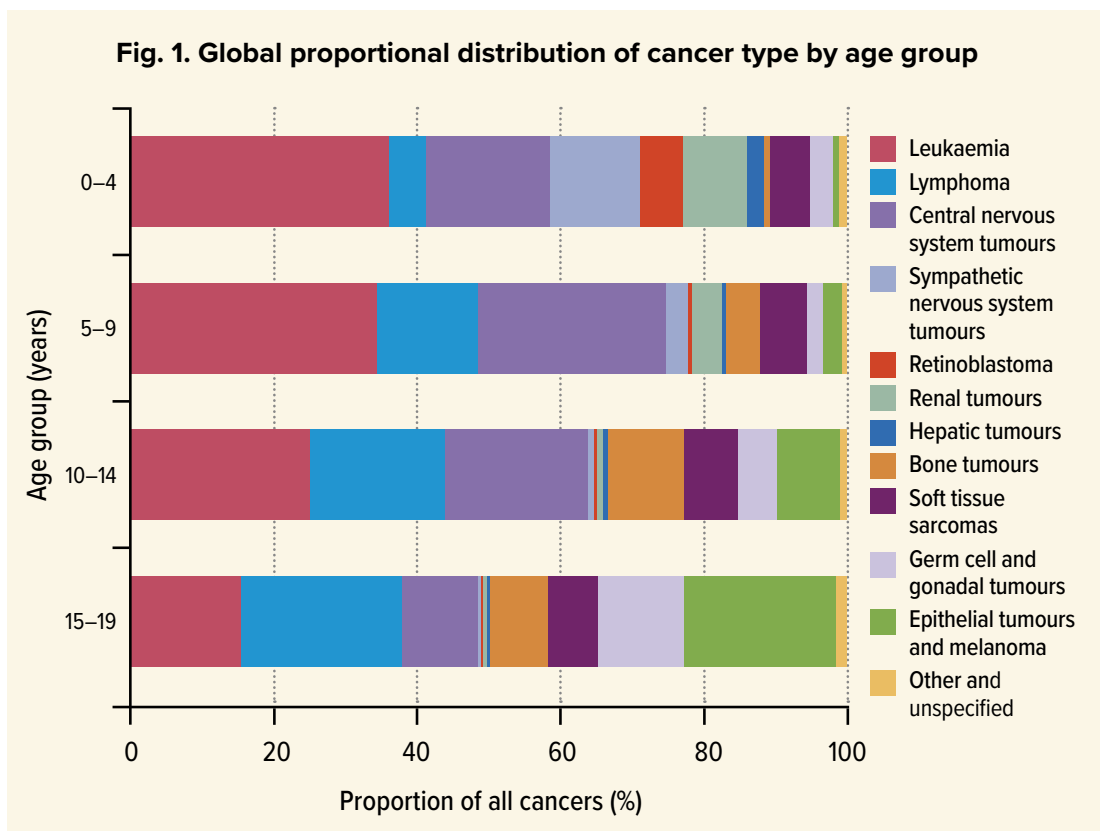
- **Childhood cancer encompasses a heterogeneous group of cancers defined by the age group in which they occur.**
- **Most childhood cancers are aggressive, meaning establishing a diagnosis and initiating treatment quickly is important.**
- **Different types of cancer tend to affect children at different ages, with some more common in young children and others more common in adolescents.**
- **Survival has been increasing rapidly since the 1980s, but significant disparities endure between and within countries.**



The term childhood cancer is used to encompass a heterogeneous group of cancers predominantly defined by the age group in which they most typically occur (broadly defined as childhood and/or adolescence) and classified by the histology and location of the primary tumour (Steliarova-Foucher et al., 2005; National Cancer Institute, 2022a). While some low-grade tumours occur in these age groups, most childhood cancers are quick growing and malignant (National Cancer Institute, 2022a). This contributes to the urgency of establishing a diagnosis and the intensity of the treatment required to achieve cure. Given growth and developmental considerations in a child, even low-grade tumours (such as low-grade gliomas) can cause significant morbidity and mortality (Upadhyaya et al., 2018).

Childhood cancer is often defined as cancers that occur between birth and 14 years of age but can also include cancers in those up to 18 or 19 years (Steliarova-Foucher et al., 2017; National Cancer Institute, 2022b). The age cut-off is somewhat arbitrary and varies by country or cancer registry (Steliarova-Foucher et al., 2017) and depends on the purpose for which the definition is being used (for instance, a clinical trial to evaluate a new treatment protocol). The epidemiologic behaviour of childhood cancers shows predominance of particular diagnoses in specific age groups and the distribution of disease varies considerably by age group (Steliarova-Foucher et al., 2017). For example, the frequency of acute lymphoblastic leukaemia (ALL), retinoblastoma and renal tumours decreases through the 0–4, 5–9 and 10–14 age groups (Steliarova-Foucher et al., 2017), but the distribution is not always exclusive to a specific age group. Several typical childhood cancer diagnoses, such as Wilms tumour and neuroblastoma, can occur in adulthood (Esiashvili et al., 2007; Modi et al., 2016). The incidence of several cancers, including Hodgkin lymphoma, testicular cancer and thyroid cancer, begins to rise in early adolescence (Cancer Research UK, 2022).

Fig. 1 shows the global proportional distribution of cancer type by age group.



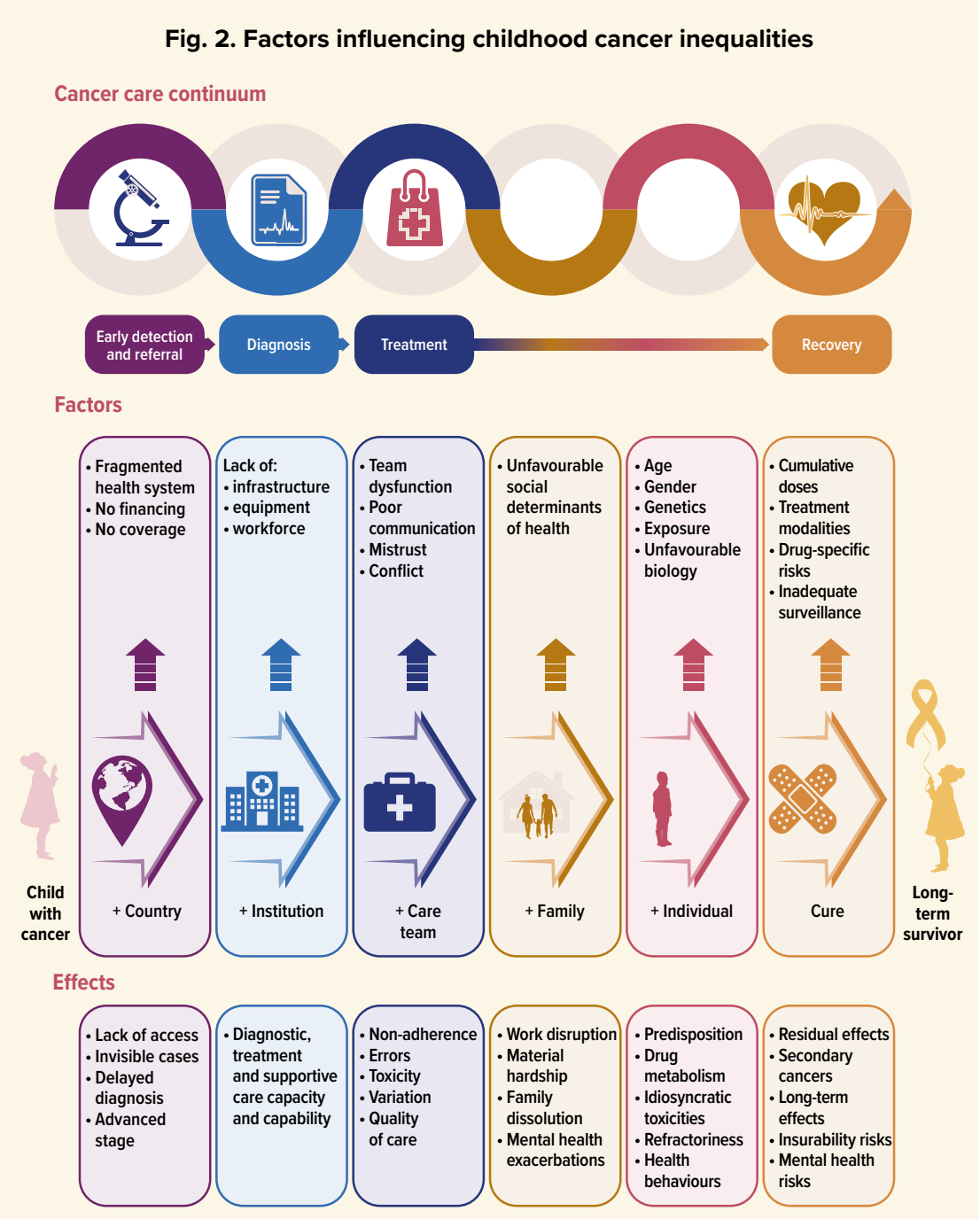
Source: Steliarova-Foucher et al. (2017). Reproduced with permission of Elsevier, International incidence of childhood cancer, 2001–10: a population-based registry study, *The Lancet Oncology*, Volume 18, Issue 6, Elsevier, 2017 under Creative Commons CC-BY-NC-ND license.

An important reason to highlight childhood cancers as a group is the rapid trajectory towards improved survival observed over the past six decades. In several European and north American countries, the five-year overall survival for children with cancer has increased from nearly 30% in the 1960s to over 80% (Phillips et al., 2015; Winther et al., 2015; Ellison et al., 2021). As this report highlights, however, noteworthy residual disparities and challenges persist across the Region, many of which are amenable to improvement utilizing a health systems approach.

2.1 The conceptual approach to childhood cancer inequities

Several conceptual models have been utilized to illustrate and/or understand the complex variety of factors that influence childhood cancer outcomes and survivorship (Bhatia, 2011; Friedrich et al., 2014a, 2014b, 2016). Two perspectives are particularly helpful. One stems from social epidemiology and utilizes ecological models to understand the layers of influence (Friedrich et al., 2014a, 2016). This approach takes into account characteristics of the child, such as their sex, age, genetic predisposition and the biology of the disease, the characteristics of the family (psychosocial and financial) that surrounds the child, the characteristics of the care team and institution they are able to access, and the characteristics of the broader country or health system, which through governance and health-care financing mechanisms impacts nearly all levels.

The other perspective is the patient care continuum and the treatment cascade (Howard et al., 2018). This approach considers access and the chance of being diagnosed, having the correct diagnosis, treatment being initiated, fatal treatment-related toxicities being identified and addressed, and treatment completed in the pathway to cure. These two perspectives have been combined into one approach that simultaneously considers the layers of influence and the patient care continuum (Friedrich et al., 2014b, 2019). An adaptation of this combined perspective to understanding childhood cancer disparities is shown in Fig. 2.



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2.2 Relevant factors and their magnitude

Most of the factors illustrated in Fig. 2 will be discussed in the subsequent chapters, including the available evidence to inform their current magnitude and impact across the Region. It is important to note upfront, however, that the relevance and impact of these factors varies across higher- and lower-resource settings. In higher-income settings, large disparities in access, infrastructure, quality of care and financial risk have often been addressed. Residual disparities may exist based on, for example, immigration status or specific health behaviours of the age group (Kyrölähti et al., 2020; Aristizabal et al., 2021). Typically, the magnitude of impact at population level is relatively lower. This context favours prioritizing the understanding of individual-level molecular and epidemiologic differences that explain differences in outcomes and thoroughly addressing the impact of more subtle or complex individual-level health behaviours. In more variable-income settings, the prevalence and magnitude of health system challenges is higher and intentionally prioritizing them is key to making progress to address existing childhood cancer inequalities (Atun et al., 2020).



**CONTRARY TO ADULT CANCERS, THE
ROLE OF PREVENTION IN CHILDHOOD
CANCERS IS EXCEEDINGLY LIMITED**



One noteworthy distinction between this model and an adult cancer continuum model is the omission of prevention from the childhood cancer continuum. Contrary to adult cancers, except for very specific childhood cancers that develop in the context of particular cancer predisposition syndromes, the role of prevention is exceedingly limited (Spector et al., 2015; Erdmann et al., 2019a). At present, prevention through highly targeted surveillance mostly is done in specialized centres with dedicated subspecialized genetics and predisposition services.

Primary prevention would be a very welcome alternative given that childhood cancer survivors have several disadvantages later in life, including a higher risk of developing a second malignancy. Despite an abundance of research, however, few causes of childhood cancer have been scientifically established; among those, none qualify for larger-scale population-based prevention strategies as applied to many adult cancers (Spector et al., 2015; Schüz & Erdmann, 2016).

It is premature to develop a general primary prevention programme for many reasons. Some genetic conditions, high and low birth weight and exposure for ionizing radiation from therapeutic or diagnostic applications or from natural sources are established risk factors, but preventive potential is small. For instance, approximately 8.5% of childhood cancer cases have been found to be associated with a germline alteration in a gene that could predispose to cancer (Zhang et al., 2015). Genetic counselling is therefore recommended whenever feasible. Some benefits are seen with maternal folate supplementation and with breastfeeding, while some occupational or domestic exposures may pose risk; promoting or preventing these factors have implicit benefits in themselves.

Some of the identified risk factors, including genetic factors and birth weight, are not (or not easily) modifiable. Others are part of larger prevention endeavours; while it is useful to point out their beneficial effect in preventing childhood cancer, it is counterproductive to include them in a separate programme specifically targeting childhood cancer, as it would lead to confusion. This includes the promotion of breastfeeding and folic acid supplementation for women during pregnancy, and tobacco-control programmes to stop smoking.

For a few risk factors, the benefit has to be balanced against the harm. Higher doses of ionizing radiation are known to cause childhood cancer, but their origin is mainly from medical applications, especially radiation treatment and higher-dose diagnostic examinations such as computed tomography (CT). Treatment and CT examinations can be life-saving, so no prevention programme is applicable, but measures should be developed to apply necessary radiation exposure while avoiding unnecessary exposure.

Some types of childhood leukaemia may be preventable through adequate training of the child's immune system through, for instance, frequent social contacts with other children in day-care settings at early ages. The pathways of leukaemia development, however, are not yet sufficiently well understood to define a prevention programme that can easily be implemented. For many other factors, especially those related to the environment, the scientific evidence base is too controversial to roll out large population-based prevention programmes. Studies of some environmental chemicals, including pesticides, point towards an increase in childhood cancer risk, but the specific active ingredients have not been identified.

3

Inequalities across countries



KEY POINTS

- Inequalities can be observed in the childhood cancer incidence, mortality and survival rates of different countries.
- Incidence rates vary by region, with a general pattern of greatest incidence in countries with the highest positions in the Human Development Index (HDI), but childhood cancer is a higher proportion of all cancers in countries with lower HDI scores. There is growing evidence that most of the variations in incidence rates are due to particularly high levels of underdiagnosis and underreporting in some regions.
- Conversely, for thyroid cancer, differences in incidence between countries, particularly among adolescent girls, may be due to overdiagnosis.
- Significant gaps exist in the data relating to survival, but disparities in survival rates between higher- and lower-income countries for childhood cancer are wider than for most adult cancers.
- Use of standard therapeutic guidelines, precise and timely diagnosis and access to first-line diagnostics, contemporary therapy and supportive care currently are the best options to reduce childhood cancer mortality.
- An estimated 3% of childhood cancers went undiagnosed in western European countries in 2015, with higher proportions in southern and eastern Europe – similar data for central Asian countries are limited.
- Lack of universal access to high-quality laboratory, pathology and imaging services can lead to incorrect diagnosis, incorrect staging and, in turn, inappropriate clinical management and poorer patient outcomes.
- Improved professional information, public information and collaboration may support earlier detection of paediatric cancers.
- Families of children with cancer can face high financial costs in health systems where a copayment is expected as part of the cost of treatment, but even in HIC with social health insurance or national health service-type schemes, public payers can sometimes not afford the high prices of some cancer medications, medicines and nutritional supplements for side-effects of chemotherapy.
- The configuration of health-care services can affect families' ability to access appropriate care, with centralization in specialist centres and collaboration between paediatric and oncology teams viewed as important for improving care quality.
- Staging can be challenging in childhood cancer, but specific childhood cancer staging guidelines have recently been developed for this purpose.
- Research and innovation in the field of childhood cancer are as important as ever, despite relatively few prevention measures existing for these cancers.



It has been estimated that globally there will be 13.7 million new cases of childhood cancer between 2020 and 2050, with 44.9% of these cases being undiagnosed. Between 2020 and 2050, 11.1 million children will die of cancer if no additional investments are made to improve access to health-care services and childhood cancer treatment (Atun et al., 2020). There are significant differences in the overall cancer profile of children (aged 0–14) and adolescents (aged 15–19).

Inequalities in childhood cancer between countries can be observed in terms of incidence, mortality, survival and survivorship follow-up care. Multiple factors affect these indicators, ranging from the prevalence of certain exposures and quality and completeness of available diagnosis data, to the extent to which people are able to access health services and navigate through them in the countries in which they live.



THERE ARE SIGNIFICANT DIFFERENCES IN THE OVERALL CANCER PROFILE OF CHILDREN AGED 0–14 AND ADOLESCENTS AGED 15–19



Children with cancer across the Region experience inequalities in access to the best available standard diagnostics, treatment, care and research protocols. These disparities contribute to differences in survival of 20% or more and are of greater concern in particular eastern European countries than those in northern and western Europe. For instance, the estimated five-year survival from rhabdomyosarcoma (a soft-tissue malignancy) was 39% in eastern Europe in 2005–2007 compared to 69% in northern Europe during the same time period (Gatta et al., 2014). The corresponding estimates for Ewing's sarcoma, a bone tumour, were 46% and 71%. Central nervous system (CNS) tumour survival ranged from 54.5% in eastern to 65.4% in northern Europe (Gatta et al., 2014).

A lack of state-of-the-art treatments covering certain minimum standards of care within national paediatric haemato-oncology centres is an important contributor to these significant disparities (Kowalczyk et al., 2014). Models such as the European Reference Network for Paediatric Oncology (ERN PaedCan) in cooperation with the European Society for Paediatric Oncology (SIOPE) Clinical Research Council are striving to address these inequalities in the European Union (EU) and could serve as an example that can be contextualized to other settings.

WHO's Global Initiative for Childhood Cancer has launched the CureAll Framework, which sets out four pillars for focusing efforts to improve childhood cancer services: establishing centres of excellence; achieving universal health coverage (UHC); developing regimens for management of disease; and evaluating and monitoring. These are to be supported by enablers that include advocacy, leveraged financing and linked governance. The framework aims to increase the capacity of countries to provide quality services for children with cancer and support prioritization of childhood cancer at global and national levels (WHO, 2021a).

