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Trends in childhood cancer incidence in sub-Saharan Africa: Results from 25 years of cancer registration in Harare (Zimbabwe) and Kyadondo (Uganda)

Ole Stoeter[1] | Tobias Paul Seraphin[1,2] | Inam Chitsike[3] | Eric Chokunonga[4] | Joyce Balagadde Kambugu[5] | Henry Wabinga[6] | Donald Maxwell Parkin[7,8,9] | Eva Johanna Kantelhardt[1,10]

[1]Institute of Medical Epidemiology, Biometrics and Informatics, Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany

[2]Department of Gastroenterology, Hepatology and Infectious Diseases, University Hospital, Heinrich-Heine-University, Düsseldorf, Germany

[3]Department of Paediatrics and Child Health, University of Zimbabwe, Harare, Zimbabwe

[4]Zimbabwe National Cancer Registry, Harare, Zimbabwe

[5]Department of Paediatric Oncology, Uganda Cancer Institute, Kampala, Uganda

[6]Kampala Cancer Registry, Makerere University School of Medicine, Kampala, Uganda

[7]Cancer Surveillance Unit, International Agency for Research on Cancer, Lyon, France

[8]Nuffield Department of Population Health, University of Oxford, Oxford, UK

[9]African Cancer Registry Network, INCTR, Oxford, UK

[10]Department of Gynaecology, Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany

Correspondence
Eva Johanna Kantelhardt, Institute of Medical Epidemiology, Biometrics and Informatics, Martin-Luther-University Halle-Wittenberg, Magdeburgerstrasse 8, 06112 Halle (Saale), Germany.
Email: eva.kantelhardt@uk-halle.de

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Abstract

We examined trends in childhood cancer incidence in sub-Saharan Africa using data from two population-based cancer registries in Harare (Zimbabwe) and Kyadondo (Uganda) with cases classified according to the International Classification of Childhood Cancer and explored reasons for observed variations and changes. Over the whole 25-year period (1991-2015) studied, there were only small, and nonsignificant overall trends in incidence. Nevertheless, within the period, peaks in incidence occurred from 1996 to 2001 in Harare (Zimbabwe) and from 2003 to 2006 in Kyadondo (Uganda). Kaposi sarcoma and non-Hodgkin lymphoma accounted for the majority of the cases during these periods. These fluctuations in incidence rates in both registries can be linked to similar trends in the prevalence of HIV, and the availability of antiretroviral therapy. In addition, we noted that, in Harare, incidence rates dropped from 2003 to 2004 and 2007 to 2008, correlating with declines in national gross domestic product. The results indicate that the registration of childhood cancer cases in resource-poor settings is linked to the availability of diagnostic services

Abbreviations: APC, annual percentage change; ART, antiretroviral therapy; BL, Burkitt lymphoma; CI, confidence interval; DCO, death certificate only; EBV, Epstein-Barr virus; GDP, gross domestic product; IARC, International Agency for Research on Cancer; ICCC-3, International Classification of Childhood Cancer—Third Edition; ICD-O-3, International Classification of Diseases for Oncology—Third Edition; KS, Kaposi sarcoma; KSHV, Kaposi sarcoma-associated herpesvirus; MV, morphologically verified; NHL, non-Hodgkin lymphoma.

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mediated by economic developments. The findings highlight the need for specialised diagnostic and treatment programmes for childhood cancer patients as well as positive effects of HIV programmes on certain childhood cancers.

KEYWORDS

childhood cancer, incidence, population-based cancer registry, sub-Saharan Africa, trends

1 | INTRODUCTION

Worldwide, childhood cancer incidence appears to be on the rise—except for sub-Saharan Africa, where Steliarova-Foucher et al estimated that the age-standardised rate per million person years for children aged 0-14 years decreased from 81.0 (1980s) to 56.3 (2001-2010).[1] Although this estimate is based on data from six centres, some 70% of the childhood cases were from just one (South Africa). Generally, childhood cancer incidence is not expected to change considerably over time as most cases have a genetic link,[2] although certain infectious diseases, such as HIV, do affect the risk of some childhood cancers[3,4]: Two of the most common childhood cancers in sub-Saharan Africa—Burkitt lymphoma (BL) and Kaposi sarcoma (KS)—are associated with infectious agents.[4,5]

In this article, we present time trends in the incidence of childhood cancers in two populations in sub-Saharan Africa; Kyadondo (Uganda) and Harare (Zimbabwe), which are both served by high quality population-based cancer registries that have been in continuous operation for more than 25 years—the longest continuous history of cancer registration in sub-Saharan-Africa. They have contributed multiple times to "Cancer Incidence in Five Continents," which is published every 5 years by the International Agency for Research on Cancer (IARC) and comprises high-quality data from population-based registries. Their results also appear in volumes II and III of the International Incidence of Childhood Cancer, also published by IARC.[6,7] Previous work already described how the cancer profile in adults in these populations has changed over time,[8-10] but although population-based data on childhood cancer from Uganda and Zimbabwe have been published,[4,6,11] time trends in incidence have not been analysed in detail until now.

Our study presents time trends in childhood cancer incidence for Kyadondo (Uganda) and Harare (Zimbabwe) for the 25-year period 1991-2015, and discusses the possible reasons for observed variations and changes.

What's new?

These authors tracked childhood cancer rates in sub-Saharan Africa over a 25-year period, from 1991 to 2015. They analyzed data collected in Harare, Zimbabwe, and Kyadondo, Uganda. Compared with high-income countries, these regions had markedly lower rates of childhood cancers, particularly leukemia. The incidence did not trend upward or downward overall, but peaks in incidence corresponded with HIV prevalence, while dips coincided with decline in national GDP, when families might be unable to afford consultation and treatment. This data suggests it will be challenging to meet the WHO's target of over 60% childhood cancer survival by 2030.