3.1 Main indicators

Globally, there is much observed geographical variation in the incidence of, and survival from, childhood cancer. Incidence rates reported by cancer registration by region – as, for instance, in the International Incidence of Childhood Cancer (IICC) series published by the International Agency for Research on Cancer (IARC) (Steliarova-Foucher et al., 2017) – vary more than fourfold. There is a general pattern of greatest incidence rates in countries with the highest positions in the HDI and lowest in some parts of Africa and Asia. This tendency is even more pronounced for the most common type of childhood cancer, leukaemia. There is accumulating evidence that most of the variations in incidence rates are due to particularly high levels of underdiagnosis and underreporting in some regions of the world (Johnston et al., 2020). For thyroid cancer, however, evidence has emerged that differences in incidence across countries, particularly among adolescent girls, may be due to overdiagnosis (Vaccarella et al., 2021).

Cancer registries can only report cases captured by the health-care system, so attempts to account for potential underrecording have resulted in global annual numbers of childhood cancers that are 60% higher than are captured by cancer registration, which is in the order of 360 000–400 000 cases (Ward et al., 2019; Johnston et al., 2020). Geographical variations in incidence rates may result from genuine differences in rates but are more likely to arise from geographical differences in the extent of underascertainment. Extreme caution therefore needs to be applied when interpreting incidence differences in terms of possible causes of childhood cancer (Schüz & Roman, 2021); the only surely established cause explaining geographical variation is that of infection-related cancers such as Burkitt lymphoma caused by Epstein-Barr virus.

3.1.1 Incidence

The most common cancers in children and adolescents globally and in the WHO European Region are leukaemias, brain and CNS tumours and lymphomas (WHO, 2021a).

Cancer incidence appears greater in countries with a higher HDI score than in countries with lower HDI scores, but the number of cancers in the childhood age group as a proportion of total cases in the population is higher in countries with lower HDI scores, as these countries generally have a different demographic

structure with younger populations (Magrath et al., 2013). There is growing evidence that most of the variations in incidence rates are due to particularly high levels of underdiagnosis and underreporting in some regions, with 40% of children with cancer globally being undiagnosed (Lam et al., 2019). A possible exception is thyroid cancer, whose incidence is increasing in several places in the world due to overdiagnosis and overdiagnosis (see below).

More than two thirds of the world's paediatric cancers currently are diagnosed in LMIC. Patterns of occurrence of childhood cancer in LMIC compared with HIC and the lack of population-based cancer registries suggest that many patients in these countries die from undiagnosed or untreated cancer, and that the burden of childhood cancer is underestimated (Esiashvili et al., 2018).

Time to diagnosis for childhood cancer in Kazakhstan

A snapshot analysis of 150 childhood cancer cases dating from 2017 and 2018 conducted retrospectively by the Scientific Research Institute of Oncology and Radiology found that boys aged 0–14 waited on average 2.2 days between obtaining a cancer diagnosis and first treatment, compared with a figure of 4.2 days for girls. In adolescents (aged 15–19), the figure was 3.1 days for boys and 0.9 for girls. ALL was the condition diagnosed most frequently in both boys and girls aged 0–14 and 15–19 within this sample. When the sample was analysed to compare the length of time between the first visit to a doctor and diagnosis, the figure was 51 days for boys aged 0–14 and 25 days for girls aged 0–14. This compares with 37 days for adolescent boys aged 15–19 and 17.5 days for adolescent girls.

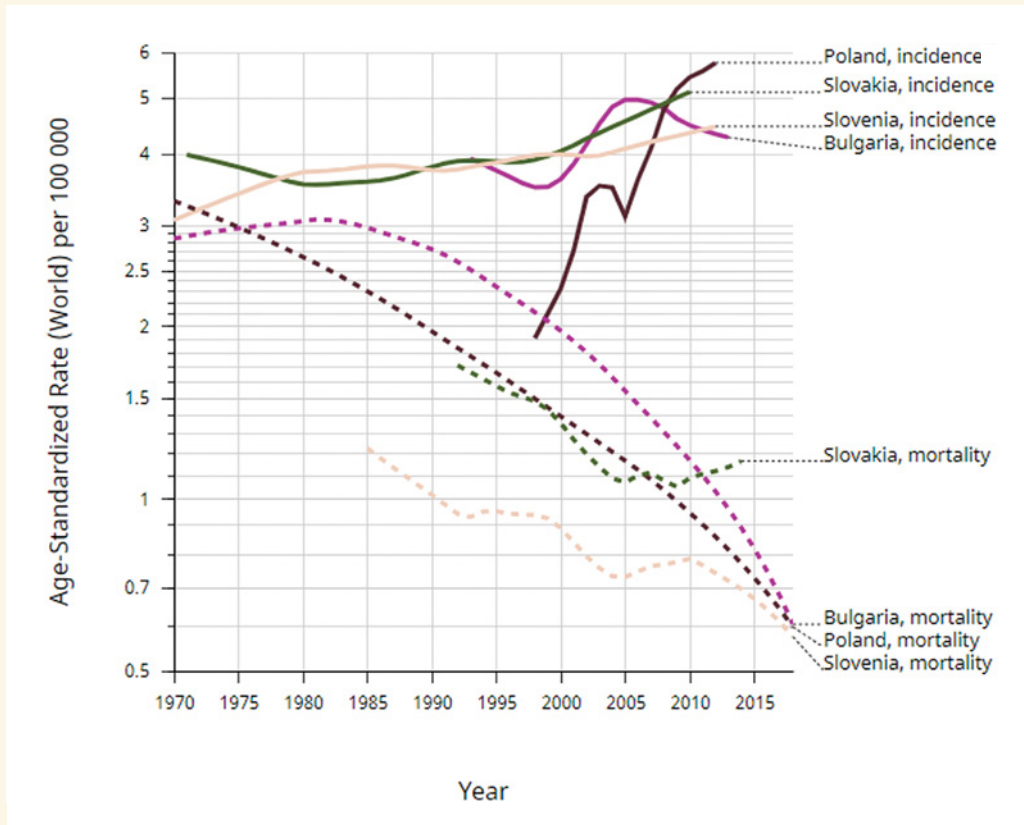
Note: outlier cases were omitted from the analysis.

Source: reproduced with permission of the Kazakh Scientific Research Institute of Oncology and Radiology (analysis by WHO team).

3.1.1.1 Cancer incidence and mortality in the WHO European Region

Variation in observed incidence rates is much less in the WHO European Region than globally, and the tendency of higher observed incidence rates in the north and west compared to south and east appears to be closing with time. Instead, it is the similarities that start to become striking. For instance, variations across Europe for lymphoblastic leukaemia are smaller than for adult cancers known to be related to lifestyle, environmental factors or infections, suggesting there is less impact of these factors on childhood cancer risk than there is for adult cancers (Schüz & Roman, 2021). As Fig. 3 shows, although incidence of childhood leukaemia is increasing, mortality generally has been decreasing. This pattern can be observed across many countries in the Region.

Fig. 3. Leukaemia incidence and mortality in males aged 0–19 years^a in Bulgaria, Poland, Slovakia and Slovenia



^a Data are preliminary. Data for Poland are subnational.
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Cancer incidence in children and adolescents in Europe increased significantly in the period between 1991 and 2010 according to data from 53 cancer registries in 19 countries. Increases in incidence differed by diagnostic group, cancer type and region, and over time. Incidence of CNS tumours increased in the west, but little change was reported in the other regions. Incidence of leukaemia was stable in the north but increased in other regions. There was a suggestion of stabilization in the trend for all cancers in adolescents across the dataset for the whole of Europe (Steliarova-Foucher et al., 2018).

Analysis of CNS tumour incidence rates in children (which also includes non-malignant tumours) within registries in 11 south-eastern European countries found incidence decreased gradually with age in all countries except Turkey and Ukraine. Overall age-adjusted incidence rates for malignant tumours were highest in Croatia and Serbia. A statistically significant increase in age-adjusted incidence rates was observed in Bulgaria, while significant decreases were seen in Belarus, Croatia, Cyprus and Serbia (Papathoma et al., 2015). It is unclear to what extent any

of these changes can be attributed to changes in risk, rather than more complete ascertainment of cases. Research at country level tends to support this picture. For instance, analysis of childhood and adolescent cancer incidence and survival in Spain over the period between 1983 and 2002 showed that the incidence pattern was similar to that for Europe (Peris-Bonet et al., 2010; Marcos-Gragera et al., 2018). Analysis of data relating to all malignant tumours diagnosed in children aged 0–14 in Estonia between 1970 and 2016 also showed overall incidence increasing, this time at a rate of 0.5% per year. The study authors stated that even though some of the increasing incidence in some sites may at least partially be attributable to better diagnostics (also reflected in the decreasing incidence of unspecified neoplasms), overall cancer incidence in children seems to be rising (Paapsi et al., 2020).



GLOBALLY, THYROID CANCER INCIDENCE HAS INCREASED IN CHILDREN, PARTICULARLY AMONG ADOLESCENT GIRLS, MIRRORING A PATTERN SEEN IN ADULTS



Though incidence rates of lymphoblastic leukaemia were substantially lower (around 20%) in eastern Germany than western Germany at the time of reunification, this was followed by a remarkable increase in eastern Germany across both sexes and age groups until around 2000, when incidence rates reached the same levels as those in western German federal states. While myeloid leukaemia rates were stable in western Germany, an increasing tendency was also observed in eastern Germany, driven by older children, mostly during the early 2000s and in recent years. The underlying mechanisms for these differences are unclear (Wellbrock et al., 2021).

3.1.1.2 The case of thyroid cancer

Globally, thyroid cancer incidence has increased in children, particularly among adolescent girls, mirroring a pattern seen in adults. It has been suggested that overdiagnosis may play a significant role, as has already been proven to be the case for adults, leading in turn to overtreatment, lifelong medical care and side-effects that can negatively affect quality of life. Given the large and rapid increase in incidence possibly due to overdiagnosis, estimates of survival should be interpreted with great care. Researchers have suggested that existing recommendations against screening for thyroid cancer in the asymptomatic adult population who are free from specific risk factors should be extended to explicitly recommend against

screening for thyroid cancer in similar populations of children and adolescents (Vaccarella et al., 2021).

The Chernobyl' accident in 1986 had the temporary effect of increasing thyroid cancer among children and young adolescents in the contaminated areas of Ukraine, Belarus and the Russian Federation (WHO, 2006). This temporary effect triggered in response the introduction of the extensive use of screening ultrasound examination of the thyroid (one between 11–15 years of age for all children in Belarus) in addition to periodic (age 1 month, 6 years and 15 years in the Russian Federation and 14–15 years in Belarus) abdominal and kidney ultrasound examination in all children as part of a routine medical check-up of children in these countries. These practices, although very labour-intensive and carrying the potential harm of overdiagnosis and additional public anxiety, demonstrated no additional value in reducing mortality from childhood cancers in these countries compared with countries with no mass ultrasound screening for children.



DISPARITIES IN SURVIVAL RATES BETWEEN HIGH-INCOME AND LOW-INCOME COUNTRIES FOR CHILDHOOD CANCER ARE WIDER THAN FOR MOST ADULT CANCERS



3.1.2 Survival

The concepts of incidence, survival and mortality represent the occurrence of a specific cancer (incidence), occurrence of death from any cause (survival) or occurrence of death from a specific cancer (mortality) (Ellis et al., 2014). Survival data generally are deemed to be more meaningful, as mortality depends heavily on incidence rates. Mortality-to-incidence ratios therefore are helpful where no survival data are available, but only where mortality data are known, since treatment abandonment can affect data quality.

Disparities in survival rates between high-income and low-income countries for childhood cancer are wider than for most adult cancers. In HIC, four of five children with cancer survive, with survival rates continuing to improve (Gatta et al., 2014).

While broad trends in the Region point towards increasing survival, variations can be observed in different parts. A Europe-wide study into cancer survival among children aged 0–14 drawing from 74 population-based cancer registries in 29 countries found five-year overall survival for all cancers combined was 79.1% in children in the period

between 2005 and 2007, compared to 76.1% between 1999 and 2001. The greatest improvements were found in eastern Europe, notwithstanding the disparities in outcome highlighted earlier, where five-year survival rose from 65.2% in 1991–2001 to 70.2% in 2005–2007 (Gatta et al., 2014).

Despite continuous improvements in the health-care system and available cancer treatment options, survival rates for childhood cancers in Estonia have also been observed to remain lower than the European average, with underreporting of nonfatal childhood cancer cases to the Estonian Cancer Registry having potentially led to a considerable underestimation of both incidence and survival rates in the country (Paapsi et al., 2017).

Using standardized treatment protocols can yield good results and has contributed considerably to substantial survival improvements in HIC. Research into the use of recommended paediatric protocols in Serbia, a middle-income country, found that of 87 children diagnosed with medulloblastoma and treated at the Institute for Oncology and Radiology between 2000 and 2013, 51 (58%) were alive and 31 (35.6%) had died as of October 2015, with five (5.7%) lost to follow-up. The authors report that in HIC, 70–80% of children with this condition are cured. They advocate using international treatment guidelines and recommendations, available resources and an experienced team of professionals dedicated to paediatric neuro-oncology (Bokun et al., 2018). Another Serbian study into treatment of Ewing's sarcoma found a five-year survival rate of 43.8% compared with an average for eastern Europe of 46% and for southern Europe of 74% (Paripovic et al., 2018), highlighting further the differences in survival.

Research conducted in the Russian Federation into soft tissue sarcomas in children found that between 2000 and 2009, survival rates were broadly comparable to other eastern European countries (Kachanov et al., 2012).

Analysis of Spanish childhood leukaemia cases between 1983 and 2007 found that five-year survival increased from 66% in 1991–1995 to 76% in 2001–2005. Survival was lower in infants (0 years) and adolescents (15–19 years) than in other age groups, with no similar improvement in five-year survival observed for these age groups (Marcos-Gragera et al., 2016).

In Switzerland, overall five-year survival for childhood cancer patients increased from 64% between 1976 and 1983 to 88% between 2004 and 2013 (Schindler et al., 2017), and analysis of cancer survival among children of Turkish descent in Germany between 1980 and 2005 found that at the time of publication (2008), Turkish migrant status had no bearing on the outcome of childhood cancer treatment in Germany, probably as a result of highly standardized treatment protocols used for all children (Spix et al., 2008). Similarly, an analysis of the effect of ethnicity and socioeconomic status on the survival of a population-based cohort of 1979 children diagnosed with cancer between 1974 and 1995 in Yorkshire, United Kingdom found neither ethnicity nor socioeconomic status appeared to influence survival after taking other factors into consideration (McKinney et al., 1999).

Measures to improve outcomes in Ukraine

Recent adverse cases in Ukraine demonstrate the importance of improved training, greater adherence to treatment protocols, access to safe blood products and diagnostics, and increased childhood cancer awareness, in improving outcomes.

An 8-year-old girl with ALL was infected with hepatitis C as a result of donor blood transfusion. As a consequence, she was unable to proceed with allogeneic stem cell transplantation before the infection was brought under control. In some regions where donor blood is not tested using the polymerase chain reaction method, almost all children may catch hepatitis B, C or both by the end of treatment. At present, standards, staff qualifications and access to laboratory testing are not uniform across the country. More training, the introduction of standardized operational procedures, improved access to equipment and reagents and reform of the state blood transfusion system are needed to avoid such situations in future.

An 18-month-old boy had something resembling a naevus or a node on his chin removed in a children's hospital. The removed sample was not sent for histology examination. Two months later, a neoplasm appeared in the same place and started growing progressively. He was diagnosed with embryonal rhabdomyosarcoma and ultimately died.

In 2017, a 15-year-old girl complained of fatigue, weakness and loss of appetite. Following a positive Mantoux test taken at school, the girl was treated for tuberculosis over a two-year period. Her condition did not improve, and she was stigmatized in her social life as a person with tuberculosis. Ultimately, she was referred to a paediatric oncologist and diagnosed with lung adenocarcinoma, stage four. She received immunotherapy and target therapy, but the disease progressed and the girl ultimately died in 2021 when she was 19 years old.

Timely and proper diagnostics depend on whether or not medical doctors in the primary and secondary care tiers are competent and aware of childhood cancer. Low childhood cancer awareness among paediatricians and other paediatric specialists and absence of patient referral pathways when cancer is suspected can be drivers of inequalities in access to treatment for childhood cancer patients. To address this issue, the medical training of paediatricians needs to be brought in line with international standards, with a childhood cancer course included in the curriculum and as a part of continuing medical education.

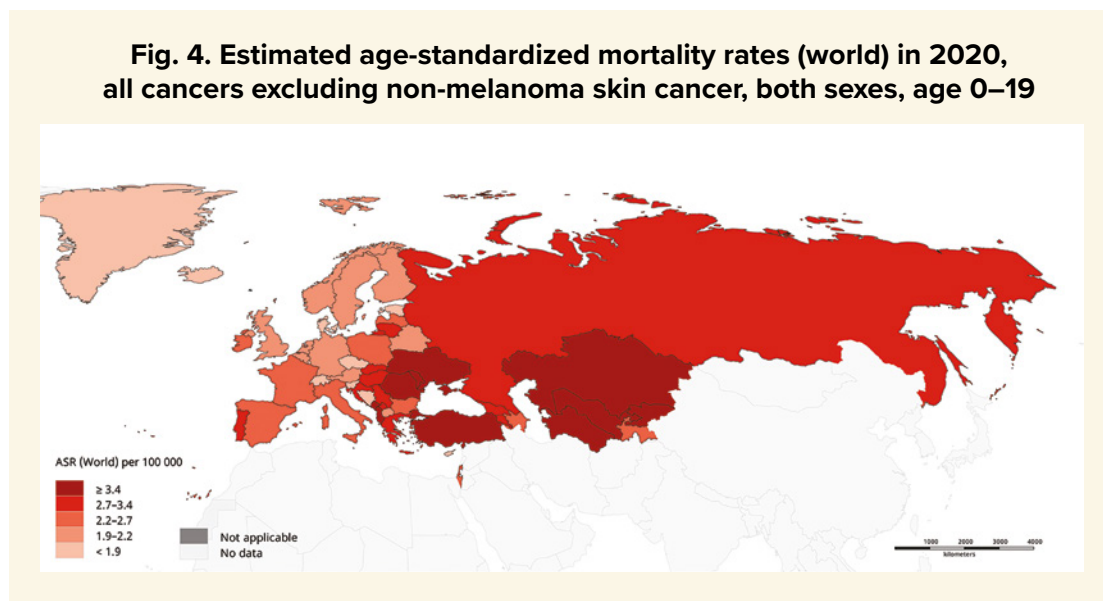
Source: Tabletochki Charity Foundation, Kyiv, Ukraine.

As noted above, more than 80% of children currently survive more than five years after a cancer diagnosis in HIC, but many LMIC do not capture these data at population level. In Europe in 2010, only 66.4% of the population of 0–14-year-olds and 46.1% of 15–19-year-olds were covered by registries contributing to IICC-3. Where overall childhood cancer survival has been monitored in LMIC, it has been found to be much lower, but there is some evidence that the gap can be reduced using measures encompassing improved awareness, earlier diagnosis, access to appropriate diagnostics and therapy, and provision of adequate supportive care (Piñeros et al., 2021).