2 | MATERIALS AND METHODS

2.1 | Cancer registration

The Zimbabwe National Cancer Registry was established in 1985 and is located within the Parirenyatwa Group of Hospitals complex in Harare. It is population-based (recording all incident cancers) for the capital city of Harare. Case finding is conducted through active and passive methods. The cancer registrars regularly visit hospitals, outpatient clinics and diagnostic services (especially pathology and haematology). In addition, they receive notifications from the Harare Death Registry. The Kampala Cancer Registry was founded in 1951. The registry staff gather data on cancer cases occurring among the residents of Kyadondo County, which includes the Ugandan capital Kampala. The registry also closely collaborates with hospitals and other health providers in the area. There is only limited civil registration of deaths in Uganda, but the registry uses use death certificates issued in hospitals as a source of information. Both registries process information using the IARC/IACR CANREG software. As members of the African Cancer Registry Network, the registries adhere to standards of registration and research for example, ≥70% coverage of the target population.[12]

Anonymised data on black (African) cancer cases aged 0-19 years resident in Harare were obtained from the Zimbabwe National Cancer Registry and on residents of Kyadondo County from the Kampala Cancer Registry, for the period 1991-2015. The variables recorded on each case include: sex, age at diagnosis, date of diagnosis, topography and morphology (coded according to the International Classification of Diseases for Oncology, Third Edition [ICD-O-3][13]) and the most valid basis of diagnosis.

2.2 | Population data

Population census data were available for the black (African) population of Harare by sex and 5-year age groups for the years 1992, 2002

and 2012 from the Zimbabwe National Statistics Agency and for Kyadondo for the years 1991, 2002 and 2014 from the Ugandan Bureau of Statistics.[14,15] Intercensal annual population estimates were obtained by assuming a constant growth rate within sex and 5-year age groups. Postcensal projections assumed a linear population increase (by sex and age group). The proportionate age distribution during the 25-year period remained stable in both Harare and Kyadondo.

2.3 | Data analysis

RStudio Version 1.2.5033 was used for data analysis. According to the International Classification of Childhood Cancer, Third Edition (ICCC-3), we subdivided childhood cancer in 12 main diagnostic groups and 47 diagnostic subgroups by using the ICD-O-3 topography and morphology codes.[16] Crude and age-specific (5-year age groups) rates per million person years were calculated. Trends of the overall crude rate by registry are shown as 3-year moving averages. Crude rates are presented for ages 0-19 years and per million person years unless otherwise indicated. We did not use age standardised rates for comparisons of incidence; in the limited age ranges studied, the age-specific weights of the usual standard populations are very similar for each 5-year age group, so that age standardised rates are almost identical to the crude rates.

The annual percentage change (APC) in incidence was estimated using the Joinpoint Trend Analysis Software, Version 4.8.0.1 by the National Cancer Institute, USA.[17] The number of joinpoints was set to a maximum of four. The software fits the simplest joinpoint model to the incidence data inserting the minimum number of joinpoints which still provide statistically significant APCs. It uses a Monte Carlo Permutation method to test for significance.[18]

Information on population prevalence of infection with HIV was obtained from UNAIDS—the Joint United Nations Programme on HIV and AIDS.[19] UNAIDS compiles statistics including HIV epidemiology and HIV control, providing data up to subnational level. As UNAIDS does not provide subnational data for Uganda, population estimates from the United Nations Population Division were applied to calculate the national HIV prevalence.[20] Changes in annual gross domestic product (GDP) in Zimbabwe were taken from World Bank national accounts data.[21]

3 | RESULTS

3.1 | Overview

During the 25 years of registration (1991-2015), 1881 cases of childhood cancer were recorded in Harare and 3357 cases in Kyadondo.