3.1.3 Mortality

Fig. 4 and Table 2 show that in 2020, age-standardized cancer mortality rates among males and females aged 0–19 generally were higher in south-eastern countries in the WHO European Region than in northern and western countries. Although gaps remain, mortality from childhood cancer has decreased significantly in recent decades all over the Region and existing strong networks of paediatric oncology societies continue to work to ensure that treatment advantages reach everyone. With further support for such activities, this is a realistic aim.

Fig. 4. Estimated age-standardized mortality rates (world) in 2020, all cancers excluding non-melanoma skin cancer, both sexes, age 0–19



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Table 2. Estimated age-standardized mortality rates (world) in 2020, all cancers excluding non-melanoma skin cancer, both sexes, age 0–19

Population	Age-standardized mortality rate (per 100 000 population)	Population	Age-standardized mortality rate (per 100 000 population)
Turkmenistan	6.2	Tajikistan	2.4
Uzbekistan	6.0	France	2.3
Turkey	4.7	Latvia	2.3
Kazakhstan	4.1	Ireland	2.3
Ukraine	4.0	Israel	2.2
Albania	3.8	Belarus	2.2
Montenegro	3.8	Norway	2.2
Kyrgyzstan	3.7	Austria	2.2
Republic of Moldova	3.6	Sweden	2.1
Romania	3.4	North Macedonia	2.1
Georgia	3.4	United Kingdom	2.1
Lithuania	3.3	Finland	2.0
Armenia	3.2	Belgium	2.0
Portugal	3.1	Germany	1.9
Slovakia	3.1	Netherlands	1.9
Hungary	3.1	Switzerland	1.8
Croatia	3.0	Denmark	1.8
Russian Federation	3.0	Czechia	1.8
Greece	2.8	Bosnia and Herzegovina	1.5
Azerbaijan	2.7	Malta	1.1
Italy	2.6	Estonia	0.73
Bulgaria	2.4	Cyprus	0.66
Poland	2.4	Luxembourg	0.65
Spain	2.4	Slovenia	0.0

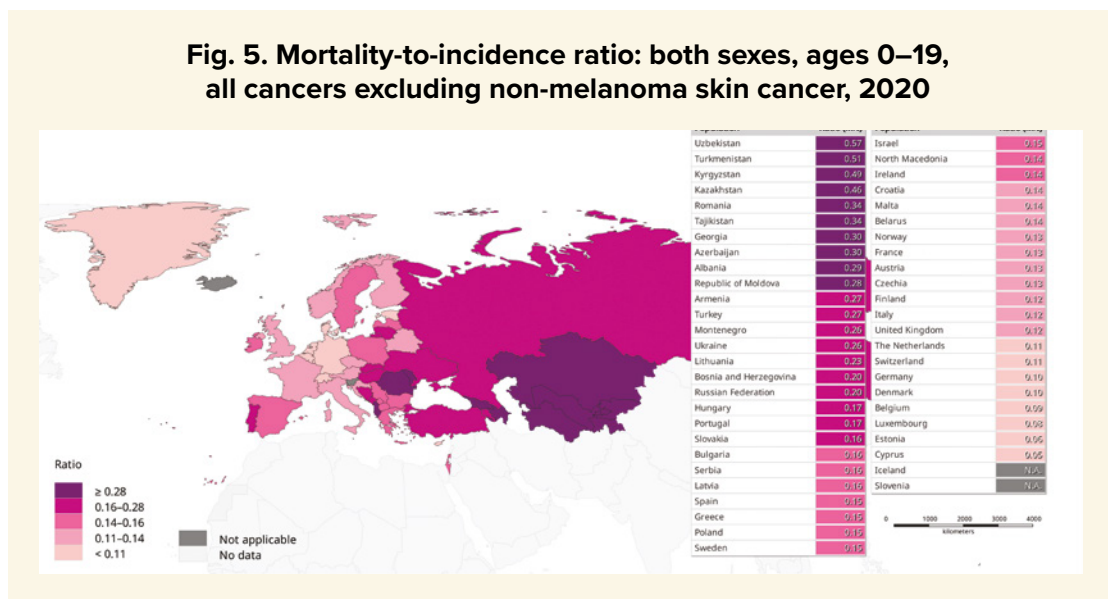


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Health-care delivery methods and adherence to treatment protocols appear to play a role in mortality trends in south-eastern European countries. Research into mortality and survival disparities among children with lymphoma residing in south-eastern European countries and in the United States of America found that while variable decreasing mortality trends were noted among south-eastern European countries between 1990 and 2014, overall mortality rates were higher than in the sample from the United States. The authors highlighted “substantial geographic, disease subtype-specific, and age-specific outcome disparities pointing to persisting gaps in the implementation of new treatment modalities and indicating further research needs” (Karalexi et al., 2016). Analysis of childhood CNS tumour mortality data across 14 cancer registries from southern and eastern European countries between 1983 and 2014 found cross-country mortality and survival variations, possibly reflecting suboptimal levels of health-care delivery and cancer control in some regions of southern and eastern Europe (Karalexi et al., 2015).

Central and western European countries have tended to see patterns of decreasing mortality and increasing incidence in children’s cancer. For instance, a study of patients aged 0–14 between 1994 and 2016 in Czechia found decreasing mortality rates and an overall five-year survival increase of 10%, attributed to improvements in diagnostic and treatment methods and the concentration of childhood cancer patients in children’s cancer centres (Krejci et al., 2020).

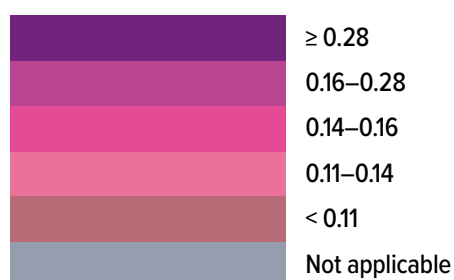
Mortality-to-incidence ratios can be helpful as they give an indication of survival for countries where no specific survival data exist. As with survival data, mortality-to-incidence ratios are highest (meaning poorer outcomes) in south-eastern countries of the Region (Fig. 5–7 and Table 3–5).



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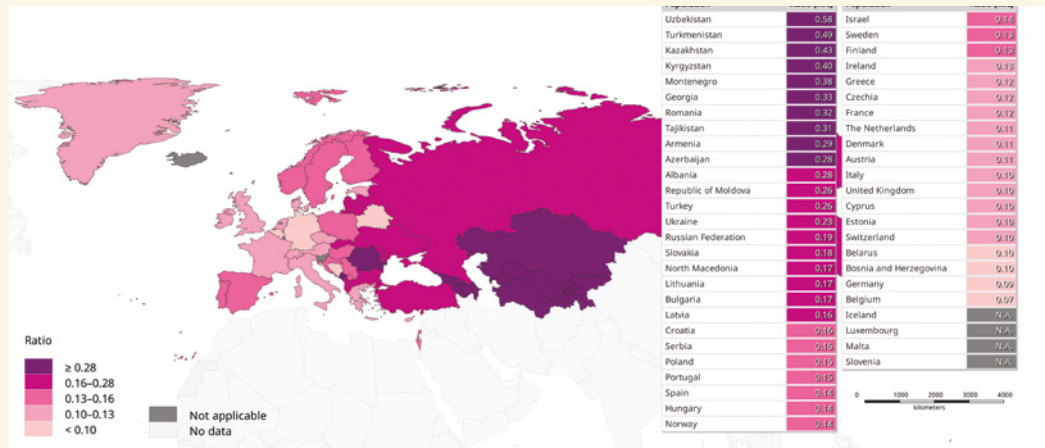
Table 3. Mortality-to-incidence ratio: both sexes, ages 0–19, all cancers excluding non-melanoma skin cancer, 2020

Population	Mortality-to-incidence ratio	Population	Mortality-to-incidence ratio
Uzbekistan	0.57	Poland	0.15
Turkmenistan	0.51	Sweden	0.15
Kyrgyzstan	0.49	Israel	0.15
Kazakhstan	0.46	North Macedonia	0.14
Romania	0.34	Ireland	0.14
Tajikistan	0.34	Croatia	0.14
Georgia	0.30	Malta	0.14
Azerbaijan	0.30	Belarus	0.14
Albania	0.29	Norway	0.13
Republic of Moldova	0.28	France	0.13
Armenia	0.27	Austria	0.13
Turkey	0.27	Czechia	0.13
Montenegro	0.26	Finland	0.12
Ukraine	0.26	Italy	0.12
Lithuania	0.23	United Kingdom	0.12
Bosnia and Herzegovina	0.20	The Netherlands	0.11
Russian Federation	0.20	Switzerland	0.11
Hungary	0.17	Germany	0.10
Portugal	0.17	Denmark	0.10
Slovakia	0.16	Belgium	0.09
Bulgaria	0.16	Luxembourg	0.08
Serbia	0.16	Estonia	0.06
Latvia	0.16	Cyprus	0.05
Spain	0.15	Iceland	NA
Greece	0.15	Slovenia	NA



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Fig. 6. Mortality-to-incidence ratio: females, ages 0–19, all cancers excluding non-melanoma skin cancer, 2020



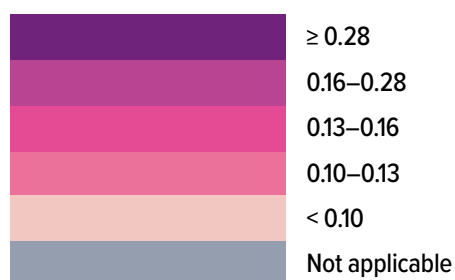
Source: reproduced with permission of the International Agency for Research on Cancer.

Table 4. Mortality-to-incidence ratio: females, ages 0–19, all cancers excluding non-melanoma skin cancer, 2020

Population	Mortality-to-incidence ratio	Population	Mortality-to-incidence ratio
Uzbekistan	0.58	Lithuania	0.17
Turkmenistan	0.49	Bulgaria	0.17
Kazakhstan	0.43	Latvia	0.16
Kyrgyzstan	0.40	Croatia	0.16
Montenegro	0.38	Serbia	0.16
Georgia	0.33	Poland	0.15
Romania	0.32	Portugal	0.15
Tajikistan	0.31	Spain	0.14
Armenia	0.29	Hungary	0.14
Azerbaijan	0.28	Norway	0.14
Albania	0.28	Israel	0.14
Republic of Moldova	0.26	Sweden	0.13
Turkey	0.26	Finland	0.13
Ukraine	0.23	Ireland	0.13
Russian Federation	0.19	Greece	0.12
Slovakia	0.18	Czechia	0.12
North Macedonia	0.17	France	0.12

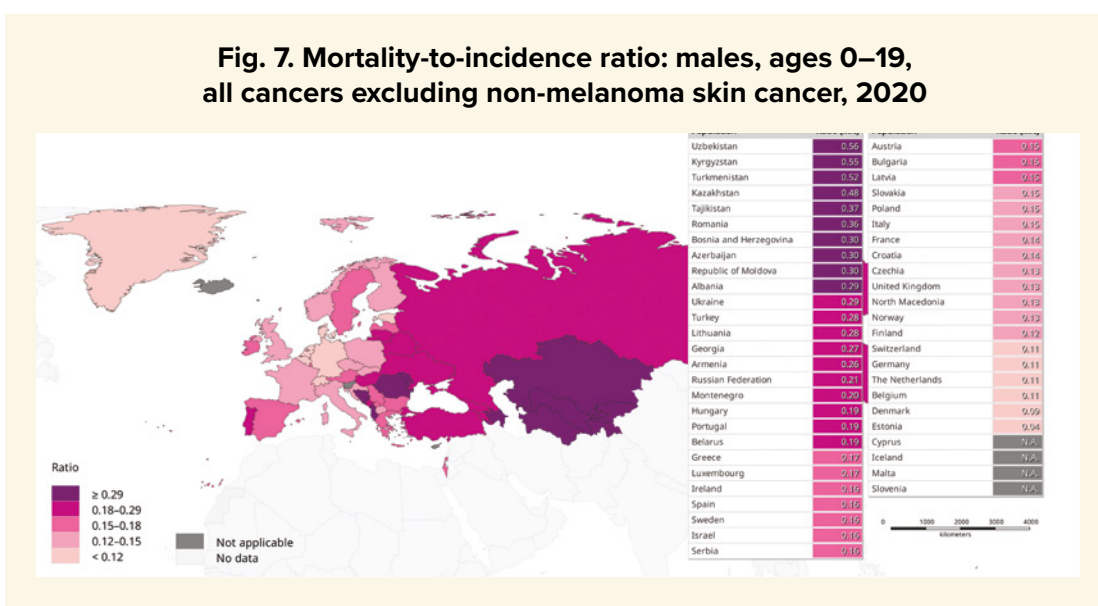
Table 4. contd

Population	Mortality-to-incidence ratio	Population	Mortality-to-incidence ratio
The Netherlands	0.11	Belarus	0.10
Denmark	0.11	Bosnia and Herzegovina	0.10
Austria	0.11	Germany	0.09
Italy	0.10	Belgium	0.07
United Kingdom	0.10	Iceland	NA
Cyprus	0.10	Luxembourg	NA
Estonia	0.10	Malta	NA
Switzerland	0.10	Slovenia	NA



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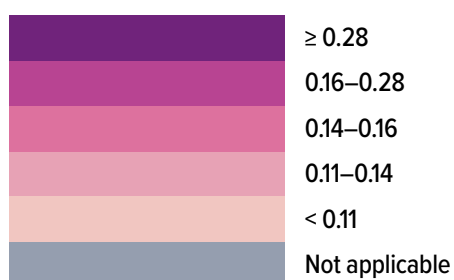
Fig. 7. Mortality-to-incidence ratio: males, ages 0–19, all cancers excluding non-melanoma skin cancer, 2020



Source: reproduced with permission of the International Agency for Research on Cancer.

Table 5. Mortality-to-incidence ratio: males, ages 0–19, all cancers excluding non-melanoma skin cancer, 2020

Population	Mortality-to-incidence ratio	Population	Mortality-to-incidence ratio
Uzbekistan	0.56	Israel	0.16
Kyrgyzstan	0.55	Serbia	0.16
Turkmenistan	0.52	Austria	0.15
Kazakhstan	0.48	Bulgaria	0.15
Tajikistan	0.37	Latvia	0.15
Romania	0.36	Slovakia	0.15
Bosnia and Herzegovina	0.30	Poland	0.15
Azerbaijan	0.30	Italy	0.15
Republic of Moldova	0.30	France	0.14
Albania	0.29	Croatia	0.14
Ukraine	0.29	Czechia	0.13
Turkey	0.28	United Kingdom	0.13
Lithuania	0.28	North Macedonia	0.13
Georgia	0.27	Norway	0.13
Armenia	0.26	Finland	0.12
Russian Federation	0.21	Switzerland	0.11
Montenegro	0.20	Germany	0.11
Hungary	0.19	The Netherlands	0.11
Portugal	0.19	Belgium	0.11
Belarus	0.19	Denmark	0.09
Greece	0.17	Estonia	0.04
Luxembourg	0.17	Cyprus	NA
Ireland	0.16	Iceland	NA
Spain	0.16	Malta	NA
Sweden	0.16	Slovenia	NA



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As explained in Chapter 2, despite an abundance of research, few causes of childhood cancer have been established scientifically. Among those that have, none qualify for larger-scale population-based prevention strategies as are applied for many adult cancers (Spector et al., 2015; Schüz & Erdmann, 2016). Not much can be done to reduce childhood cancer incidence, but a lot can be done to reduce mortality and ensure each country in the world achieves the cure rates above the 80% achieved in many HIC. Early diagnosis is particularly relevant here; in many childhood cancers, early diagnosis means the cancer will be easier to treat, with less toxicity.

The use of standard therapeutic guidelines, precise and timely diagnosis, and access to first-line diagnostics, contemporary therapy and supportive care currently are the best options for reducing childhood cancer mortality, though as previously noted, levels of availability vary across the Region. Primary prevention, if achievable, would be a welcome alternative given that childhood cancer survivors have several disadvantages and potential late effects later in life, which include a higher risk of developing a second malignancy.

3.1.4 Stage data

Accurate patient staging is not possible without appropriate laboratory, pathology and medical imaging services. The current lack of robust worldwide population-based staging data for childhood cancer is largely due to a lack of these services, which is most pronounced in low-resource settings.

Stage is not easily or consistently defined in childhood cancer, with leukaemias and some CNS tumours posing the greatest challenges. Most cancer registries, particularly those focused on childhood cancer, do not routinely record data on stage. This is because tumour, node and metastasis (TNM)-based staging systems most commonly are used for adult cancers (which focus on primary tumour site, regional lymph node involvement and presence or otherwise of distant metastatic spread) are not applicable to most childhood cancers, and access to necessary clinical data sources to assign tumour stage is difficult. Criteria for staging cancers vary by cancer type, have advanced over time and differ to some extent by cooperative clinical trial group.

In 2014, an international panel of experts developed consensus staging guidelines for paediatric cancers known as the Toronto Childhood Cancer Stage guidelines. The guidelines comprise a set of tiered, paediatric-specific staging systems with coding guidelines and were piloted in Australia and several central American countries in 2016 (Gupta et al., 2016). The team behind the guidelines subsequently updated them and recommended that population-based cancer registries should collect both stage and non-stage prognosticators to ensure robust stratification by risk (Gupta et al., 2020): the staging system for neuroblastoma, for example, has changed twice in 10 years (Pinto et al., 2015; Irwin et al., 2021)).

3.2 Universal health coverage across the cancer continuum

WHO has made achieving UHC a global priority, with the goal of 1 billion more people benefiting from UHC by 2023. This does not mean free access to every possible health service for every person, and WHO recognizes that every country has a different path to achieving UHC and deciding what to cover based on the needs of its people and the resources at hand. It does, however, emphasize the importance of access to health services and information as a basic human right (Thomson et al., 2019; WHO, 2022).

The availability of UHC can have a significant impact on the ability of families to access treatment for children who receive a cancer diagnosis. Differential availability of health services can have an effect at every stage of the patient's journey, from early detection and diagnosis to treatment and survivorship.

3.2.1 Early detection and diagnosis

Early diagnosis is important. Delays in diagnosis and treatment can influence survival and overall outcome, as childhood cancers progress and metastasize quickly. Timely diagnoses and treatment of childhood cancer can be achieved through tailored risk-based assessment, judicious early diagnosis programmes in primary care, targeted educational interventions and campaigns addressing lag times across the cancer care continuum (Mullen et al., 2021). Vision screening in newborns and early childhood conducted at the right intervals by skilled staff in primary care could support early diagnosis of retinoblastoma (Jullien, 2021). Work to estimate the level of undiagnosed childhood cancer suggests that in 2015, 3% of cancers went undiagnosed in western Europe, with higher proportions in southern and eastern Europe (Ward et al., 2019).



DELAYS IN DIAGNOSIS AND TREATMENT CAN INFLUENCE SURVIVAL AND OUTCOME, AS CHILDHOOD CANCERS PROGRESS QUICKLY



3.2.1.1 Family and society

Analysis of literature on diagnosis delays in childhood cancer identified three categories of causes of delay: patient and/or parent; disease; and health care. Main factors related to diagnosis delay were the child's age at diagnosis, parents' level of education, type of cancer, presentation of symptoms, tumour site, cancer stage and first medical specialty consulted (Dang-Tan & Franco, 2007).

Measuring patient and family experience of children's cancer services in the United Kingdom (England)

In October 2021, the National Health Service (NHS) in England published the results of the first ever all-England survey of children and young people with cancer and their families' experiences of care. Although the NHS has routinely surveyed adults on their cancer care for some years, these results mark the first time this type of feedback has been systematically collected from children and young people.

Four in five (80%) children responding to the survey, conducted by international health and social care charity Picker, said that they were "very well" looked after by health-care staff, and 92% of parents or carers rated their overall experiences of their child's care as 8 or higher (out of 10). Similarly, 89% of parents and carers said that their children were "always" treated with respect and dignity, and 96% said that they felt involved in their child's care and treatment.

A sizable majority of parents/carers (87%) said that staff "definitely" gave them information in a way that they could understand, but children and young people were less likely to report this. Seven in 10 (69%) children said that they "always" understood what staff said, with this falling to 63% for children aged 8–11.

The survey, commissioned by NHS England and NHS Improvement, was sent to parents of children and young people aged 16 or under who had received a confirmed cancer or tumour diagnosis and been treated at one of England's 13 NHS principal treatment centres in 2020. Parents or carers were asked to give feedback about their child's care, and children and young people aged 8–15 were invited to give their own views. More than 1100 responses were collected, representing a 35% response rate overall.

Source: Picker (2021).

Analysis of incidence, time of diagnosis and treatment of paediatric cancer patients in Germany during the COVID-19 pandemic found that more or similar numbers of paediatric cancer patients were newly diagnosed each month throughout 2020, both overall and across diagnostic groups, in comparison to the previous five years. Results from a qualitative survey indicated that diagnostic processes, timeliness of diagnosis and delivery of treatment were hardly affected during the COVID-19 pandemic. It appeared nevertheless that psychosocial supportive care and non-urgent appointments were considerably reduced during the lockdown periods



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in Germany. The authors speculate that this may be down to increased parental attention to early symptoms during the pandemic period (Erdmann et al., 2021a). This implies that earlier diagnosis may be potentially possible with greater awareness of cancer warning signs in children.

3.2.1.2 Health-care facilities and workforce

High-quality laboratory, pathology and imaging services are required for diagnosis, staging and restaging of childhood cancer. Lack of universal access to these resources can lead to incorrect diagnosis, incorrect staging and, in turn, inappropriate clinical management and poorer patient outcomes. In 2017, only 26% of low-income countries reported having pathology services generally available in the public sector (Singh, 2019).

IMAGINE, the International Atomic Energy Agency (IAEA) medical imaging and nuclear medicine global resources database, shows that on average, 25 000 people are served by one CT scanner in HIC, compared with 79 000 inhabitants per scanner in upper-middle-income countries, 227 000 inhabitants per scanner in LMIC and 1.7 million per scanner in low-income countries. CT scanning is often critical to disease staging and frequently guides surgical or radiotherapy planning (IAEA Human Health Campus, 2022). It is particularly important with infants and

children that the feasibility of alternative techniques that do not use ionizing radiation (such as ultrasound and magnetic resonance imaging) be considered. This is even more important in children with chronic diseases (IAEA, 2012; Image Gently Alliance, 2014).

Improved professional education, public information and collaboration may also support early detection of paediatric cancers. ERN PaedCan supports Member States to cooperate to streamline the patient journey for conditions that require specialist expertise and when tools are not widely available because of low case volumes at national level.

3.2.1.3 Universal health coverage

Health reforms in LMIC since the late 1980s have focused on promoting user fees for health services and increasing the role of the private for-profit sector in health-care provision, meaning that individuals with poor health have increasingly faced the burden of paying for their treatment. Researchers have suggested that research into health-care financing strategies and related mechanisms for coping with the direct and indirect costs of illness is urgently required to inform the development of appropriate social policies to improve access to essential health services and break the vicious cycle between illness and poverty in these countries (McIntyre et al., 2006).



HIGH-QUALITY LABORATORY, PATHOLOGY, AND IMAGING SERVICES ARE VITAL FOR DIAGNOSIS, STAGING AND RESTAGING



3.2.2 Treatment

With the exception of very small states that access services in neighbouring countries, all WHO European Region countries have radiotherapy services. The level of resources – including equipment and trained staff – varies widely, however; this is likely to affect the quality of care given to childhood cancer patients and outcomes achieved.

Once outliers are removed, the number of megavoltage external beam machines in Member States varies from 0.2 to 9.7 machines per million people. This can be compared with an IAEA recommendation of approximately one megavoltage external beam radiotherapy machine per 180 000 people – at present, only 20 of the 53 WHO European Region Member States meet this criterion and 11 in the

south-east of the Region fall below half of this capacity. Clearly, expansion will be necessary in these countries to allow time for complex processes such as whole CNS radiotherapy or the treatment of young children requiring anaesthesia.

Between 2010 and 2013, the IAEA conducted surveys of global radiotherapy centres treating children to examine clinical service delivery, equipment and quality measures. The analysis found that multidisciplinary treatment decision-making became less common as economic resources fell and, in some countries, coordination with paediatric oncology seemed poor. Additionally, access to supportive facilities such as radiotherapy patient hostels and free transport services was reduced, as was follow-up of survivors into adulthood to monitor and treat late effects (Anacak et al., 2021).

Data from 34 centres in 13 WHO European Region countries were included in the study (23 centres in nine HIC and 11 in four middle-income countries). Higher numbers of children were being treated in the facilities in centres in middle-income countries, but the numbers of trained radiotherapy staff were lower, most concerningly in medical physics where clinically qualified staff play a key role in the quality-assurance processes necessary for safe delivery of treatment.

All the centres had access to CT scanning and could offer Linac-based 3D conformal radiotherapy, but centres in middle-income countries were less likely to have a dedicated CT simulator and a higher percentage of children were still being treated with cobalt units. Important ancillary equipment such as immobilization equipment in child sizes and advanced radiotherapy techniques such as intensity-modulated radiation therapy, stereotactic radiotherapy and total body irradiation were less commonly available. Whole CNS radiotherapy – essential in the treatment of children with medulloblastoma – was often performed prone and without the recommended moving junction technique.

Most departments in the cohort had a radiotherapy quality-assurance programme and universal commitment to the use of protocols was evident, but it was noted that published international guidelines sometimes lacked relevance and even major units in middle-income countries often opted to develop local guidelines. Resource-adaptive guidelines reflecting the capacity and needs of LMIC therefore are required. Involvement in paediatric academia and research activity, which correlates with high-quality service delivery, is less common in middle-income environments.

Cancer patients can face high financial costs in health systems where a copayment is expected as part of the cost of treatment, but even in HIC with health systems based on a national health service or social health insurance, public payers can sometimes not afford the high prices of some cancer medications. Challenges include fragmentation (where individual hospitals must purchase drugs), the creation of budget silos via dedicated cancer drug schemes and the rejection of new treatments when the price is deemed too high (Vogler, 2021).

Ensuring supply of quality-assured childhood cancer medicines to LMIC

A new initiative by WHO and St. Jude Children's Research Hospital, United States of America – the Global Platform for Access to Childhood Cancer Medicines – launched in December 2021, will provide an uninterrupted supply of quality-assured childhood cancer medicines to LMIC. St. Jude is making a six-year, US\$ 200 million investment to launch the platform, the first of its kind, which will provide medicines at no cost to countries participating in the pilot phase. This is the largest financial commitment for a global effort in childhood cancer medicines to date.

The new platform aims to provide safe and effective cancer medicines to approximately 120 000 children between 2022 and 2027, with the expectation to scale up in future years. This platform will provide end-to-end support by: consolidating global demand to shape the market; assisting countries with the selection of medicines; developing treatment standards; and building information systems to track that effective care is being provided and to drive innovation.

During an initial two-year pilot phase, medicines will be purchased and distributed to 12 countries through a process involving governments, cancer centres and nongovernmental organizations already active in providing cancer care. Discussions are already ongoing with governments to determine the countries that will participate in this pilot phase. By the end of 2027, it is expected that 50 countries will receive childhood cancer medicines through the platform.

Source: WHO (2021b).

Globally, 42.1% of patients in low-income countries and LMIC surveyed in 2017 lacked full access to chemotherapy packages (Cohen et al., 2018). A survey into the availability of 68 medicines for childhood and adolescent cancer, including 24 on the WHO List of Essential Medicines for children (EMLc) 2017, with results from 34 European countries, found that 35% of all medicines were prescribed off-label in at least one country and that only 44% were always available in more than 90% of countries. Only 63% of the EMLc 2017 medicines were reported as always available. The main determinant of unavailability was shortages, reported for 72% of medicines in at least one country, and out-of-pocket costs were reported in eight countries. Twenty-seven per cent of orally administered medicines were never available in child-friendly formulations (Vassal et al., 2021).

Access to medications in Serbia

A child diagnosed with ALL and treated with bone marrow transplantation had to take an off-label drug, deflazacort 30 mg, for a long period. The family had to set aside around €100 per month, despite their monthly income amounting to around only €250. This medicine was provided through donations by the local parents' organization, but due to the COVID-19 pandemic, parents' organizations have become impoverished, with a growing lack of money to purchase medicines.

Source: reproduced with permission of Childhood Cancer International Europe.

Similarly, survey-based research by the European Commission's Joint Action on Rare Cancers has found that out-of-pocket costs were being incurred for medicines by families of children with cancer in eight out of a subset of 30 countries in the WHO European Region. Countries affected included Bulgaria, Estonia, Finland, Latvia, Poland, Romania, Spain and Turkey. Costs incurred by families ranged from between 2% to 18% for medicines used in each country. While during the two-year period covered by the survey no medicines on the WHO EMLc were reported as being unavailable due to budget limitations in any of the participating countries, more than half of the remaining medicines (22 of 44) were reported as not available for this reason in at least one country (Joint Action on Rare Cancers, 2019a).

Access to essential and novel medicines is a specific area marked by inequalities in the Region's paediatric haematology oncology sector. A recent survey of availability of essential medicines used to treat children with cancer in the Region found that lower-income countries experienced financial barriers most, and that even access to pain control differed between countries and regions in Europe (Vassal et al., 2021).

Access to child-friendly formulations in the Russian Federation

The availability of paediatric drug formulations and dosing regimens in the Russian Federation remains a concern. Some medications are not licenced, while others are licenced but do not have appropriate indications or dosing. Pharmaceutical representatives claim that the licencing of paediatric drug formulations is unprofitable for the industry. There is a serious need for medications officially approved for use in children in paediatric oncology and haematology, including chemotherapeutic agents and supportive therapy drugs.

Source: reproduced with permission of the Dmitry Rogachev National Medical Research Centre of Paediatric Haematology, Oncology and Immunology, Moscow, Russian Federation.

Profound disparities in the accessibility of European Medicines Agency-approved medications and technologies exist between central, eastern and south-eastern European countries and neighbouring western European countries. It has been suggested that more rapid reimbursement decisions and introduction of novel drugs in routine clinical practice, along with better access to clinical trials and treatment according to standardized treatment protocols, are needed to address these disparities, alongside higher investment in cancer care and more organized value-oriented application of novel diagnostic and treatment approaches. This should be augmented by greater involvement of patient organizations in cancer research, and clinical research and reimbursement processes (Thallinger et al., 2020).

Drug shortages in Bosnia and Herzegovina

There has been a long-term shortage of methotrexate in Bosnia and Herzegovina. When therapy was postponed for a large number of children, the parents' organization in Sarajevo mobilized friends and members to buy and transport medicine from all over the EU and from neighbouring countries.

Source: reproduced with permission of Childhood Cancer International Europe.

Access to innovative therapies in early phase academic-led clinical trials can provide a second chance at life for children with relapsed or hard-to-treat malignancies. Currently, only 10% of patients in need of these experimental modalities have access to them. Indeed, these trials are available only in a few centres and countries in the Region and often are not considered standard care, consequently necessitating out-of-pocket payments and/or special arrangements. The opportunity to participate in early phase clinical trials should be recognized as standard care for children with cancer in relapse or treatment failure to optimize their chance of cure (Joint Action on Rare Cancers, 2019b).

Joint Action on Rare Cancers has produced a series of recommendations to support countries in improving the provision of care for childhood cancer patients (Joint Action on Rare Cancers, 2020):

- national cancer control plans should include a clearly designated section on paediatric cancers integrating specific provisions concerning: epidemiology; health-care organization and quality; access to the best possible multimodal standard treatment; clinical research and access to innovative therapies; access to the social needs of patients and families; and survivorship;
- coordinated research and health policies and programmes are ideally placed at regional level, given the rarity of individual paediatric cancers and their huge burden across countries; and
- the multistakeholder-endorsed *SIOPE strategic plan – a European cancer plan for children and adolescents* (SIOPE, 2021) can serve as guidance for childhood cancer strategies at national and European levels.

3.2.2.1 Care of adolescents with cancer

The configuration of health services can also play a role in patients' ability to access appropriate care. Research into children treated for cancer in Spain between 2007 and 2010 revealed that 87% of adolescents aged 14–19 years were never seen at paediatric oncology units, while 40% were treated at up to 20 different medical oncology departments in institutions without paediatric oncology expertise. The authors recommended centralization to a small number of specialist centres and thorough paediatric and oncology team collaboration as a means of improving care and survival for Spanish adolescents with cancer. They also suggested the creation of specific adolescent tumour boards in main tertiary hospitals so that adolescents can benefit from the shared expertise of medical and paediatric specialists (Berlangua et al., 2016).

“I was diagnosed with leukaemia when I was 15 years old and treated in an adult unit. On a mental level, during my stay in the hospital, I missed being in an environment that was appropriate for my age. Also, from the very beginning I was required to have an adult attitude. All the information related to my diagnosis, survival and complications that arose were told to me while I was alone, without my parents. They called it an adult protocol. After my experience I kept reiterating the need for creation of specific units for adolescents, or the possibility of adolescents being treated in paediatric units.”

Spanish adolescent cancer patient

Source: reproduced with permission of Childhood Cancer International Europe.

Research into adolescent and young adult cancer care in Australia, the United Kingdom and the United States has identified the creation of multidisciplinary teams that integrate medical and psychosocial care, efforts to centralize complex care, providing access and equity for all adolescents and young adults, promoting clinical trials and helping facilitate transition to healthy survivorship as principles underpinning care in these countries (Osborn et al., 2019).

In 2021, the Russian Federation adopted a law allowing patients who started their cancer treatment before the age of 18 to complete their treatment at a children's hospital when over 18 to ensure continuity and sustainability of treatment.

Access to paediatric facilities in Kazakhstan

The case of an adolescent male cancer patient in Kazakhstan demonstrates the importance of ensuring that adolescents have access to paediatric services when necessary. In May 2020, the patient, born in 2003, was admitted with a verified diagnosis after an operation. He had a dislocated colostomy, which made it difficult for him to remain in the paediatric hospital. He was also prescribed an adult treatment protocol, so was treated at the centre for abdominal oncology but registered at the paediatric oncology centre.

He was experiencing discomfort and extreme psychological distress as he was in the same room as an adult and not allowed to be in the paediatric ward. His mother was also very reluctant to disclose his diagnosis to him. He was kept in the dark for some time.

After the end of treatment, there were difficulties in closure of the colostomy tube; this surgery is conducted in the institute for patients from 18 years, but is not carried out in the paediatric institute. The patient therefore had to wait several months before reaching adulthood and experienced anxiety and emotional decline, although the chemotherapy treatment was successful.

Source: reproduced with permission of the Kazakh Institute of Oncology and Radiology.

The EU Cross-border Healthcare Directive was introduced in 2011 to remove barriers to accessing care in EU Member States. This is underpinned by a reference network of expert centres, the European Expert Paediatric Oncology Reference Network for Diagnostics and Treatment (ExPO-r-Net), which aims to integrate the SIOPE's standard of care initiative in the Region (Vassal et al., 2014). Today, this vision is being implemented through a reference network of expert centres (ERN PaedCan) that was piloted through the EU ExPO-r-Net project and was officially launched with the support of EU Member States and the European Commission in 2017. The ERN PaedCan links specialist centres across Europe to exchange professional expertise in a virtual setting, foster twinning, educational initiatives and clinical guideline consolidation building on the SIOPE standard of care initiative in the Region (Vassal et al., 2014), and facilitate travel for highly specialized interventions when needed.

3.2.3 Supportive care and survivorship

In the context of a growing paediatric cancer burden in the Region and increasing survivorship, ensuring high-quality follow-up care is becoming more important. There is evidence of unmet need in relation to quality of life, adverse psychosocial consequences in adult life and somatic late effects, with at least a quarter of

cancer survivors reporting long-term poor health and disability. In response, health systems have been urged to develop national plans to support childhood cancer survivors' specific needs. These survivorship care plans, or aftercare plans, describe medical and non-medical interventions for the post-acute treatment phase and may include rehabilitation and monitoring.

The European Commission Joint Action on Cancer Control (CanCon) has analysed how survivorship is included in all European national cancer plans in general and made recommendations for the development of national plans. These include steps to fight cancer stigma, work to anticipate survivors' late effects management and tertiary prevention needs, improved early detection of needs and better access to services, coordination of community providers and services, better anticipation of late health and psychological impacts on child, adolescent and young adult survivors, and more research to gather data on late effects and the cost-effectiveness of supportive care, palliative, psychosocial and rehabilitation interventions.

In addition, the CanCon guide highlights good practice examples from EU countries stretching beyond health care, such as an Italian regulation enabling cancer patients to switch from full-time to part-time employment while undergoing treatment before switching back to full-time, and the inclusion of cancer in disability protections under the United Kingdom's Equality Act, passed in 2010 (De Lorenzo et al., 2018). Specific guidelines for follow-up for survivors of childhood and adolescent cancer have been drawn up by the PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies (PanCareSurFup) consortium, alongside research into late effects of cancer treatment (PanCareSurFup, 2022).

3.2.4 Palliative care

Globally, an estimated 3.95 million children required palliative care in 2017. Children and adolescents aged 0–19 comprise 7% of total global palliative care needs. The WHO Eastern Mediterranean Region accounts for 12% of the total, whereas the European Region has only 2.8%. Cancers account for 4.1% of palliative care need among children globally (Worldwide Hospice Palliative Care Alliance & WHO, 2020).