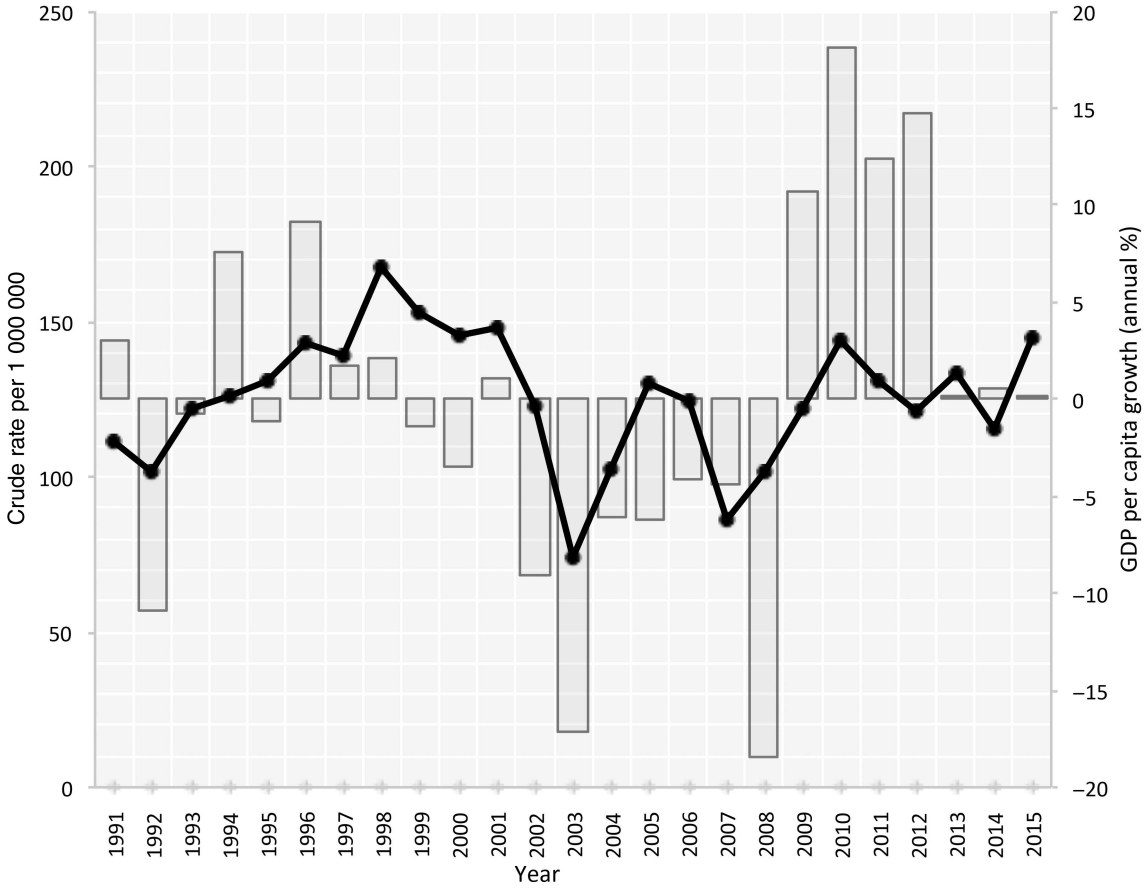

FIGURE 1 Crude rate per 1 000 000 of all cancer types in Harare (Zimbabwe) (all registered years included) and annual change in GDP per capita in Zimbabwe, years 1991–2015; GDP, gross domestic product; ICCC-3, International Classification of Childhood Cancer, Third Edition

In Harare, considerably fewer cases than expected were registered for the years 2003-2004 and 2007-2008, and the correspondingly low incidence rates appear to be associated with sharp decreases in national GDP (Figure 1). The GDP per capita in Zimbabwe decreased by up to 18% annually during these years,[21] while political conflicts evolved around the presidential elections of 2002 and 2008.[22] Previous analysis of data from the registry had shown the deficit of cases in 2007-2008, a period when most departments of government central referral hospitals operated below capacity and some of them closed altogether, and one of the key information sources—the private Clinical Laboratories, lost its entire histological database for 2007 and 2008 due to computer system failure.[10] Therefore, the years 2003-2004 and 2007-2008 were excluded, leaving 1653 cases for further analysis for Harare.

3.2 | Summary for whole period

For the whole period 1991 to 2015, the overall crude rate for ages 0-19 years was 132.5 per 10^6 in Harare and 146.6 per 10^6 in Kyadondo; for ages 0-14 years, it was 130.0 per 10^6 in Harare and 147.2 per 10^6 in Kyadondo (Table 1). Lymphomas and soft tissue sarcomas were the most frequent cancer groups in both areas (Harare: 37.1%, Kyadondo: 58.8%).

TABLE 1 Age-specific rates per 1 000 000, relative frequency, male/female ratio and basis of diagnosis by ICCC-3 main diagnostic groups

	Harare (Zimbabwe)									
	Age-specific rates per million						% Rel. Freq.	M/F	% Basis of diagnosis	
Diagnostic groups by ICCC-3	0–4	5–9	10-14	15–19	0–14	0–19			DCO	MV
I. Leukaemia	17.4	19.3	22.7	13.7	19.5	18.0	13.6	1.6	2.2	97.3
II. Lymphoma	10.8	21.4	24.7	21.3	18.0	18.8	14.2	1.7	3.8	92.3
III. Brain, spinal	9.8	15.9	18.1	8.0	14.0	12.5	9.4	1.3	14.1	49.4
IV. Neuroblastoma	5.8	2.0	1.2	0.6	3.3	2.6	2.0	1.5	6.1	90.9
V. Retinoblastoma	20.0	4.1	0.4	0.0	9.5	7.1	5.4	1.3	0.0	95.5
VI. Renal tumours	26.9	13.6	2.7	2.2	16.0	12.5	9.4	0.9	1.3	94.2
VII. Hepatic tumours	2.1	1.7	5.4	6.1	2.9	3.7	2.8	1.2	13.0	32.6
VIII. Bone tumours	1.8	2.7	14.6	15.9	5.7	8.3	6.2	1.1	1.0	87.4
IX. Soft tissue sarcomas	26.4	31.5	27.7	36.3	28.4	30.4	22.9	1.4	4.7	73.4
X. Germ cell	3.7	2.4	1.9	7.6	2.8	4.0	3.0	0.1	2.0	80.0
XI. Carcinomas	3.4	4.4	10.4	15.3	5.7	8.1	6.1	0.8	2.0	96.0
XII. Other and unspecified	4.2	2.4	6.5	12.7	4.3	6.4	4.8	1.0	21.3	17.5
All	132.3	121.4	136.4	139.8	130.0	132.5	100	1.2	5.1	79.2
	Kyadondo (Uganda)									
	Age-specific rates per million						% Rel. Freq.	M/F	% Basis of diagnosis	
Diagnostic groups by ICCC-3	0–4	5–9	10–14	15–19	0–14	0–19			DCO	MV
I. Leukaemia	8.7	14.9	15.3	10.7	12.6	12.1	8.3	1.5	4.7	85.6
II. Lymphoma	31.1	75.3	47.5	24.2	49.8	43.5	29.7	1.5	1.7	70.8
III. Brain, spinal	3.1	5.0	4.0	2.3	3.9	3.5	2.4	1.3	3.7	28.4
IV. Neuroblastoma	1.5	0.9	0.4	0.2	1.0	0.8	0.5	1.3	0.0	66.7
V. Retinoblastoma	15.2	2.2	0.6	0.0	6.8	5.2	3.5	1.1	0.8	65.3
VI. Renal tumours	22.8	7.7	2.6	2.1	12.2	9.7	6.6	1.2	0.9	76.6
VII. Hepatic tumours	1.3	0.7	2.4	3.9	1.4	2.1	1.4	1.4	2.1	55.3
VIII. Bone tumours	0.9	3.9	11.1	12.6	4.8	6.7	4.6	1.2	1.9	58.4
IX. Soft tissue sarcomas	34.7	44.6	43.5	49.7	40.4	42.7	29.1	1.3	1.2	78.5
X. Germ cell	1.0	0.9	3.8	8.5	1.8	3.4	2.4	0.2	0.0	65.8
XI. Carcinomas	1.2	3.3	6.8	15.3	3.5	6.4	4.3	0.9	0.7	96.6
XII. Other and unspecified	9.1	8.4	9.3	15.3	9.0	10.5	7.2	0.8	0.8	7.1
All	130.6	167.9	147.2	144.8	147.2	146.6	100	1.2	1.6	69.0

Abbreviations: DCO, death certificate only; ICCC-3, International Classification of Childhood Cancer, Third Edition; MV, morphologically verified.