A survey of nursing experts in EU countries found that in 14 countries (56% of the group), palliative care was not identified as a mandatory subject in undergraduate nursing education. Wide awareness and use of the European Association for Palliative Care 2004 guide, however, shows how policy measures can influence the development of palliative care education (Martins Pereira et al., 2021).

4

Inequalities within countries



KEY POINTS

- Within individual countries, inequalities across groups can be seen in terms of cancer detection and outcome – this finding is true in high-, low- and middle-income countries.
- In HIC, boys with cancer tend to have poorer outcomes than girls, whereas data from LMIC suggest that girls are registered less frequently than boys, with indications that girls are being underdiagnosed.
- Children of families with higher socioeconomic status tend to experience higher survival rates than children from families with lower socioeconomic status.
- Geography plays a significant role in inequalities, with centralized services requiring patients to travel large distances for care while dispersed services can sometimes lack sufficient numbers of expert staff, leading to a lower standard of care.
- There are relatively few data available regarding childhood cancer in migrant groups, but children of international migrants tend to use general care, primary care and oral health services less than non-migrants and use emergency rooms and are hospitalized more frequently.

Inequalities in childhood cancer exist within individual countries and between countries in the WHO European Region. Inequalities across socioeconomic groups can be seen in incidence, cancer detection and outcome. This finding is true in LMIC and in HIC. Potential explanations for these inequalities vary substantially depending on whether inequalities in occurrence or inequalities in outcome are being discussed, and can also vary depending on the characteristics of the country in question. There is in general a lack of data on survival inequalities and a better evidence base is required to understand more fully the inequalities that exist in relation to survivorship.

Gender-based inequalities are evident across the Region, as are socioeconomic inequalities, which can be identified by stratifying patients' families into groups based on parental level of education or income and the neighbourhood of the place of residence. Inequalities in access to care stemming from geography and differential ability to access care are also present.

Children who have migrant status, who belong to families with a migrant background or are part of a seldom-reached group also experience inequalities in relation to access to, and utilization of, health care, with accumulating evidence of impact in relation to childhood cancer in some countries. Inequalities linked to differences in family structure and certain cultural and religious factors can also be seen, although there is a significant lack of data in this area.

4.1 Gender as a cause of inequalities

The role of gender as a driver of inequalities in children's cancer appears to be different in HIC and in LMIC. In HIC, boys with cancer tend to have poorer outcomes than girls. For instance, males aged 0–19 years in a study in the United States were found to have worse overall survival and a higher risk of death from ALL, ependymoma, neuroblastoma, osteosarcoma, thyroid carcinoma and malignant melanoma, although the association between sex and death was found to be mediated by stage of disease for neuroblastoma, thyroid carcinoma and malignant melanoma (Williams & Spector, 2019). Another study, also using data from the United States, found girls with leukaemia had a 14% decreased risk of dying relative to boys, with this sex difference persisting even after controlling for factors such as tumour cell type, race, age at diagnosis, year of diagnosis and number of primaries. These disparities were not completely explained by treatment received, tumour prognostic or sociodemographic factors (Holmes Jr et al., 2012), and biology potentially plays a role here.



GIRLS ARE BEING REGISTERED LESS FREQUENTLY THAN BOYS, WITH STRONG INDICATIONS THAT GIRLS WITH CANCER ARE SUBSTANTIALLY UNDERDIAGNOSED



By contrast, data from LMIC suggest that girls are being registered less frequently than boys, with strong indications that girls with cancer are substantially underdiagnosed compared to boys. For instance, analysis of cancer incidence data taken from Five Continents reports dating from 1998 to 2002 and comprising information from 225 cancer registries indicates that most countries have an age-standardized cancer rate sex ratio of less than 1.4 (males to females). Increasing cancer rate sex ratio was significantly associated with an increasing proportion of people living on less than Int\$ 1 a day, decreasing gross domestic product (GDP), decreasing life expectancy, decreasing physician density, decreasing per capita health expenditure and increasing infant mortality rates (Bhopal et al., 2012). Such differences have been observed even when haematological malignancies (known to have higher incidence in boys) were excluded from the analysis (Bhopal et al., 2011).

In some LMIC, this discrepancy may be explained at least in part by gender bias in care-seeking. A study of gender bias in 57 LMIC found that girls aged under 5 were



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less likely to receive care than boys in Colombia, Egypt, India, Liberia, Senegal and Yemen, with an ecological analysis finding gender bias in care-seeking was more likely in countries with unequal income distributions, and improved care-seeking for boys in countries with a higher Muslim population. More research is needed to better understand the effects of religion and culture on care-seeking and to determine whether this ecological association is found at individual level analyses or is due to an ecological fallacy (Costa et al., 2017).

A further potentially significant factor is the influence health systems exert in reinforcing patients' traditional gender roles and neglecting gender inequalities in health. Gender equality policies in health care have been found to be associated with greater representation of female physicians, which is in turn associated with better health outcomes (Hay et al., 2019).

4.2 Parental socioeconomic and education status as a driver of inequalities

A clearer pattern in terms of outcomes can be seen for inequalities linked to the socioeconomic status of the child's family. There is also some evidence of a relationship between family socioeconomic status and decisions to abandon cancer treatment in LMIC.

Children of families with higher socioeconomic status tend to experience higher survival rates than children from families with lower socioeconomic status. This trend can be seen in both high-income and low-income countries, with variation

in the size of the gap between survival rates for those with highest and lowest socioeconomic status between different countries. It should be noted, however, that different studies use different measures of socioeconomic status, and the meaning of certain measures of socioeconomic status varies substantially between countries and calendar period.

Survival inequalities in childhood cancer have been seen to affect high-income populations (including those in the WHO European Region), and a childhood cancer diagnosis may have implications for the parents' socioeconomic situation and for the child surviving the disease later in life (Erdmann et al., 2019b). This point is explored in greater detail in Chapter 5.



CHILDREN OF FAMILIES WITH HIGHER SOCIOECONOMIC STATUS EXPERIENCE HIGHER SURVIVAL RATES



Research in Denmark has found that children whose parents have attained higher levels of education and higher income face a greater risk of developing different cancers. For instance, one study found increased risks of ependymoma and embryonal CNS tumours in association with higher parental education and higher risk of all tumour types in association with higher maternal income, with associations often being stronger for children diagnosed between ages 5 and 19 (Erdmann et al., 2020a). Medium and high levels of parental education were associated with a higher risk of acute myeloid leukaemia (AML), mainly driven by diagnoses in children aged 0–4, with a modestly increased risk for lymphoid leukaemia in association with higher level of parental education, but only in children diagnosed between ages 5 and 19 years. Higher parental income was associated with an increased risk of lymphoid leukaemia but not AML among children aged 5–19 years at diagnosis (Erdmann et al., 2021b). A slightly-to-moderately increased risk for most childhood non-CNS solid tumours was identified in association with higher maternal income and parental education (Erdmann et al., 2021c).

While tumour incidence was found to be associated with higher socioeconomic status in these Danish studies, there is also evidence that lower socioeconomic status has been associated with worse survival after childhood cancer. For instance, a review of 24 studies found several indicated a social gradient, with higher mortality among children from families with lower socioeconomic status. Different measures

of socioeconomic status appeared to be of importance in the studies, implying mechanisms may vary between cancer types and health-care contexts (Mogenson et al., 2018).

Analysis of registry data in Norway found mortality was reduced by about 15% for children with highly educated mothers and those without siblings. This analysis, encompassing all Norwegian children diagnosed with cancer between 1974 and 2007, found the most pronounced effects were for cancers predicted to require intense long-lasting treatments resulting in chronic health problems. Neither earnings nor the marital status of parents were found to have affected children's survival.

One possible explanation is that children of well informed and strongly involved parents may either be offered better treatment, even in a universal health-care setting with limited private alternatives and standardized treatment protocols in place, or may be able to make better use of what is offered. Children of these families may be healthier at the outset or more likely to avoid later health problems unrelated to the cancer (Syse et al., 2011). Some research has suggested the possible existence of a socioeconomic gradient in the use of general practice before a childhood cancer diagnosis (Friis Abrahamsen et al., 2018).

Research in other countries in the Region shows a similar picture. Analysis of Hungarian childhood cancer incidence and survival data for all cases of childhood leukaemia and myelodysplasia spanning 45 years between 1971 and 2015 found a reverse association in the survival probability of leukaemia by degree of deprivation (Jakab et al., 2017).

A study of all Swiss cancer patients aged under 16 diagnosed between 1991 and 2006 found higher socioeconomic status, particularly parents' education, was associated with a lower five-year cumulative mortality. Results varied by type of cancer, however, with no association for leukaemia and particularly strong effects for CNS tumour patients. This is despite Switzerland having a high-quality health system and mandatory health insurance (Adam et al., 2016).

An evaluation of socioeconomic and clinical factors in childhood ALL survival in Greece found that children of mothers who were unmarried, who had achieved a low level of educational attainment or who were living far away from the treatment centre tended to have lower survival. Researchers also found that two factors predictive of disease occurrence (number of siblings and attendance at day care) may also predict survival, leading the authors to conclude that socioeconomic factors are likely to influence survival from ALL in at least some sociocultural contexts and that factors that could influence ALL incidence through modulation of herd immunity may also have prognostic implications for the disease (Charalampopoulou et al., 2004). A later study also of Greek data found similar results with regard to ALL, but not for AML, for which there were no noteworthy associations implicating socioeconomic status (Sergentanis et al., 2013).

By contrast, analysis of the impact of selected sociodemographic characteristics on overall and event-free survival of children in western Germany diagnosed with ALL between 1992 and 1994 found that socioeconomic determinants did not affect survival. Excellent access to health care, lifestyles and treatment were suggested by the study authors as reasons why findings were different in western Germany than many other countries (Erdmann et al., 2014).

These findings reflect a more general pattern of substantially higher death rates and poorer self-assessments of health in adults with lower socioeconomic status in European countries, albeit with much larger gaps in some countries than others (Mackenbach et al., 2008).



OUT-OF-POCKET PAYMENT SYSTEMS PLACE FINANCIAL STRAIN ON INDIVIDUALS AND HOUSEHOLDS, LEADING PATIENTS TO DELAY OR FOREGO NECESSARY CARE



Poor socioeconomic conditions have also been linked to children's attitudes towards cancer in one HIC, with a French study finding children from deprived backgrounds were more likely to believe that the illness is systematically deadly and less likely to consider it to be a treatable illness. They were also less likely to associate cancer with risky behaviours, particularly alcohol consumption (Denois et al., 2018).

No specific analysis of childhood cancer survivorship rates by socioeconomic status in LMIC in the WHO European Region exists, but globally the probability of dying in childhood in LMIC is related to the socioeconomic position of the child's family, with the magnitude of inequality varying between countries and over time (Houweling & Kunst, 2010).

A lack of prepayment mechanisms and the means and resources to pool risks has limited the capacity of many health-care systems in LMIC particularly to provide access to high-quality health-care services. Instead, health systems generally have relied on private payments in out-of-pocket costs. In 2016, out-of-pocket payments constituted 56% of total health expenditure in LMIC compared with 39% in lower-income countries and 30% in upper-middle-income countries. In addition to being less efficient, out-of-pocket payment systems place financial strain on individuals and households, which can lead people to delay or forego necessary care (Essue et al., 2017).

These patterns are also seen globally, with socioeconomic gradients in which low socioeconomic status is associated with inferior childhood cancer survival being ubiquitous in LMIC and common in HIC (Gupta et al., 2014). Research (not specific to childhood cancer) conducted by the WHO Regional Office for Europe has shown that in general, catastrophic health spending, defined as out-of-pocket payments that exceed 40% of a household's capacity to pay for health care, is consistently heavily concentrated among the poorest consumption quintile. Households with catastrophic spending are slightly more heavily concentrated among the poorest quintile in countries where the overall incidence of catastrophic health spending is low (Thomson et al., 2019).

In addition, the socioeconomic status of the child's family is understood to be a significant factor in decisions to abandon treatment for childhood cancer in LMIC. A survey of physicians in 101 countries involved in the care of children with cancer found that in LMIC, socioeconomic factors such as families' low socioeconomic status, low education and long travel times were most influential in increasing the risk of treatment abandonment. By contrast, in both LMIC and HIC, treatment-related considerations such as preferences for complementary and alternative medicines and concerns about treatment adverse effects and toxicity were perceived to play an important role in treatment abandonment decisions (Friedrich et al., 2016).

Risks for treatment abandonment in Uzbekistan

Treatment abandonment is still a potential risk in the WHO European Region. Clinicians in Uzbekistan spoke of parents having refused chemotherapy in the past when clinics had insufficient medicines, meaning parents had to source drugs themselves. In addition, parents sometimes sought non-traditional treatments.

Thankfully, the provision of medicines in Uzbekistan has improved significantly in recent years and there are now sponsors, foundations and volunteers who are often able to help, meaning cases of treatment abandonment due to lack of funds have significantly decreased.

Due to insufficient funds, however, treatments such as bone marrow transplantation, chimeric antigen receptor T-cell therapy and some expensive targeted drugs are still not available in the country.

Source: reproduced with permission of the Research Institute of Haematology and Blood Transfusion, Tashkent, Uzbekistan.

4.3 Geographic causes of inequalities and the urban/rural divide

The WHO European Region comprises a diverse range of countries, with marked differences in population density, degree of urbanization, topography and quality and extensiveness of transport infrastructure, coupled with differences in organization of, and access to, health-care services. These factors can interact with health system design.

For instance, in countries where children's cancer services are centralized in a small number of specialist facilities, childhood cancer patients living outside major cities face far greater challenges in accessing care than peers whose homes are in urban centres, with families with more financial resources living outside major cities being better able than less well-off families to pay travel costs to access specialist facilities in urban centres. Telemedicine is a potential route to addressing some of these challenges.

Where services are dispersed across multiple centres, however, there can be insufficient expert staff, leading to a lower standard of care (WHO Regional Office for Europe, 2021). Access to clinical trials can also vary within countries, depending on whether cancer centres are participating in collaborative clinical study groups.

Some countries within the Region (such as Germany, France, Italy and the United Kingdom) have developed so-called hub and spoke models to provide children's cancer care. Under this approach, a limited number of specialist hubs provide diagnostics, risk-stratified treatment decisions and complex treatments, as well as specialist treatments such as complex surgery, high-precision radiotherapy and high-dose chemotherapy in some cases. They work closely with local centres closer to the patient's home, which provide less complex treatments such as simple chemotherapy and components of supportive care, alongside monitoring. Only a limited number of centres in the Region offer this higher expertise, and these models are more relevant to large countries with potentially greater travel distances.

Another focal point that requires further improvement is interdisciplinary and intradisciplinary collaboration. These are not complete in some health systems, where health-care professionals struggle to work coherently across specialties and liaise with peers. Such behaviours can be reinforced by hierarchical structures and can act as a barrier to patients benefiting from a wider range of expertise.

ERN PaedCan cooperates with the SIOPE Clinical Research Council, which includes all European clinical trial groups, in pursuing its mission to provide the best possible state-of-the-art diagnosis, treatment, care and research protocols for children and adolescents with cancer no matter where they live in the EU. It represents a pioneering model to counter inequalities between countries and regions (Couespel & Price, 2020; Joint Action on Rare Cancers, 2019a).

The European Expert Paediatric Oncology Reference Network for Diagnostics and Treatment (ExPO-r-Net)

Supported by the European Commission, ExPO-r-Net's goals were to link pre-existing hubs of coordination in childhood cancer treatment and care, enable treatment of children and young people with cancer in a EU Member State other than the country in which they live, empower patients affected by complex and rare disease to choose and be reimbursed by public and private health-care providers across the EU, and improve access to high-quality health care for all young people and children with cancer.

Under the three-year initiative, which ended in 2017, ExPO-r-Net built a roadmap to approved expert referral sites and tumour advisory boards for health-care providers across Europe, strengthened cooperation between patients, professionals and health-care authorities and adopted IT and e-health solutions that enabled information and knowledge, rather than patients, to be moved wherever possible.

Source: ExPO-r-Net (2017).

The EU Cross-border Healthcare Directive and the ERN PaedCan model aim to provide clear rules for reimbursement of cross-border care in the EU and a roadmap of specialist centres. Importantly, the ERN PaedCan emphasizes whenever possible the transfer of knowledge in a secure virtual environment rather than patient travel; this is done to minimize the burden on families and enable them to be treated according to state-of-the-art protocols in their own country. It is important that medical centres from non-EU countries should be included in such work.

Travelling for surgery in Bulgaria

In Bulgaria, an EU Member State, a child with neuroblastoma was unable to have surgery in their home country and clinicians recommended that the child should travel abroad for the operation. The child's parents started a fundraising campaign and the family travelled to Germany for treatment. The child is currently undergoing treatment in Germany and is well.

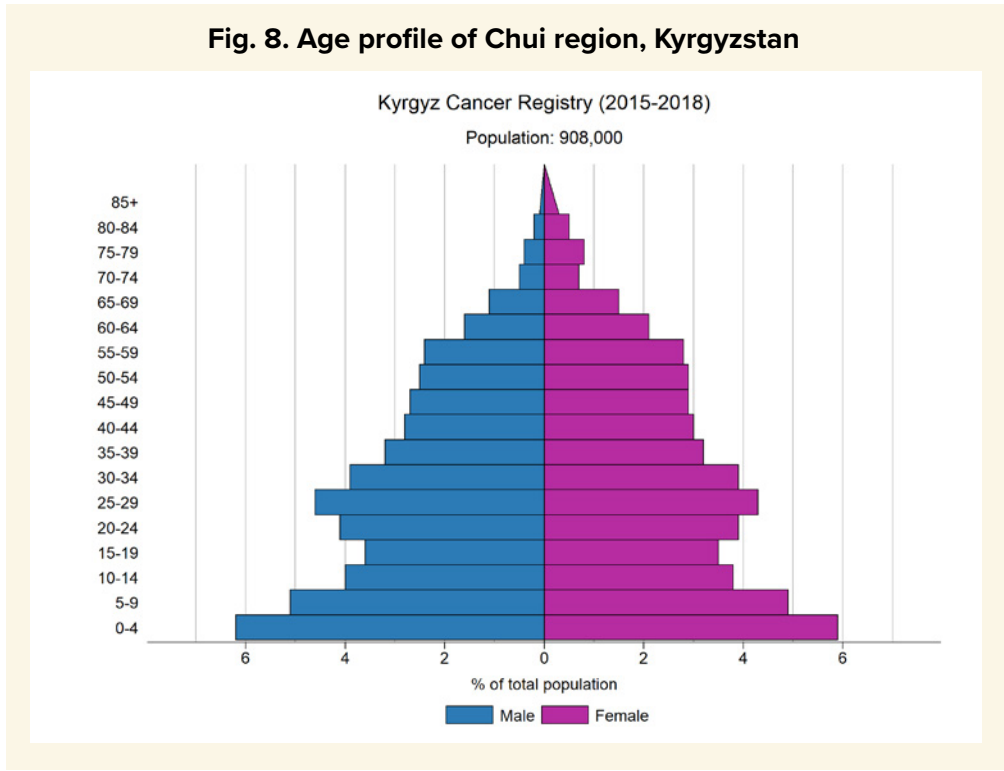
Source: reproduced with permission of Childhood Cancer International Europe.