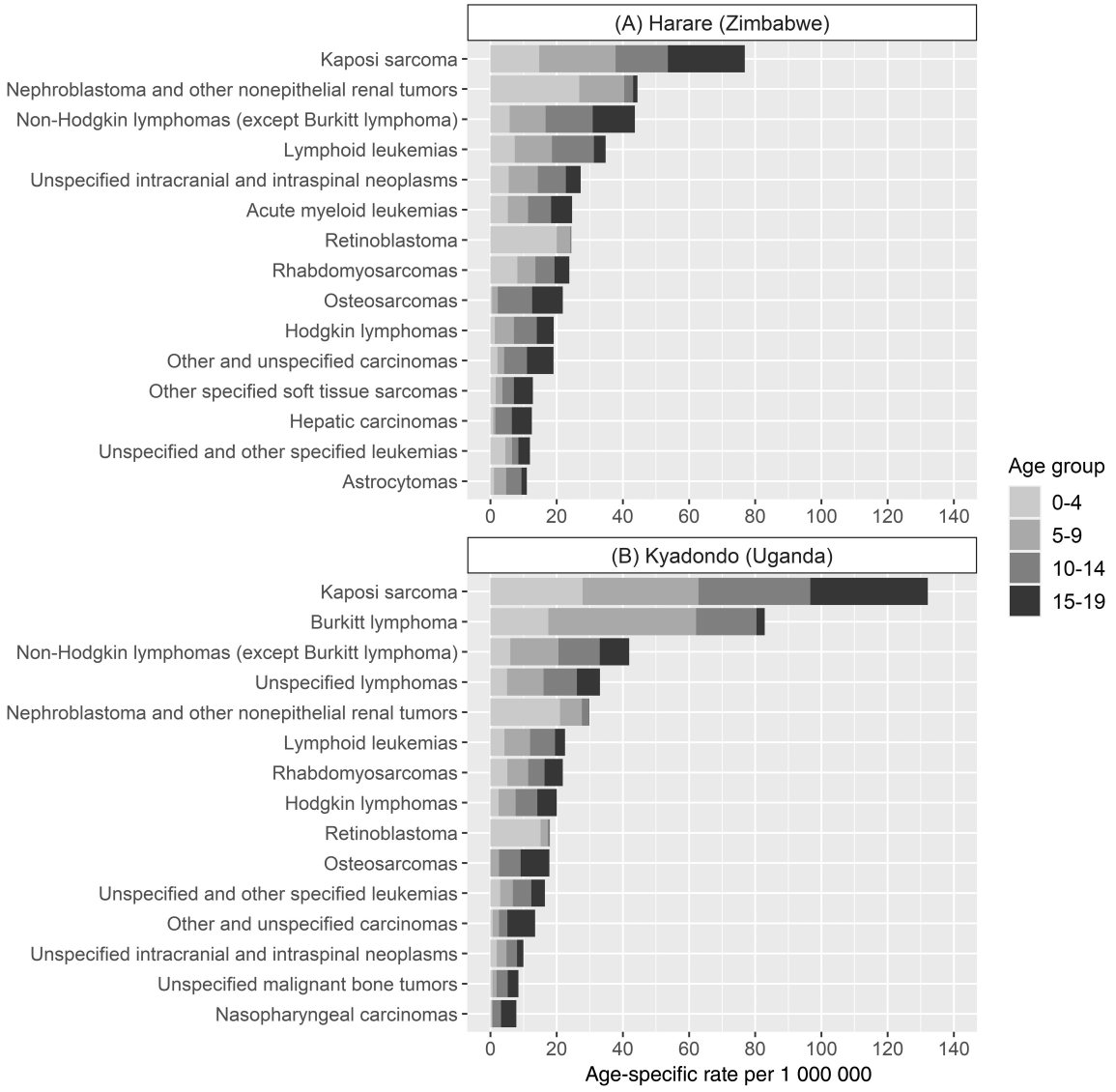

FIGURE 2 A, Harare (Zimbabwe) and B, Kyadondo (Uganda); age-specific rates per 1 000 000 for the top 15 ICCC-3 subgroups, ages 0–19 years, years 1991-2015; ICCC-3, International Classification of Childhood Cancer, Third Edition

The incidence of lymphomas and soft tissue sarcomas was considerably higher in Kyadondo than Harare. Rates of leukaemias (ICCC-3 I) and brain tumours (ICCC-3 III) were higher in Harare (18.0 and 12.5 per 10^6 respectively) than in Kyadondo (12.1 and 3.5 per 10^6). The most common subgroups were KS, nephroblastoma (VIa) and non-Hodgkin lymphoma (NHL) (except BL) in Harare, and KS, BL and NHL (except BL) in Kyadondo (Figure 2). In Kyadondo, most cases of BL were in the 5-9 years age group. KS cases were more evenly distributed between the four age groups.

3.3 | Sex and age distribution

Tumour types differed between age groups. The age-specific rate of all cancers was highest for the 15-19 year age group in Harare (139.8 per 10^6) and for the 5-9 year age group in Kyadondo (167.9 per 10^6) (Table 1). The median age of all cancers for the whole period was 9 years in both registries. Regarding the main diagnostic groups, neuroblastomas, retinoblastomas and renal tumours were most frequent in the 0-4 year age group (Table 1, Supporting Information 2). Hepatic and bone tumours, as well as carcinomas appeared mainly in older age groups (Table 1). The overall male to female ratio was 1.2 in both Harare and Kyadondo. Leukaemias and lymphomas occurred more often among males (M/F 1.6 and 1.7 in Harare, 1.5 and 1.5 in Kyadondo).

3.4 | Time trends

Over the whole 25-year period, there was no significant overall trend in incidence of childhood cancer in either population (APC 0.0% (95% confidence interval [CI] −0.7, 0.7) in Harare; −1.0% (95% CI −2.2, 0.2) in Kyadondo). However, there were fluctuations in the actual rates, in

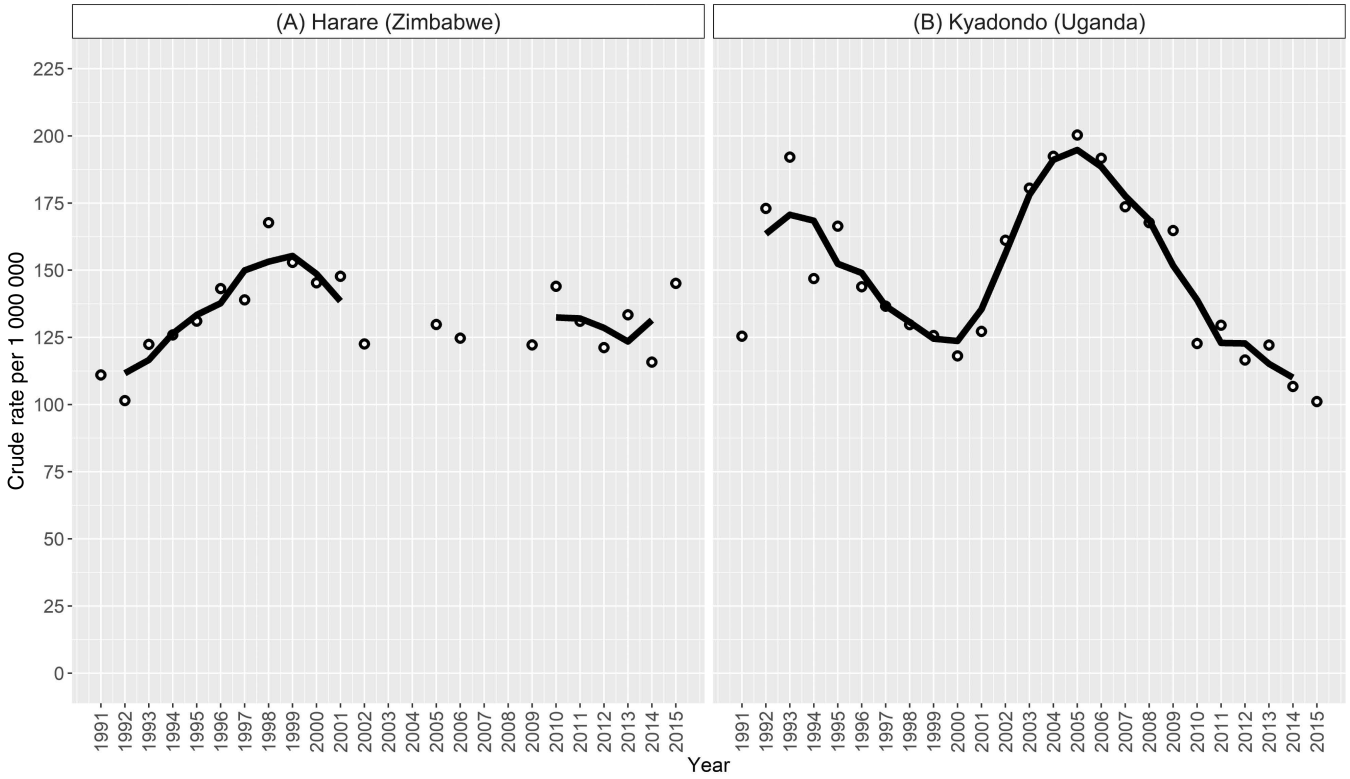

FIGURE 3 A, Harare (Zimbabwe) and B, Kyadondo (Uganda); crude rate per 1 000 000 of all cancer types, ages 0-19 years, years 1991-2015, trend line shows 3 year moving average, dots represent exact values

both Harare and Kyadondo. In Harare, the rate was considerably higher in 1996-2001 compared to the following years (Figure 3). The highest annual crude rate was 167.7 in 1998. In Kyadondo, after an initial decline, the overall incidence increased from 2000, reaching a peak of 200.3 per million in 2005, before declining.

Figure 4 shows the crude rate per 1 000 000 at ages 0-19 years for the 12 main groups of ICCC-3 by registry, for the years 1991-2015. In Harare, it is notable that the incidence rates of lymphomas (ICCC-3 II) and soft tissue sarcomas (ICCC-3 IX) peaked in 1998-1999 (rates of 31.1 and 54.4 respectively) (Figure 4). These changes were due to trends in the diagnostic subgroups of KS (ICCC-3 IXc) and NHL (except BL) (ICCC-3 IIb), and the trend in these two cancers accounts for the peak in the overall incidence seen in Figure 3.

In Kyadondo, the incidence rates of lymphomas and soft tissue sarcomas showed more fluctuations than in Harare. Two subgroups accounted for the trends in these main diagnostic groups—IXc (KS with a maximum rate of 51.8 in 2004) and IIc (BL, with a maximum of 38.1 in 2003), and it is these trends that lead to the peaks in overall incidence seen in Figure 3.

To examine associations of cancer incidence and infections, we compared trends in NHL (incl. BL; ICCC-3 IIb and IIc) and KS (IXc) to HIV prevalence trends in children aged 0-14 years (Figure 5). In Harare, the high rates of NHL (incl. BL) and KS from 1998-2000 were associated with a high prevalence of HIV in the 0-14 year age group; the incidence of other cancers, not associated with HIV, showed little change (Figure 5). In Kyadondo, the incidence rates of NHL (incl. BL) and KS showed some fluctuation in the first decade, but there has been a decline in the incidence of both since about 2003-2005, coinciding with decreasing HIV prevalence.