Regional differences in survival rates nevertheless can still be observed in individual countries in the European Region. Analysis by the United Kingdom’s four public health bodies found regional differences in survival rates for childhood and teenage/ young adult CNS tumours and for teenage and young adult leukaemias, with higher survival in Wales than in the rest of the United Kingdom (Public Health England et al., 2021).

Childhood cancer in rural Kyrgyzstan

The Chui region of Kyrgyzstan is a rural area in the north of the country with a population of 896 200 people, 82% of whom live in rural areas. The population is young, with a large proportion of 0–4 and 5–9-year-olds (Fig. 8).

Fig. 8. Age profile of Chui region, Kyrgyzstan



Source: Kyrgyz Republic Scientific and Production Centre for Preventive Medicine of the Ministry of the Health of the Kyrgyz Republic.

Analysis of childhood cancer cases in the Chui region shows that children with cancer in the region are more likely to live in rural areas. However, children from areas closer to the capital city, Bishkek, where all diagnostic facilities are concentrated and where treatment is provided, are more likely to come for treatment. In the Chui region, only palliative care services are available (Table 6).

continues overleaf

Childhood cancer in rural Kyrgyzstan (contd)

Table 6. Proportion of childhood cancer patients living in urban and rural areas in each age group, Chui region, Kyrgyzstan

	Ages (years)							
	0–4		5–9		10–14		15–19	
	Urban	Rural	Urban	Rural	Urban	Rural	Urban	Rural
Percentage	21.40	78.50	28.50	71.40	12.50	87.50	20	80

Source: Kyrgyz Republic Scientific and Production Centre for Preventive Medicine of the Ministry of the Health of the Kyrgyz Republic.

Children in the Chui region also experience substantial delays between diagnosis of their cancer and first treatment (Table 7). These delays have been attributed to economic factors, as the state does not cover most of the cost of diagnosis and treatment. There is also the stigma that cancer is incurable. In a significant number of cases, no treatment is recorded, as a patient may have received treatment abroad or not received any treatment at all.

Table 7. Average number of days from diagnosis to first treatment, childhood cancer patients, Chui region, Kyrgyzstan

	Ages (years)			
	0–4	5–9	10–14	15–19
Days (average from diagnosis to first treatment)	146	96	165	141
No date about treatment (percentage)	42	34	25	40

Source: Kyrgyz Republic Scientific and Production Centre for Preventive Medicine of the Ministry of the Health of the Kyrgyz Republic.

A survey of parents and guardians of children with oncological diseases in the Russian Federation found that while more than a third of people surveyed (67.4%) had refused treatment due to an unfavourable prognosis, almost a quarter (21.9%) had been unable to pay for travel to the place of treatment (Rykov et al., 2020).

Where families face long journeys to access care, charitable organizations sometimes provide free or subsidized hotel accommodation near to specialized children's hospital facilities. Availability of this type of support is not universal, however. For instance, the global charity Ronald McDonald House has a presence in 27 of the 53 WHO European Region countries according to its website, but its local chapters tend to be in northern, western and southern European countries, with more patchy coverage in Balkan and Baltic countries and a more limited presence still in countries of the Commonwealth of Independent States (Ronald McDonald House Charities, 2022). Parents' associations in Childhood Cancer International Europe member

countries provide free accommodation for patients and their parents in parents' houses located near hospitals. This kind of opportunity is available in Bosnia and Herzegovina, France, Germany, Portugal, Serbia, Spain and many other countries.

4.4 Other inequalities

In addition to the factors described above, other factors affect the ability of different groups of children to access and benefit from care. Migrants and refugees face specific challenges when using health services in their new countries. These challenges can sometimes span multiple generations.

Some effects have also been observed in relation to familial structure, although the evidence is conflicting and inconclusive. Cultural, religious and ethical concerns can also affect the ability of patients and families to access care.

4.4.1 Migrants and underserved groups

There are relatively few data available regarding childhood cancer in migrant groups, particularly in relation to differences in access to care between documented and undocumented migrants. Children of international migrants tend to use primary care and oral health services less than non-migrants, and use emergency rooms and hospitals more frequently (Markkula et al., 2018). Research into migrants' use of health care in Germany shows they use specialist care, medication, therapist consultations and counselling, rehabilitation and disease prevention such as early cancer detection, prevention programmes for children and oral health check-ups less than non-migrants. This is particularly the case for international (first-generation) migrants and for children whose parents are both migrants, migrant children and adolescents, and migrant women.

“We treat a high number of children with a migrant background and malignant diseases in Germany. The cultural, religious and social differences, the different attitudes towards life and death, the often traumatic experiences these children have had during flight and displacement are a constant challenge for the entire treatment team. Thanks to the German social system, we have never experienced serious restrictions and have also been able to carry out extremely demanding, cost-intensive therapy modalities, including all stem cell transplantation procedures or gene therapy procedures.”

Arndt Borkhardt,
Director of the Clinic for Paediatric Oncology, Haematology and Clinical
Immunology, Heinrich Heine University, Düsseldorf, Germany.

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Inequalities in service use cannot be explained by socioeconomic status, with authors suggesting they could instead be due to differences in need, preferences, information, language and formal access barriers such as charges, waiting times, travel distances or lost earnings (Klein & von dem Knesebeck, 2018).

“When arriving in an asylum centre in Switzerland, children will be seen by a team of nurses with their parents and a translator to ensure that there is no urgent medical condition. If there is, they will be seen in an emergency department in a hospital. If there is a known medical condition that needs a prompt referral to a specialist, it will be done as well.

“If the child is known to be in a good health, they will be referred to the HEL [hôpital de l’enfance, which is the general hospital for children in Lausanne]. There they will be seen by a paediatrician to start medical follow-up and vaccination catch-up.

“The paediatric follow-up is the same as for Swiss children, but in this clinic, there are paid translators and social workers as well. All medical bills will be paid by health insurance that is automatically given to every asylum seeker’s family. In the first appointment, a full blood count will be performed to rule out any blood diseases like anaemia and a Mantoux or [tuberculosis] stop will also be done. If the paediatrician considers a need to refer the patient to a specialist, it will be done.

“Dental care is not paid by insurance in Switzerland, so if the child needs treatment, social workers will have to find funds for this. On top of the physical follow up, there is also a psychological follow-up that is offered to the patient and their family if needed.

“Children who are refused the right to stay in Switzerland after their situation was evaluated by the Swiss confederation won’t have insurance. For them, only necessary treatment will be undertaken. I am almost sure that a cancer treatment is considered as one of these.”

**Caroline Maendly,
Paediatric and Adolescent Medicine, CHUV Pédiatrie,
Lausanne, Switzerland.**

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In the specific case of treatment for childhood cancer, being a Turkish migrant or a child of Turkish migrants in Germany has been found to have no bearing on the effect of childhood cancer therapies in the country, possibly in part because of the inclusion of more than 95% of all childhood cancer cases in standardized treatment protocols (Spix et al., 2008).

By contrast, and despite equal access to public health care, Finnish paediatric cancer patients with a foreign background or whose parents are migrants had higher five-year mortality compared to those born in Finland and with non-migrant parents. Cancer survival in the five-year follow-up was higher if the mother or father was born in Finland. Authors suggest cultural difficulties, linguistic obstacles and difficulties in navigating the health system may contribute, along with genetic and biologic factors (Kyrönlaht et al., 2020).

Some parallels can be found with studies of childhood cancer incidence and mortality in indigenous children in HIC such as Australia, New Zealand and the United States. Indigenous children have been found to have similar or lower incidences of cancers and distributions of cancer type to non-indigenous children in their own countries but have lower five-year survival rates in some studies. Problems also exist with recording indigenous status in cancer and death registries, which might lead to “considerable underestimation of cancer incidence and mortality rates and biased survival rates” (Valery & McBride, 2020).

Roma people and some other traveller communities are known to experience barriers to accessing health care. These include lacking the correct documentation to register with health-care systems and providers, experiencing discrimination when accessing and using services, lack of cultural awareness on the part of health-care providers, linguistic and health literacy barriers, and economic barriers relating to health-care costs (where applicable) and travelling to appointments. Research has identified some specific sensitivities around palliative care and cancer treatment, leading to a suggestion that people from some traveller communities may avoid health care because of so-called fatalism, although such interpretations have been questioned (McFadden et al., 2018).

4.4.2 Familial structure

Several studies have suggested an association between number of siblings and position in the family and childhood cancer survival, but the picture in relation to this characteristic is complex and inconclusive.

A Danish study, for instance, found that having biological siblings and increasing birth order were associated with reduced survival from ALL and AML, with the strongest association observed in relation to AML. Children with older parents showed a tendency toward inferior ALL survival, while young maternal age was related to poor survival for AML. Based on smaller numbers, a trend toward poorer survival from non-Hodgkin lymphoma was observed for children having siblings and for children of younger parents (Erdmann et al., 2016). A Swedish study into

survival from childhood leukaemia, however, found a tendency towards better ALL survival among children with one or more social siblings, though this mainly was limited to children with low-risk profiles. An indication of better AML survival among children with siblings was also seen, but this diminished after adjusting for birth order (Mogensen et al., 2021). A Greek study found that children whose parents were married experienced better ALL outcomes (Sergentanis et al., 2013).

4.4.3 Cultural, religious and ethical causes of inequalities

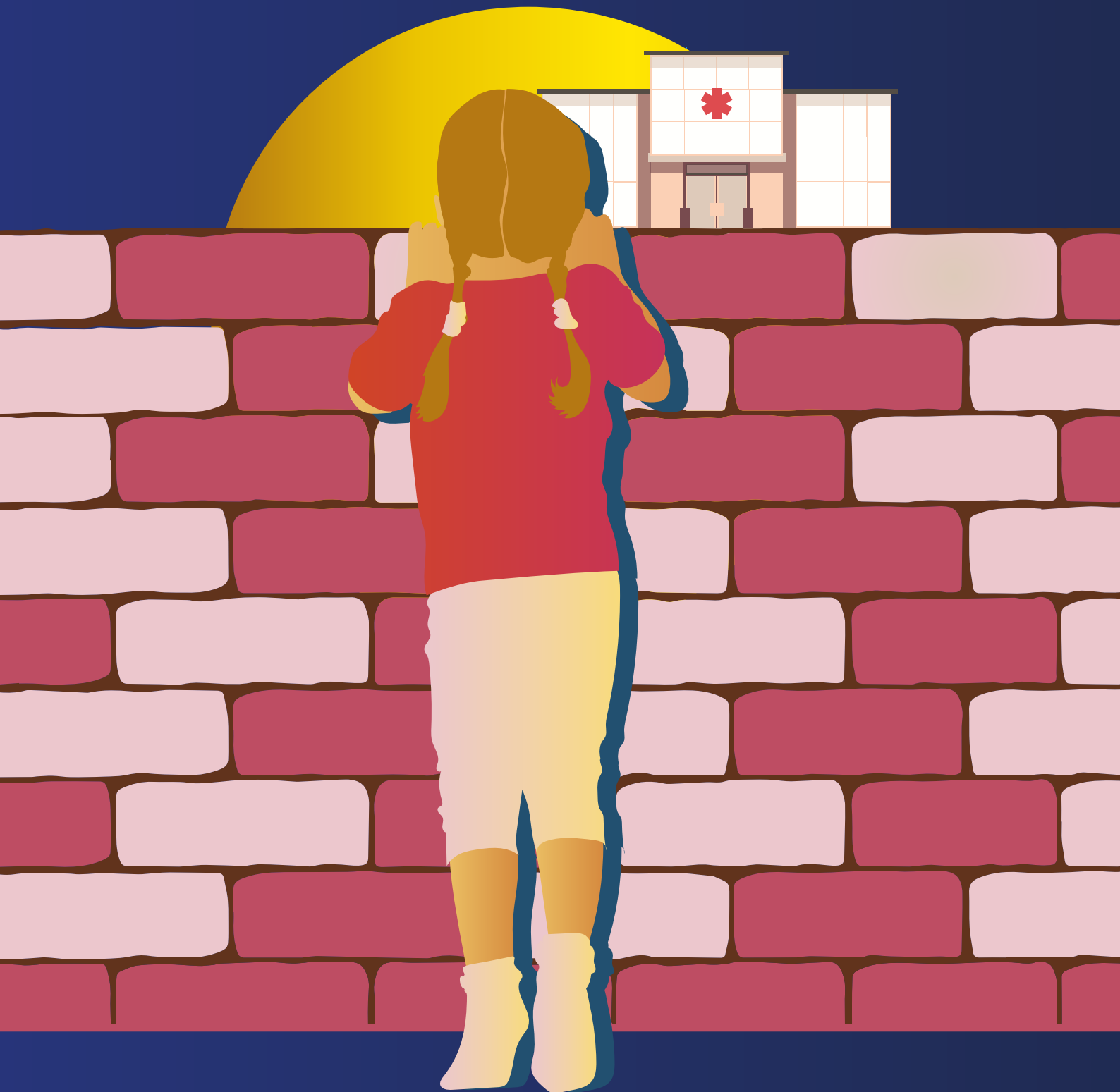
Cancer stigma in some cultures can limit the ability of patients and their families to seek social support. Providing access to sources of support such as talking with other affected families has been proposed as a potential solution to this problem. Where cancer is associated with guilt, self-blame and stigma, failing to work with families to determine mutually agreed approaches for medical discussions can undermine educational efforts, inadvertently undermine the family and may inhibit collaboration between the family and the medical team (Gray et al., 2014).

4.4.5 Age of the patient

The age of the patient seems to have a bearing on outcomes across multiple cancer types (see, for example, Gatta et al. (2013), Stark et al. (2015) and Alken et al. (2020)), but this is likely in large part to be a biological rather than a sociological factor. Survival trends for teenagers and young adults with cancer nevertheless can often vary significantly from patterns for younger children and adults. Research into survival of teenagers and young adults with cancer in the United Kingdom between 1992 and 2006 found an improving trend, with five-year survival from all cancers increasing from 75.5% in 1992–1996 to 82.2% in 2002–2006. Statistically significant improvements were seen for all disease groups except osteosarcoma, rhabdomyosarcoma, non-gonadal and ovarian germ cell tumours and ovarian and thyroid carcinomas (O'Hara et al., 2015).

5

Childhood cancer as a driver of inequalities



KEY POINTS

- A childhood cancer diagnosis can lead to significant short- and long-term inequalities in the life of the child and the entire family.
- Somatic effects vary depending on the child's age, sex, cancer type and treatment, but can include secondary cancers, cardiovascular late effects and chronic conditions, decreased height, problems with adaptive functioning, lung problems and fertility problems.
- Childhood cancer patients sometimes are not sufficiently well informed about their treatment history on reaching adulthood, which can affect their ability to access appropriate follow-up care.
- Transition between children's and adults' services is known to be a critical point for childhood cancer survivors and it can be challenging to find the right time to initiate the transition process.
- While post-traumatic stress is not significantly more prevalent among childhood cancer survivors than the general population, a substantial proportion experience this in later life, with females being more likely to report symptoms than males.
- Research suggests survivors of childhood cancer can have worse health-related quality of life than the general population, both in childhood and adulthood.
- Children with cancer may experience a wide range of developmental vulnerabilities in physical health and well-being and lower academic achievement than peers without cancer. They may also be less likely in some cases to achieve educational milestones.
- Childhood cancer survivors have been found to face greater difficulty in affording required health care and meeting high out-of-pocket medical expenses. Problems in obtaining medical insurance lead to more frequent reliance on government insurance.
- When a child is diagnosed with cancer, the immediate family can face financial difficulties and experience poorer quality of life in terms of their own physical and mental health and well-being and in their social relationships – this effect can extend to grandparents.



child's cancer diagnosis can be a cause of social inequalities beyond the period of acute illness in the life of a child who survives cancer. The impacts can be deep and wide-ranging, including somatic late effects and effects on the well-being, education and career prospects of the child and the well-being and socioeconomic conditions of the wider family.

In some cases, these effects can endure beyond the period of acute illness and into the childhood cancer survivor's later life, with somatic late effects such as increased

risk of long-term conditions and an elevated risk of second cancers. This has led oncologists to call for an expanded focus on research to reduce acute, chronic and late-onset toxicities, particularly morbidity that can directly or indirectly affect the risk of subsequent premature mortality. They advocate implementing precision medicine approaches to identify high-risk patients and preventable deaths and designing or testing interventions for prevention and early detection of chronic or late-onset morbidity associated with premature mortality (Williams et al., 2021).

Further social and socioeconomic impacts affecting cancer survivors in adult life have been identified, with some survivors reporting difficulties in accessing health care or maintaining secure employment. Mental health problems such as post-traumatic stress syndromes can affect some survivors in later life and may also affect their parents' risk of psychiatric disorders and mental health issues.



NAVIGATING CHALLENGES CAN BE MADE DIFFICULT IF A CHILDHOOD CANCER SURVIVOR HAS AN INCOMPLETE UNDERSTANDING OF THE TREATMENT THEY RECEIVED



5.1 Somatic late effects in children with cancer

Childhood cancer survivors may experience a wide range of somatic late effects. These can vary depending on cancer type, age at diagnosis, sex and particularly the nature and intensity of the treatment the survivor has received. Examples include chronic conditions such as diabetes, decreased height after cranial or spinal radiation therapy and problems with adaptive functioning, lung problems relating to radiotherapy or chemotherapy, second cancers, cardiovascular late effects and impacts on both male and female fertility. Navigating these challenges can be made more difficult if a childhood cancer survivor has an incomplete understanding of treatment they received at an early age, or if they have experienced a disconnect in their care during the process of transitioning from children's to adults' services, or at another point.

5.1.1 Risk of somatic late effects

Survivors of childhood cancer can experience to varying degrees a wide range of adverse health outcomes resulting from previous treatment exposures that can affect almost any organ or body system. Multiple studies have found effects

ranging from higher risk of chronic health conditions, including severe/disabling, life-threatening or fatal conditions, evidence of consistently elevated risks of hospital contacts or visits to physicians for somatic diseases in a lifelong perspective, and increased likelihood of hospitalization and outpatient visits (Erdmann et al., 2020b).

Knowledge about past disease, treatment and possible late effects has been found to be low in childhood cancer survivors. Respondents to a survey-based study in the Netherlands into demand for a website resource on late effects found that the majority saw the need for late effects information as a high priority (Knijnenburg et al., 2013).

5.1.2 Development and cognitive skills

Decreased growth in height is common in children with cancer during treatment, but most are able to experience catch-up growth after they complete therapy (Landier et al., 2015).

Problems with adaptive functioning have been documented in multiple studies involving survivors of paediatric brain tumour (Puhr et al., 2021a), with late effects known to include specific deficits in core functions of attention, working memory and processing speed (Rey-Casserly & Diver, 2019).

5.1.3 Long-term conditions

Analysis of cancer registry data in Nordic countries has identified an increased risk of diabetes mellitus for survivors of Wilms tumour, leukaemia, CNS neoplasms, germ cell neoplasms, malignant bone tumours and Hodgkin lymphoma. The risk for type 2 diabetes mellitus was slightly higher than for type 1 (Sällfors Holmqvist et al., 2014).

Childhood brain tumour survivors treated with radiotherapy experienced late consequences as young adults typically associated with ageing, with a prevalence of cerebrovascular disease, small and large vessel disease of 52%, 38% and 16% respectively. Ischaemic infarcts or transient ischaemic attacks were diagnosed in 11% of the survivors, lacunar infarcts in 10% and cerebral haemorrhage in 3%. White matter lesions were noted in 49%. Survivors had lower cognitive performance in all neuropsychological domains than controls (Remes, 2019).

Although refined radiation therapy techniques have resulted in decreased pulmonary toxicity, patients who have received pulmonary radiation during childhood remain at risk of declining pulmonary function over time. Some chemotherapy drugs are also associated with lung damage, and pulmonary toxicity may be increased when combined with radiation (Landier et al., 2015). Cancer survivors experience a sixfold increased risk of subsequent malignant neoplasms that are histologically distinct from the primary malignancy when compared with an age-matched and sex-matched general population (Landier et al., 2015). Compared with individuals without a prior cancer diagnosis, survivors of childhood cancer with a second primary malignancy have been found to experience inferior



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outcomes (Brown et al., 2019). Female survivors of childhood cancer have a high risk of subsequent breast cancer, and mortality after breast cancer has been observed to be higher in childhood cancer survivors than in women with de novo breast cancer. Authors state this increased mortality reflects the burden of comorbidity and highlights the need for risk-reducing interventions (Moskowitz et al., 2019).

5.1.4 Fertility

Fertility problems are potential adverse side-effects of cancer treatment. Limited data are available on the impact of chemotherapy exposure before puberty in males (Delessard et al., 2020), but it is known that abnormalities of both germ cell and gonadal endocrine function can result from exposure to chemotherapy, radiation or surgery in male cancer survivors (Landier et al., 2015).

Two types of ovarian failure have been described in female childhood cancer survivors: acute, which occurs during or shortly after completion of treatment; and premature, when a female survivor experiences menopause before age 40 (Landier et al., 2015).

The perceived impact of potential or confirmed infertility on romantic relationships of adult survivors of childhood cancer has been found to vary across individuals and time, its presence typically depending on life circumstances (Lehmann et al., 2019).

“When friends told me that they had decided to have a baby and asked me whether I want to have children in future, I found myself answering ‘I don’t know’. Because I don’t know whether I can, since the only thing I am aware of is that it might be difficult due to treatments that may have damaged my reproductive system. At the clinic they’ve told me that, regarding my difficult situation, I should hurry up if I really wish to have my own children. Pressure is present, but even then, I may worry about the chance that my hypothetical future child might suffer from some sort of impairment due to my cancer history. Maybe it would have been easier to think and talk about having children if I had received better education about my fertility throughout treatment and follow-up care.”

Austrian childhood cancer survivor

Source: reproduced with permission of Childhood Cancer International Europe.

5.1.5 Attitudes towards long-term follow-up care

Follow-up care varies greatly within the Region, but a study into attitudes of childhood cancer survivors in the United Kingdom about long-term care found that the majority were satisfied with the care they received and felt it was important to attend. Some, however, were not well informed about their cancer treatment history, the purpose for attending the clinic or the risk of late effects. Barriers associated with long-term follow-up included provision of information, lack of interpersonal relationships, and practical and logistic challenges. These barriers can be addressed through better provision of written and verbal information, use of care plans to ensure survivors know their cancer history, risk of late effects and the purpose of long-term follow-up care at transition to adult services and beyond, enhanced choice and flexibility and use of risk-stratified pathways to encourage supported self-management (Knighting et al., 2020).

Participants in an interview-based study into unmet needs of childhood cancer survivors relating to their long-term survivorship found that the key themes were lack of psychosocial support, lack of collaboration and decentralization of care, the feeling of “starting from zero” and the need for centralized, specialized and individualized services. The findings revealed a demand for integrating psychosocial support in long-term follow-up care and a strong need for personalized, centralized and interdisciplinary long-term follow-up care (Hendriks et al., 2021a).

An interview-based study with 21 adolescent and young adult survivors of childhood cancer aged between 14 and 25 in Belgium found that the survivors did not feel

their cancer experience dominated their current daily life, yet it had an important impact on their functioning (Belpame et al., 2019).

Transition between children's and adults' services is known to be a critical period for childhood cancer survivors, and it can be challenging to find the right time to initiate the transition process. Survivor-related factors such as level of personal responsibility concerning health or knowledge of long-term effects can influence transition readiness, meaning a proper assessment of an individual's readiness to transition is necessary. In a Swiss study, tools such as the Cancer Worry Scale and the Self-management Skill Scale were found to be helpful in this regard when used longitudinally. The tools also enabled staff to individualize the transition process for childhood cancer survivors (Otth et al., 2021).

Austria, Belgium, Germany, Italy, Lithuania and Spain currently are piloting a survivorship passport for childhood cancer survivors as part of a European scheme to make patient information more easily available to survivors and their clinicians. The passport provides instant access to the medical history of patients who have completed cancer treatment, making survivors and health-care professionals aware of potential risks or late effects stemming from the previous disease and treatment received. The passport also stores clinical data to facilitate monitoring and research and offer recommendations for appropriate follow-up depending on individual risk factors. It is accessed via a dedicated secure website and mobile phone app.



SURVIVORS OF CHILDHOOD CANCER ARE AT HIGHER RISK OF ANY PSYCHIATRIC HOSPITAL CONTACT THAN THEIR SIBLINGS



5.2 Mental health and quality of life

Survivors of childhood cancer have been found to be at higher relative risk of any psychiatric hospital contact than their siblings and matched individuals, with the higher risk persisting at the age of 50 years. Survivors have also been seen to have a higher burden of recurrent psychiatric hospital contacts and had more hospital contacts for different psychiatric disorders than their siblings and matched individuals (Frederiksen et al., 2021).

While post-traumatic stress is not necessarily significantly more prevalent among childhood cancer survivors than the general population, a substantial proportion of survivors experience this in later life, with females being more likely to report

post-traumatic stress symptoms than males. Survivors are also more likely to receive antidepressants and to have a lower quality of life.

5.2.1 Post-traumatic stress

Research conducted in the Netherlands involving 500 long-term survivors of childhood cancer found that 12% of the sample had post-traumatic stress disorder (PTSD) scores in the severe range, with 20% of female survivors scoring in this range compared with 6% of male survivors. Being female, unemployed, attaining a lower level of education, diagnosis type and severe late effects or health problems were associated with post-traumatic stress symptoms. Although the proportion of survivors reporting symptoms was well within the proportions found in the general population, a substantial subset of survivors reported having PTSD symptoms (Langeveld et al., 2004).

A study of 199 children with cancer and 108 healthy acquaintance control children in the United States found that children with cancer did not report higher levels of post-traumatic stress than their healthy peers. Personality factors such as adaptive style were much more salient determinants of post-traumatic stress than health history, raising questions regarding the value of a traumatic stress model for understanding the experiences of children with cancer (Phipps et al., 2009).

In a further study from the United States, survivors of childhood cancer with post-traumatic stress symptoms were found to report significantly more psychosocial and neurocognitive late effects and were more likely to engage in variable use of health care (Crochet et al., 2019).

5.2.2 Depression

A study of a cohort of 5452 Danish children treated for cancer between 1975 and 2009 found that childhood cancer survivors were at increased risk of having antidepressants prescribed, with an excess absolute risk of antidepressant use of 2.5 per 1000 person-years, equivalent to an excess of 2.5 survivors for every 100 survivors followed for 10 years. The highest risk was among children treated with haematopoietic stem cell transplantation, and no modifying effect related to parental socioeconomic position and psychiatric disease was found (Lund et al., 2015).

5.2.3 Health-related quality of life

Research suggests adult survivors of childhood cancer can have worse health-related quality of life than the general population, both in childhood and in adulthood.

An increased risk of mental health problems among childhood cancer survivors has been detected as early as preschool age. A German study focusing on 145 children (mean age 6.6 years) with cancers other than brain tumours found young childhood cancer survivors experienced more mental health problems and slightly

worse health-related quality of life than a comparison group of children without a cancer diagnosis. This could affect their subsequent school performance and educational attainment, so it has been suggested that follow-up care for young childhood cancer survivors might include early screening for mental health problems and reasons for health-related quality-of-life deficits (Neu et al., 2021).

5.3 Impact of illness and treatment on schooling and other aspects of health and well-being

As a child begins cancer treatment, their daily routine will change, with attendance at school or nursery being disrupted because of illness or periods of hospitalization to receive treatment or due to their cancer type and other clinical factors. Research has found that children with cancer may experience a wide range of developmental vulnerabilities in physical health and well-being and lower academic achievement than peers without cancer, and are less likely in some cases to pass various educational milestones. Re-entry into education following treatment can be a positive experience for childhood cancer survivors, but may be challenging because of the impact of absences, disruption to peer relationships and the need to manage treatment side-effects and exhaustion.

These factors can contribute to longer-term socioeconomic impacts stretching into adulthood, including financial hardship and difficulties in accessing health insurance where applicable, as well as difficulties in accessing secure work and presentism for those who are working.

5.3.1 Development and educational attainment

Multiple studies have identified that children with cancer can experience developmental challenges and educational setbacks with greater frequency than healthy peers, though not all studies have shown developmental impacts to be present.

In a Swedish study, children treated for a brain tumour were found to have performed worse in Swedish, mathematics and English compared to controls and had delayed graduation to a greater extent. Children treated at a young age, especially females and children whose parents had low education, were found to be particularly at risk. There were no differences between survivors with high-grade and low-grade tumours (Lönnerblad et al., 2020). A population-based register study from Sweden encompassing 475 children born between 1988 and 1996 and diagnosed with a brain tumour before their 15th birthday explored performance in five practical and aesthetic subjects. Researchers found that the odds for failing a subject were two-to-three times higher for girls treated for a brain tumour compared with controls in all these subjects, but there were no significant differences between the boys and their controls in any subject. Paediatric brain tumour survivors had lower average grades from year nine in all five subjects; girls differed from their controls in all five subjects, while boys differed in physical education and health and music (Lönnerblad et al., 2019).



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Survivors of childhood cancer have been found to be at higher risk of not going on to further education after comprehensive school. Unemployment was uncommon, but risk for early retirement significantly increased (Ahomäki et al., 2017). CNS tumour survivors and those assumed to have received CNS-directed therapy were at increased risk of educational impairment, with a lower number of cancer survivors completing intermediate, undergraduate and graduate education compared to the cancer-free population (Ghaderi et al., 2016). Further research has found that children with any health condition requiring inpatient or outpatient care at ages 10–16 were more likely to have dropped out of schooling at age 17 and age 21 (Mikkonen et al., 2018).

It has been suggested that physical problems may cause much of the health-related unemployment seen among childhood cancer survivors. While both male and female survivors with neurocognitive deficits (primarily in task efficiencies) are at risk of unemployment, employed female survivors with neurocognitive deficits may face poor occupational outcomes more often than males (Kirchhoff et al., 2011).

5.3.2 Re-entry to school or nursery

While re-entry into formal education can be seen as a positive milestone, it is not without difficulties. Re-entry to school has been found to be very challenging for most children with cancer due to treatment side-effects, prolonged absences, disrupted peer relationships, lack of preparation and lack of communication between schools, families and health-care professionals (Martinez-Santos et al., 2021).

A study into children's process of reintegration after childhood cancer treatment in Germany found that in most cases, reintegration into nursery or schooling was organized with a gradual increase in attendance, but reintegration into leisure activities was demanding because of exhaustion from obligatory activities. Barriers and facilitators to reintegration described by parents included lack of structural and social support, health status and intrapersonal aspects. Although many children reintegrated well, the process was found to take lots of effort from both parents and children. Childhood cancer survivors and families should be supported after the end of intensive treatment to facilitate reintegration (Inhestern et al., 2020).

Research from Belgium into the experiences of childhood brain tumour survivors as they re-entered school found children were pleased to return to school despite confrontation with adverse outcomes. Four main themes emerged from the research: school performance, psychosocial well-being, support and approach, and communication and collaboration. Researchers highlighted the importance of coordinated and systematic follow-up in close collaboration with health-care providers (Vanclooster et al., 2019).

Children's experience of missing school in France

Children and their families in France report different experiences of their reintegration back into schooling. One young person, Nora, told researchers, "Before I was hospitalized in my fifth year, I had friends. When I came back to school, they didn't talk to me. They didn't approach me for fear that I would pass on my cancer. I was put aside. Yet my teacher had explained to my friends what I had and what cancer was. But the fear was stronger, so I didn't like going to school any more. I think it's important that teachers explain what cancer is when a classmate has it. Or that in secondary schools there should be volunteers from associations."

However, Vincent, a parent, said, "At my child's high school, they decided to organize a day with a psychologist and the students to talk about it. It's true that they were shocked, but it's possible to get together to work on this. The reactions are not always as bad as we imagine."

Source: Union Nationale des Associations de Parents d'Enfants Atteints de Cancer ou de Leucémie [National Union of Associations of Parents of Children with Cancer or Leukaemia] (UNAPECLE) (2013).

5.3.3 Socioeconomic effects in adulthood

Childhood cancer survivors have been found to face elevated difficulties with affording necessary health care and high out-of-pocket medical expenses, as well as encountering difficulties in obtaining insurance coverage and having to rely more frequently on government-sponsored insurance (in insurance-based health-care systems such as those found in north American countries) (Nathan et al., 2018). It has been suggested that a better understanding of the relationship between childhood cancer and insurance hardships during survivorship will inform efforts to improve long-term financial security and health outcomes for survivors (Hendriks et al., 2021b).

While some childhood cancer survivors have been able to move beyond their cancer history, others continue to face hardship, with higher levels of unemployment because of ill health or being between jobs (Kirchhoff et al., 2020). Survivors reported confusion about the opportunities and services within the social security system, with most relying on personal contacts for guidance. Survivors expressed a strong need for socioeconomic and legal support for social insurance questions, especially related to disability insurance (Hendriks et al., 2021b). Survivors in a study in the United Kingdom were found to be less likely to be working than expected, with the deficit being greatest for irradiated CNS neoplasm survivors. Overall, survivors were less likely than expected to be in managerial occupations (Frobisher et al., 2017).



WHILE SOME CHILDHOOD CANCER SURVIVORS HAVE BEEN ABLE TO MOVE BEYOND THEIR CANCER HISTORY, OTHERS CONTINUE TO FACE HARDSHIP



Survivors of childhood cancer in a Norwegian study were found to have a 4.4 times higher risk of social security benefit uptake than the cancer-free population, with survivors of malignancies of bone and connective tissue, CNS tumours and malignancies of the haematopoietic system having the highest risks (Ghaderi et al., 2013). Another Norwegian study found that a significant number of physically well functioning adult survivors of paediatric brain tumour reported having received educational adjustments and substantial government benefits compared with controls, and significantly more survivors than controls were currently not engaged in regular employment or training. Factors most strongly associated with poor social outcomes were self-reported executive dysfunction, difficulties with adaptive functioning and fatigue (Puhr et al., 2021b).

Researchers also found that survivors of cancer in Norway who had received their diagnosis before the age of 25 had an increased risk of being economically dependent and unemployed. This was most pronounced in female survivors. Researchers noticed only small differences in income or representation in higher skilled occupations for most employed survivors compared with the noncancer group (Gunnes et al., 2016).

A French study into employment among young adult survivors of childhood leukaemia in the labour market found that although fewer survivors than expected were seeking a job, the number in unstable employment was significantly higher than expected. Younger age and greater frequency of late effects were risk factors for unstable employment, leading the authors to recommend the development of a strategy to identify better particular subgroups of survivors at greatest risk of difficulties in their professional achievement (Berbis et al., 2016).

When data from 1283 adult survivors of childhood cancer in the Netherlands were analysed alongside data from 25 082 reference cases, childhood cancer survivors had higher odds of not being married, not living independently and using social benefits more than reference cases. Radiotherapy to head and/or neck and an original CNS tumour diagnosis negatively influenced all social outcomes examined in childhood cancer survivors (Font-Gonzalez, 2016).

A recent systematic review found that survivors of CNS tumours, those treated with cranial radiotherapy and those diagnosed at a younger age independent of cancer type were determinants of particular adverse socioeconomic outcomes. Targeted follow-up interventions and support strategies that address socioeconomic difficulties some childhood cancer survivors face are needed, as are strategies for somatic and psychiatric late effects (Frederiksen et al., 2019).

These findings are echoed in the global literature. Research conducted in the United States found that a substantial proportion of adult survivors of childhood cancer experienced financial hardship, with vulnerable socioeconomic status and late effects being associated with hardship. Survivors with financial hardship had an increased risk of symptom prevalence and impaired health-related quality of life (Huang et al., 2019).

As of October 2021, a Right to be Forgotten law for cancer survivors has been implemented in France, Belgium, Luxembourg, the Netherlands and Portugal (Dumas et al., 2017). This means that cancer survivors will be better able to live their lives without facing enduring disadvantage because of their previous diagnosis. The provisions of the Right to be Forgotten legislation generally state that in the context of insurance or loan contracts, “the period beyond which no medical information relating to cancer can be collected by insurance companies may not exceed 10 years after the end of treatment” (European Cancer Patient Coalition, 2022). For cancers occurring in childhood, this is reduced to five years after the end of treatment. In addition, there is an exception list for cancers that have an excellent prognosis,

where there are shorter waiting periods before the Right to be Forgotten comes into force (European Cancer Patient Coalition, 2022).

5.4 Effect of the child's disease on the family (social, economic and mental health)

When a child is diagnosed with cancer, the immediate family can face financial difficulties relating to the impact on household funds of providing care for the child. They may also experience worsened quality of life in terms of their physical and mental health and well-being and social relationships. The impact of the illness can also reach members of the wider family, such as grandparents.

5.4.1 Financial costs to families of a child's illness

There is a lack of published research into the costs of illness to parents of children diagnosed with cancer, but costs vary substantially depending on the country of residence. A systematic scoping review conducted in 2018 found only 25 eligible studies published over a period of six years, of which seven came from countries in the WHO European Region. Four of these studies were from Sweden, with one each from Denmark, Portugal and Switzerland. Studies included in the review tended to use person-reported outcome measures, but these varied widely across studies, making comparison difficult. The authors nevertheless concluded that across the 25 studies, results showed that the costs of childhood cancer to parents and families were substantial and, for some, highly unfair. Major contributors to direct and indirect costs included treatment-related travel, meals and lodging, and parental work disruption to provide caregiving (Judge Santacroce et al., 2018).