The results of the Joinpoint analysis confirm and quantify the fluctuating trends for both registries (Supporting Information 1). In Harare, the crude rate increased from 1991-1998 (APC +4.7% [95% CI 1.2, 8.4]) and declined afterwards (APC 1998-2015 −1.0% [95% CI −1.8, −0.2]). In Kyadondo, the pattern differed considerably. After increasing rates during the first 3 years (APC 1991-1993 + 16.2% [95% CI −8.5, 47.6]), the incidence declined to a minimum in 2000 (APC 1993-2000 −6.4% [95% CI −9.8, −2.8]). Following a sharp increase (APC 2000-2004 + 16.3% [95% CI 5.8, 27.9]), the crude rate decreased over the course of the last period (APC 2004-2015 −6.4% [95% CI −7.5, −5.3]).

4 | DISCUSSION

To our knowledge, this is the first study to compare time trends in childhood cancer incidence using high-quality data, classified according to the ICCC-3, from two population-based cancer registries in sub-Saharan Africa. Over the period 1991-2015, there was little overall change in incidence, and no significant declines, as had been previously suspected in sub-Saharan Africa.[1]

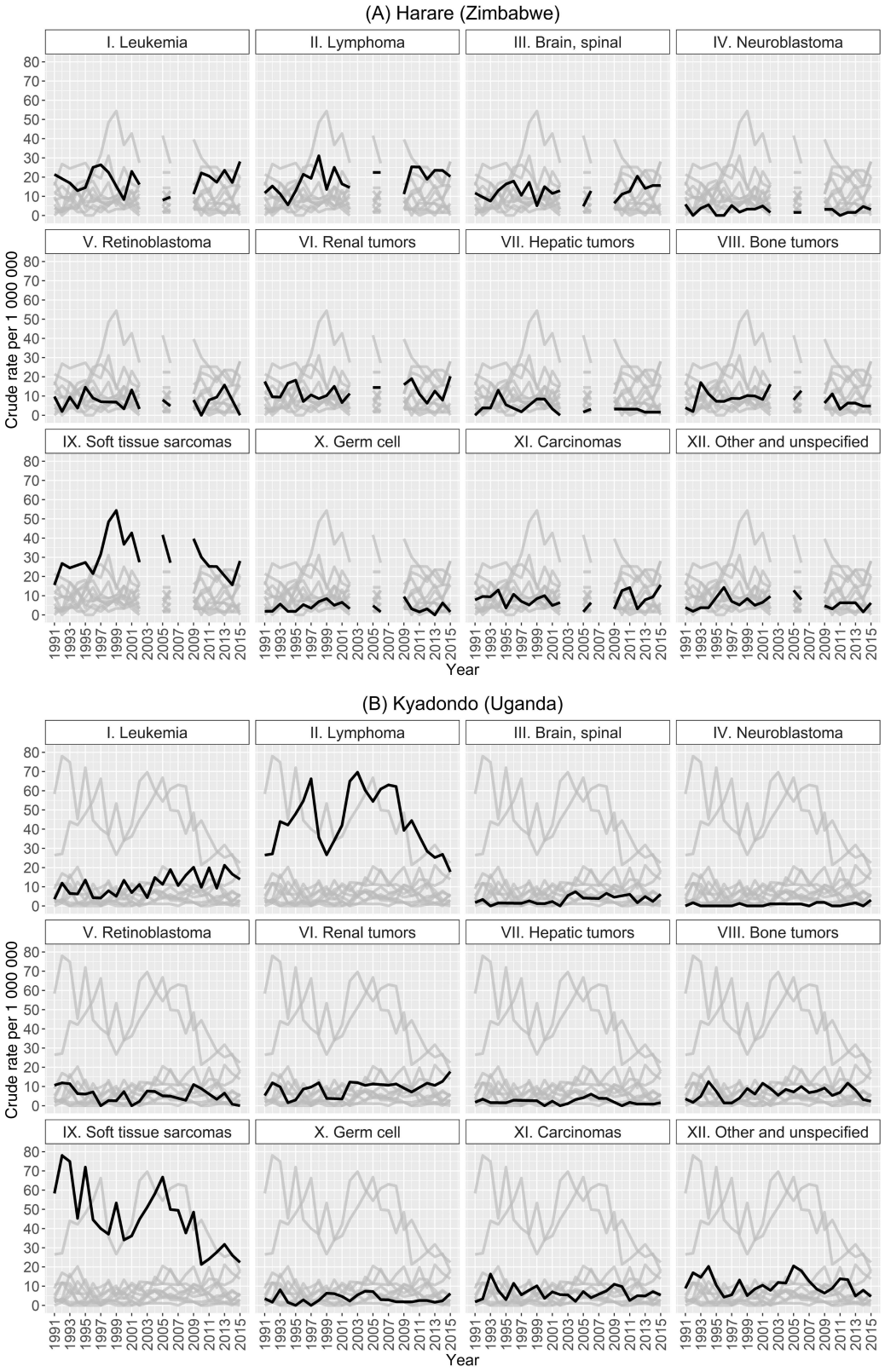

FIGURE 4 A, Harare (Zimbabwe) and B, Kyadondo (Uganda); crude rate per 1 000 000 of ICCC-3 main diagnostic groups, ages 0-19 years, years 1991-2015; ICCC-3, International Classification of Childhood Cancer, Third Edition

We investigated possible reasons for the observed fluctuations in incidence rates in the two populations. Trends in cancer incidence generally reflect changes in lifestyle, environmental conditions or infectious agents.[23] Additionally, varying access to service and/or failure to diagnose might lead to underdiagnosis and incomplete cancer registration and thereby to changes in childhood cancer incidence rates.[24]

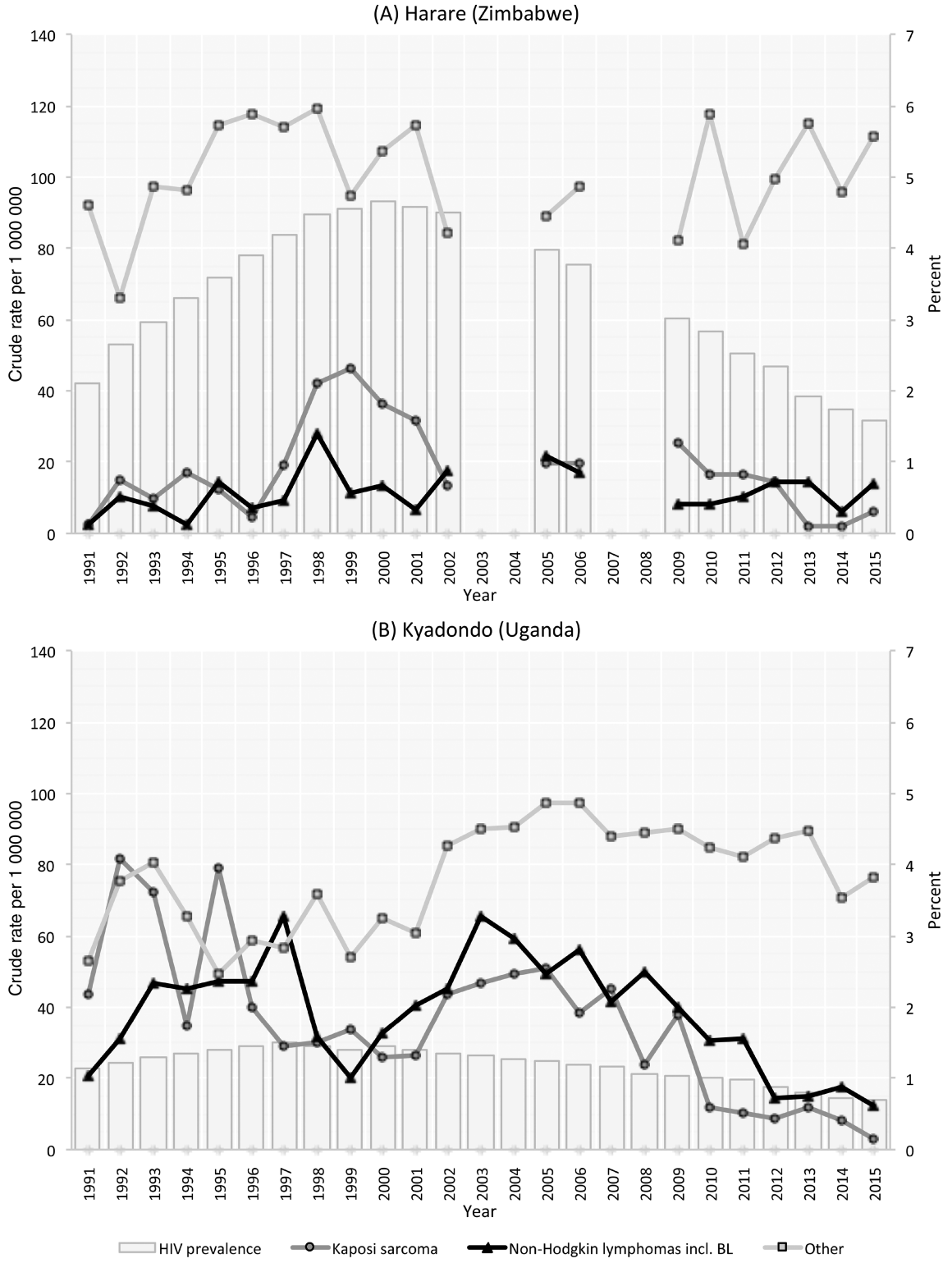

FIGURE 5 A, Harare (Zimbabwe) and B, Kyadondo (Uganda); crude rate per 1 000 000 of non-Hodgkin lymphoma (incl. BL), Kaposi sarcoma and Other cancers, and annual HIV prevalence, ages 0–14 years, years 1991-2015; BL, Burkitt lymphoma

Two entities defined within the ICCC, related to infectious agents, were driving the observed changes in incidence: KS and NHL. Both are HIV-related cancers.[25]

High rates of NHL and KS from 1998-2000 in Harare were associated with a high prevalence of HIV in the 0-14 year age group (Figure 5). In Kyadondo, a decline in the incidence of both KS and NHL since 2005 coincided with decreasing HIV prevalence and increasing availability of antiretroviral therapy (ART) for HIV-positive individuals.[26,27] For KS, it is known that HIV-induced immunosuppression leads to a higher incidence of KS in HIV-

infected children compared to HIV-negative children.[28,29] HIV in childhood mainly occurs through vertical (mother-to-child) transmission. An immediate initiation of ART in HIV-positive children appears to decrease the risk of Kaposi sarcoma-associated herpesvirus (KSHV) infection, the oncovirus associated with Kaposi sarcoma.[30]

In Harare, it was clear that registration had been markedly affected by the varying availability of diagnostic and treatment facilities, related to political and due to economic factors. Comparisons of the observed registrations of childhood cancers and changes in GDP in Zimbabwe revealed remarkable decreases in 2003-2004 and 2007-2008. We assume that the economic situation directly (and very promptly) influenced the diagnosis, and registration, of cancer, and hence we excluded the years 2003-2004 and 2007-2008 from further analysis. A variety of reasons could underlie the interrelation. As well as the simple non-availability of diagnostic and treatment facilities, at least in 2007-2008, it is likely to be difficult for families to afford the costs of consultation and investigation in times of economic hardship. Second, adequate funding of childhood cancer care is a common problem in Africa and probably worse during economic depression.[31] When specialised diagnostic facilities are unavailable, some types of childhood cancer probably remain undiagnosed.[32,33] Previous work from the United States has shown a correlation between increasing unemployment and decreasing cancer incidence rates.[34]