Financial difficulties experienced by families of childhood cancer patients in Kazakhstan

Families of a child with cancer often face financial difficulties. As children from low-income families come to cancer facilities in Kazakhstan, one of the two parents generally has to give up a full-time job because he or she has to stay at home or in hospital to care for the child.

Often, parents complain about financial difficulties. Some of them do not even have the money to renew their seasonal wardrobe. Volunteers help as much as they can.

After the treatment has ended, it is very difficult for the parents of the patients to find new employment or return to their previous jobs. Many families have to live on their children's disability allowance.

Source: reproduced with permission of the Kazakh Institute of Oncology and Radiology.

Financial difficulties experienced by families of childhood cancer patients in France

Families of childhood cancer patients in France report additional costs that include covering care for siblings and travelling. Some families can rely on relatives and friends for this, but others cannot. One parent stated, “The parents’ houses near the hospital are very good, but there are not enough of them. Financially, you can’t always afford a room in a hotel. We are farmers. For the first three chemotherapy sessions, it was heartbreaking to leave my child.”

These effects can extend beyond the death of a child. Another parent said, “After the death of our son, we decided to change our life and buy a house, but we had difficulty in getting a loan because my wife had been off work for a long time to look after our son.”

Parents’ associations in France have had some success in achieving a legal entitlement to provide leave for parents of children with cancer, along with a limited financial allowance. Many parents nevertheless have to give up work to care for ill children.

Source: Union Nationale des Associations de Parents d’Enfants Atteints de Cancer ou de Leucémie [National Union of Associations of Parents of Children with Cancer or Leukaemia] (UNAPECLE) (2013)

5.4.2 Parents’ quality of life

The impact of a child’s cancer diagnosis on the parents’ quality of life has been more widely researched, with studies focusing on impacts related to specific cancer types and variables affecting parents that could make them more susceptible to decreased quality of life.

Research has found that both mothers and siblings experience elevated and prolonged need for mental health-related health care compared to the general population (van Warmerdam et al., 2019a), and parents of children with cancer have a higher prevalence of anxiety, depression and PTSD compared with population controls. Reported prevalence is highly variable, however, hampering any conclusive findings on absolute prevalence (van Warmerdam et al., 2019b). Compared with parents of cancer-free children, mothers of children with cancer have been found to be at increased risk of hospital contacts for any psychiatric disorder, whereas no elevated risk has been seen in fathers (Mader et al., 2021).

The amount of time that has lapsed since diagnosis appears to play a role in parents’ quality of life. For parents within 12 months of the child’s diagnosis, for instance,

family-centred service provision, caregiver strain and social support explained 50% of the variation in physical health. For those whose child had been diagnosed more than 12 months previously, caregiving strain was the only factor with a direct relationship between parental psychosocial and physical health, accounting for 66% and 55% of variance respectively (Klassen et al., 2010). Long after a child's leukaemia diagnosis, parents reported lower scores in physical health and social relationship domains than the reference population. By contrast, scores for psychological health were significantly higher (Vercasson et al., 2020).

Parental distress has been found to increase around diagnosis, then returns to normal levels. Post-traumatic symptoms are common, and distress may impair vulnerable parents and impact a child's coping and adjustment. This has led researchers to recommend that “parents and caregivers of children with cancer should have early and ongoing assessment of their mental health needs, [and] access to appropriate interventions for parents and caregivers should be facilitated to optimize parent, child and family wellbeing”, with standard systematic screening for psychosocial risk (Kearney et al., 2015).



PARENTAL DISTRESS HAS BEEN FOUND TO INCREASE AROUND DIAGNOSIS, THEN RETURNS TO NORMAL LEVELS



For both parents, variance on most domains of health-related quality of life is commonly explained by psychosocial variables such as distress, emotional problems and lack of perceived social support. Mothers can experience poorer quality of life than fathers when a child is diagnosed with cancer (Rensen et al., 2019). This difference between the genders was also seen in an earlier study into the occurrence of cancer-related PTSD among parents of children on cancer treatment. It found that 33% more mothers than fathers scored as potential cases of acute stress disorder at one week after diagnosis, with 28% more as potential cases at PTSD two months after diagnosis and 22% more four months after diagnosis (Pöder et al., 2007).

However, a systematic review focusing on the experiences of fathers of children with a life-limiting condition identified specific themes affecting male parents, including fathers' experiences of uncertainty and shock around the time of diagnosis, accounts of a so-called new normal, difficulties discussing their emotions and

forming relationships with (and seeking support from) professionals, and working fathers' role conflicts. The authors recommend that health-care professionals need to recognize individual family dynamics and the evolving role of the father. They add that fathers' responses are not widely understood and research that directly addresses their own well-being is warranted (Fisher et al., 2021).

5.4.3 Impacts on the wider family

The impact of a child's cancer diagnosis can stretch beyond the immediate family. An Australian study into differences in perceived family functioning among grandparents of a child with cancer and grandparents of healthy children found grandparents of a child with cancer reported poorer family functioning than those with healthy grandchildren. Among the grandparents with a grandchild with cancer, impairments in family functioning were correlated with fewer years since diagnosis, providing care to their sick grandchild and/or siblings and living far away from the sick grandchild (Kelada et al., 2019).

Sibling well-being can also be affected when a cancer diagnosis disrupts family relationships. Older siblings can find themselves taking on caregiver roles for healthy or ill siblings and may assume other adult roles in the home. Challenges to maintaining normality and engaging in typical development activities have been reported (Abrams et al., 2016).

6

Summary





Childhood cancers encompass a wide and heterogeneous range of rare cancers defined by the age group and location in which they occur. Most are rapidly growing cancers, meaning that identifying suspected cases and referring patients to tertiary care centres for diagnosis and treatment planning quickly is important.

The age ranges classified as childhood cancer can vary depending on the country and registry providing the data. The definition often includes cancers occurring between birth and age 14, but it can extend to age 18, 19 or 21. Among different age ranges, a variety of cancer types occurs. The diagnosis and management of these groups require a multidisciplinary effort from different teams. Additionally, technology and infrastructure in some centres currently treating these patients may be suboptimal.

Significant improvements in survival have been achieved since the 1960s, but disparities persist both within the Region and globally. Factors influencing inequalities include the country in which the child lives, the institution in which they are treated, the care team, the impact on the family, the child's own response to treatment and the degree to which residual effects and secondary cancers occur.

Inequalities between countries can be observed in terms of childhood cancer incidence, mortality and survival, and in the abilities of children and families in different countries to access comprehensive health care that is free at the point of use, and differences in the social and financial support affected families can access.

Drivers of inequalities form a mixed picture, with differential levels of underdiagnosis and underreporting of childhood cancer, differences in access to (and uptake of) treatment and variation in how care is provided all playing a role. It is difficult to identify them conclusively and more research is required. In general terms, childhood cancer incidence has been increasing in WHO European Region countries in recent decades. Performance in cancer detection and treatment has been improving, with survival rates increasing, but significant discrepancies persist between countries in the Region. South-eastern European and central Asian countries in particular experience higher mortality rates than others.

Precise and timely diagnosis, introduction of targeted screening interventions in primary care (for early detection of retinoblastoma), greater uptake of recommended paediatric standardized diagnosis and treatment protocols and more emphasis on ensuring that treatment occurs in locations where there is the expertise and technology necessary for treating paediatric cancer are likely to be important in driving improvement. This final point is particularly significant for adolescents with cancer.

Significant disparities in terms of the payments individuals are expected to make for care and the availability of up-to-date and novel treatments, including drugs and nutritional supplements addressing side-effects, exist. Universal health systems,

whether provided under a national health service model or a social health insurance approach, can remove some of the financial risk associated with a childhood cancer diagnosis in the family.

Gaps in the data hinder progress in reducing inequalities in childhood cancer within countries and prevent comparisons between countries. The lack of paediatric cancer registries in some countries in the Region contributes to unclear and inaccurate survival data.

Inequalities exist within countries in the WHO European Region in terms of variations in incidence and outcome for childhood cancer. These variations are associated with different characteristics of children with cancer and their families including, but not limited to, socioeconomic conditions, social and cultural background, geographic distance from cancer facilities and the ability of families to fund care in countries where out-of-pocket payments for cancer care are required.



THE LACK OF PAEDIATRIC CANCER REGISTRIES IN SOME COUNTRIES IN THE REGION CONTRIBUTES TO UNCLEAR AND INACCURATE SURVIVAL DATA



Marginalized and seldom-reached groups such as migrants and Roma people face additional barriers when accessing care. There is also some suggestion that family size and other family conditions may play a role in generating inequality in relation to childhood cancer, although relationships in this area are less clear.

It is difficult to determine conclusively why a relationship between social and socioeconomic background and childhood cancer survival might exist, but the main underlying mechanisms for social inequalities in survival in the Region are understood to relate to access to high-quality services and education and having the competence to navigate the health-care system successfully.

In LMIC, where childhood cancer patients' families are expected to meet significant out-of-pocket costs for care, moving towards UHC would be likely to reduce financial disincentives to access treatment and provide a more efficient means of funding care for the wider population. As was the case for inequalities between countries, barriers to accessing high-quality care in different parts of a country can be reduced

by ensuring that health-care services are adequately funded and that state-of-the-art treatment protocols are used by all providers as a matter of course.

Where it has been hypothesized that inequalities stem from differential levels of empowerment among childhood cancer patients' families, there is the potential to address this through empowering children and families with lower socioeconomic status or who come from marginalized communities to make similar demands of health systems as their peers with higher levels of educational attainment or income. While the scale of this task should not be underestimated, it could potentially be achieved by clarifying entitlements under health schemes and ensuring widespread use of agreed treatment protocols.

A cancer diagnosis in childhood in itself may lead to inequalities. Inequalities between children with cancer and their peers can arise both in the short term as children undergo treatment as patients and in the longer term as survivors. Inequalities can begin immediately after diagnosis in the form of increased financial stress, reduced health and well-being and poorer quality of life for the child and their family. Immediate inequalities experienced by the child can potentially include neurocognitive impairment and increased morbidity, and educational difficulties related to illness and absence from school. These impacts will vary depending on age at diagnosis, the type of cancer and the form of treatment, and on the level of social support available to the child and their family.

Clearly, where immediate impacts endure, leading to increased risk of long-term conditions, developmental vulnerability and reduced educational attainment, there is the potential for childhood cancer survivors to endure longer-term inequalities, which can stretch into adulthood.

Adult survivors have reported financial hardship, particularly where they have vulnerable socioeconomic status and/or somatic or mental health late effects from their illness, with several studies finding evidence of lower levels than expected of employment or secure employment in adult survivors. The need to make out-of-pocket payments or arrange conditional access to health insurance schemes can exacerbate these financial challenges.

Adult survivors can also experience a range of somatic late effects depending on cancer type and the nature of the treatment they received. Managing a chronic condition or a subsequent cancer diagnosis can be challenging, particularly when the adult survivor may have imperfect knowledge of, or access to, their medical history and may have experienced fractured care when transitioning between children's and adults' services.

Fertility problems stemming from childhood cancer treatment can pose a challenge for adult survivors who wish to have a family. Researchers have identified ways in which adult survivors with a risk of being infertile can be helped to understand their chances of having healthy children and to consider the potential implications for romantic relationships.

Being able to access good follow-up care into adulthood is critically important for adult survivors of childhood cancer, who need access to high-quality information about their treatment history and clear explanations of the purpose of future treatments and medical appointments.

Care plans have been found to be beneficial for survivors, as has offering adult survivors more choice and flexibility in relation to their care and deploying risk-stratified pathways to encourage supported self-management.

The focus on physical care must not be at the expense of the psychosocial needs of this group, where needs in this area exist. While post-traumatic stress does not appear to play a significantly greater role in the lives of childhood cancer survivors than in the general public, it is still an issue for a significant number of adult survivors later in life.

Action is needed across the board to ensure that high-quality services are in place to support survivors of childhood cancer in later life. These must encompass addressing stigma, meeting long-term physical and mental health needs, countering adverse quality-of-life and social and socioeconomic consequences, and ensuring that effective legal and other services are in place to support the transition out of children's health services into adults' services. Equally important will be ensuring that research is undertaken to provide a greater understanding of the longer-term requirements of survivors in the health-care sector and beyond its parameters in terms of, for instance, survivors' educational attainment, employment and welfare support needs.

There is also evidence of higher antidepressant use, higher prevalence of psychiatric conditions in general and poorer quality of life among this group, with evidence that mental health problems and poorer quality of life may be present in very young children, with the potential for significant adverse effects in later life.

Childhood cancer survivors can experience financial hardship when their history prevents them from accessing the same health-care insurance products as people who have not experienced cancer. Some countries in the Region are implementing the Right to be Forgotten legislation to protect childhood cancer survivors who have been free from illness for specified periods.

Finally, very young children and their families may require different kinds of support so that parents are able to manage the child's ongoing needs, and that they are informed about their medical history at an appropriate point.

7

Conclusion and policy options





Although inequalities between WHO European Region countries are less pronounced than those at global level, major disparities exist between and within countries in relation to childhood cancer incidence (with probable underregistration), patients' and caregivers' experience, outcome and consequences, and mortality.

The propositions below represent positions that it is hoped all countries in the Region will aspire to achieve, but it is recognized that countries begin from different starting points and have to take different contextual factors into account. It nevertheless is hoped that the propositions are of value to decision-makers and politicians from all countries looking to target existing inequalities for children with cancer.

While eradicating differences will require long-term effort, there are some steps that can be taken now, even with small resources. Undertaking some or all of these steps will improve the situation of childhood cancer patients and families in the present. It will also help to ensure that children in all WHO European Region countries who develop cancer will be able to experience better and more equitable outcomes in future.

7.1 Reducing inequalities in childhood cancer between countries

It is suggested that countries:

- aim to provide UHC at national level for all cancer in children and, if possible, young people, whether under a national health service scheme or a national social health insurance model; as childhood cancer is rare and treatments are relatively cheap, the resources needed remain minimal;
- minimize the use of out-of-pocket payments as a means of financing treatment for childhood cancer;
- support universal access to cancer preventive public health measures that start in childhood, such as vaccination against hepatitis B and human papillomavirus;
- avoid excessive mass screening examinations for children and adults such as ultrasound screening of thyroid, abdomen and kidneys, which carry the potential harm of overdiagnosis – freed up resources could be used to further support and improve other key areas of childhood cancer early detection and treatment programmes;
- explore the causes of late diagnosis of childhood cancer by measuring delays between first symptoms, first contact with the care system, effective diagnosis and the beginning of treatment, and identifying the causes of delays, which may vary according to sex, socioeconomic status and geographic location;
- ensure that paediatric cancer evidence-based diagnosis and treatment protocols that adhere to international standards are shared widely and used wherever possible;

- ensure access to multidisciplinary treatment and care;
- ensure that the quality of care is monitored and evaluated;
- ensure that medicines on the EMLc are made available and accessible to all patients along with the appropriate level of radiotherapy technology, in accordance with WHO/IAEA technical specifications (WHO & IAEA, 2021);
- revisit the European regulatory environment to address the unmet needs of children and adolescents with cancer and bring the speed and efficiency of medicine development for this group in line with the rate of innovation observed in the adult cancer sector (for example, the EU Orphan and Paediatric Regulation);
- reinforce the importance of access to essential medicines (including medicines and nutritional supplements for treatment of side-effects of chemotherapy) for paediatric malignancies in national cancer plans or equivalent instruments guiding cancer care at national level;
- encourage greater collaboration between facilities in different countries where feasible and appropriate, particularly for complex and rare cases;
- provide social, psychological and educational support for affected families and foster the involvement of nongovernmental organizations in its provision;
- implement a right of parental leave for carers of a child with cancer;
- promote the integration of childhood cancer survivorship topics in medical education, including the dissemination of relevant guidelines on surveillance and care delivery;
- ensure that population-based cancer registries are put in place and use internationally agreed classification systems, incorporate outcome information and staging data for children's cancers based on the Toronto Childhood Cancer Stage guidelines, and regularly publish the number of cases of childhood and adolescent cancer in each country in the Region; and
- ensure steps are taken within the childhood cancer community to develop indicators to assist countries in implementing recommendations to reduce inequalities between countries and between socioeconomic groups within countries.

7.2 Reducing inequalities in childhood cancer within countries

It is suggested that countries:

- provide accommodation for families of children with cancer staying in hospital as inpatients as part of state-guaranteed benefit packages;
- support families to understand their rights to treatment and the significance of these rights, and provide them with information on how to navigate health-care systems to minimize the risk of suboptimal treatment due to information asymmetry;
- ideally, ensure that each patient and family has a so-called navigator – a nurse or social worker who is their focal point to guide them throughout diagnosis, treatment and rehabilitation and can answer their questions at any time;

- make particular efforts to ensure that marginalized and seldom-reached groups are able to access childhood cancer services as easily as the rest of the population – these efforts should extend to both documented and undocumented migrants;
- encourage health-care professionals to undertake greater collaboration between facilities within countries, in particular increasing the amount of interdisciplinary collaboration, and ensure that help is sought where needed in difficult cases;
- improve the quantity and quality of available data on the prevalence of childhood cancer among migrant and refugee groups;
- ensure recognition of early clinical trial access for children with poor prognosis as a standard of care; and
- encourage a decrease in the number of centres by region treating paediatric cancer patients and identify referral centres for more complex parts of therapies; lower complexity procedures/therapies may be administered closer to home or in less sophisticated hospitals, so patients get the best of both worlds – patients should access the expertise and technology that often are available only in larger centres for the complex part of the therapy (usually a reduced part of the whole treatment plan) and attend services closer to home for the less complex part of the treatment.

7.3 Reducing inequalities faced by survivors of childhood cancer

It is suggested that countries:

- support survivors of childhood cancer to achieve a smooth transition between children's and adults' health-care services, supported by easy access to digital medical records using approaches such as patient passport schemes;
- consider the benefits of the Right to be Forgotten legislation as a means of levelling the playing field for long-term childhood cancer survivors to enable easier access to health insurance and other financial services;
- improve physical health-care provision for adult and child survivors of childhood cancer and support survivors and their families to manage any psychological, mental, psychosocial or socioeconomic consequences of their illness and treatment;
- ensure education facilities and support for childhood cancer inpatients and for children and adolescents who are receiving care out of hospital but are too ill to attend school;
- ensure the facilitation of prospective long-term follow-up of novel therapies against childhood cancer for young people;
- collect data on long-term outcomes in national cancer or other relevant registries (according to local context), with appropriate consent procedures to foster research on the long-term health status of childhood cancer survivors; and
- empower survivors with support for nutrition, sleep, physical activity and stress management as pillars of well-being for them and their families.

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