4.1 | Differences between Harare (Zimbabwe) and Kyadondo (Uganda)

Despite parallels between Harare and Kyadondo with respect to time trends, the rather different profile of childhood cancer in the period from 1991-2015 presumably reflects regional differences in aetiological exposures. The incidence rate of soft tissue sarcomas (mainly KS) was generally higher in Kyadondo (42.7) compared to Harare (30.4). The aetiological agent of KS—KSHV—is more prevalent in Uganda, with 35.5% of children and adolescents aged 14 to 20 years being positive for the virus, compared to only 5.0% in Zimbabwe.[35] Malaria parasitaemia is related to KSHV seropositivity,[36-38] and prevalence of malaria is high in Uganda,[39] while coverage by ART is low in Kyadondo.[19]

Incidence rates of lymphomas were considerably higher in Kyadondo (43.5) than in Harare (18.8). Most of the lymphoma cases in Kyadondo were BL, which is known to be associated with malaria and Epstein–Barr virus (EBV).[40] The difference is presumably the consequence of higher prevalence of malaria (*Plasmodium falciparum*)—estimated at 432 per 1000 person years in Uganda compared to 207 in Zimbabwe in 2005—as well as transmission intensity.[39] Malaria is endemic in Uganda and seasonal in Zimbabwe.[41,42] Although, diagnosis of BL on light microscopy is known to result in some misclassification of lymphomas,[43] the overall trend of NHL as a whole is likely to be little affected.

4.2 | Differences between Harare (Zimbabwe) and Kyadondo (Uganda) and high income countries

The profile of childhood cancer in both Harare and Kyadondo was markedly different from that of paediatric cancer as reported from high-income countries. The overall incidence of childhood cancer in Harare (132.5 per 10^6) and Kyadondo (146.6 per 10^6) is lower than that observed in High Income Countries for example, the United States (165.7 per 10^6, in 1997-2007).[44] This is specific to certain diagnostic groups: incidence rates of leukaemia are low in Uganda (12.1 per 10^6) and Zimbabwe (18.0 per 10^6) in contrast to the United States (41.5 per 10^6).[44] It is possible that leukaemias in young children are being mistaken for common infectious diseases such as malaria and not referred to tertiary care.[45] Nevertheless, the common leukaemia of childhood—precursor B-cell acute lymphocytic leukaemia—is relatively rare in all series from low and middle income settings,[7] and historically the peak of incidence around ages 3-5 years only emerged as socioeconomic conditions improved in countries worldwide.[46] Several causative factors have been suggested. Greaves hypothesises that delayed exposure to infectious agents in early childhood in High Income Countries leads to excessive immune reactions and thereby a dysregulated lymphopoiesis later in life.[47] As a result, lymphoproliferative disorders rather develop in higher socioeconomic settings.

Similarly, the incidence of brain and spinal tumours is low in both registries, as in almost all series from sub-Saharan Africa, presumably due to the deficiencies in diagnostic facilities.[48]

In contrast, incidence rates of retinoblastoma and nephroblastoma were higher in Harare (7.1 and 12.3 per 10^6) and Kyadondo (5.2 and 8.3 per 10^6) than in the United States (3.2 and 5.9 per 10^6).[44] Relatively high rates of these cancers are a feature of sub-Saharan Africa.[4,49,50] Within the United States, blacks are more prone to retinoblastoma and nephroblastoma compared to non-Hispanic whites suggesting an effect of genetic and epigenetic factors.[51-53]

We consider several limitations in our study. First, information on GDP changes from the World Bank were only available at national level for Zimbabwe. We assume the economic situation in Harare to resemble the national economic development when interpreting the observed cancer incidence trends. Second, prevalence of HIV was not available at subnational level for Uganda, and we have used national HIV prevalence at ages 0-14 years. As HIV is more common in urban than in rural areas[54] and our data are from urban populations, the HIV prevalence is likely to have been higher than the national estimate. Nevertheless, the national trends in prevalence most likely reflect those in the urban populations. Third, ART coverage data could not be obtained for the whole time period from 1991-2015 from UNAIDS. We assume the available information to be similar to the longitudinal development. However, differences might prevail as varying international funding of national treatment programmes, for instance, could have an effect.

5 | CONCLUSION

Since most childhood cancers are related to (prenatal genetic) events, rather than environmental exposures, relatively rapid changes in

incidence rates are not expected to occur. Overall, we did not see any marked increase or decrease in incidence of childhood cancer, although there were fluctuations caused by the cancers related to infectious agents, specifically KS and NHL, related to infection with HIV, KSHV and EBV. In both Zimbabwe and Uganda, fluctuations in these cancers can be seen associated with trends in the epidemic of HIV-AIDS, and the availability of ART.

In addition, it is clear from the results in Harare that economic circumstances have an impact on childhood cancer registration, and, as a result, on recorded rates of incidence. One might expect that children with low socioeconomic background are vulnerable to shutdowns of public health services, and indeed to the limited access to care and varying availability of diagnostic services that prevail in much of sub-Saharan Africa. Meeting the target of the World Health Organisation's Global Initiative for Childhood Cancer of increasing child cancer survival rates to at least 60% and alleviating suffering of all children by 2030,[55] is likely to prove especially challenging in the continent.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interests.

ETHICS STATEMENT

The AFCRN research committee approved our study, as well as the respective registries. We conducted the study in accordance to the Declaration of Helsinki. The study used routinely collected, anonymised data, therefore no special ethical approval or informed consent was needed.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available from the corresponding author upon reasonable request, which will be evaluated by the AFCRN research committee. Details of the data application process are outlined on the AFRCN website (http://afcrn.org/index.php/research/how-to-apply/76-research-collaborations).

ORCID

Donald Maxwell Parkin https://orcid.org/0000-0002-3229-1784

Eva Johanna Kantelhardt https://orcid.org/0000-0001-7935-719X

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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