Infectious disease complications in children with cancer

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Infectious complications in childhood cancer contribute to increased morbidity and mortality. Factors predisposing to infection include malignancy-related immune dysregulation, cytotoxic chemotherapy-induced myelosuppression, high-dose corticosteroid use, the presence of indwelling venous catheters, malnutrition, frequent and prolonged hospital stays, and coexisting HIV infection. In the southern African context, infectious complications are associated with worse clinical outcomes than in higher-income countries. More region-specific research is needed to improve patient management and increase survival rates.

Keywords. Paediatric oncology, infectious complications, risk factors, southern Africa.

Undergraduate Res Health 2026;4(1):e3853. https://doi.org/10.7196/URHJ.2026.v4i1.3853

The student authors, Jasmine Wylie, Thomas Goddard, Owen Payne, Franco Vosloo, Naomines Kabamba (back row, left to right), Taylin Toweel-Moore, Kemaiya Govender, Claire Downing and Inga Wait (front row, left to right), conducted this literature review under the guidance of Prof. Gita Naidu during their third year of medical training at the University of the Witwatersrand. The article was submitted to the South African Undergraduate Medical Research Competition. Currently in their fourth year, the authors have a wide range of interests but share a commitment to the continuous improvement of the medical field. While the subject of this article aligned more closely with some authors' interests than others, everyone enjoyed the process of developing their literature review skills.

Between 2019 and 2023, the South African National Cancer Registry recorded 3 697 histologically confirmed cancer cases among children aged 0 - 14 years.[1-5] However, it is likely that these figures underestimate the true incidence of childhood cancer, as they do not include cases missing as a result of incomplete data collection, diagnostic delays and misdiagnosis. The management of paediatric oncology patients is complicated by various biological and psychosocial factors, with infections being a particularly important aspect to consider. This literature review critically assesses current evidence on infectious complications in childhood cancer.

This narrative review primarily focuses on research conducted in South Africa (SA), while also referencing studies from other African countries and the global literature. Through this review, we aim to identify significant research gaps in the existing evidence base and highlight specific research opportunities to inform local practice, guide policy development, and ultimately improve survival rates and the quality of care in paediatric oncology across the southern African region. The studies referenced in this review were identified through searches of Google Scholar and PubMed using terms such as 'children with cancer', 'paediatric oncology', 'infections', 'complications' and 'southern Africa', along with additional

section-specific keywords. Titles were screened for relevance, and potentially eligible articles were reviewed in full. Further searches were conducted to identify studies reporting comparable findings in both African and global contexts, with these selected for inclusion when appropriate. While the focus was on literature published since 2010, earlier studies were included where necessary to fill gaps caused by the limited availability of region-specific data. Only publications in English were considered.

Incidence of infectious disease complications in childhood cancer

Infectious complications often manifest as episodes of fever accompanied by neutropenia.[6] This clinical syndrome results from the profound immunosuppression caused by both the malignant disease and its treatment, especially cytotoxic chemotherapy. Chemotherapy-induced myelosuppression causes neutropenia, which significantly weakens the innate immune response.[7] A study conducted across five sub-Saharan African countries reported 104 episodes of fever with neutropenia among 252 childhood cancer cases over 7 months. Of these patients, 21% had prolonged neutropenia and 31% experienced profound neutropenia, and the overall mortality rate was 11%.[8] Similarly, Adekunle *et al.*[6] documented 267 cases of fever with neutropenia in 179 paediatric oncology patients over a 3-year period in Cape Town.

Table 1 and Fig. 1 compare the incidence of infectious complications in children with cancer across three SA studies. The infectious mortality rate reported at Red Cross War Memorial Children's Hospital (RCWMCH) aligns with international outcomes, such as mortality rates reported in the USA and Izmir, Turkey, of 3% and 2%, respectively.[9,10] The low infectious mortality rate at RCWMCH is attributed to ongoing monitoring for bloodstream infections, low antimicrobial resistance, and very early treatment.[11]

The outcomes observed at RCWMCH do not represent the overall results across SA, as shown by reports from Chris Hani Baragwanath Academic Hospital.[12,13] In southern Africa, paediatric oncology patients face significantly higher mortality rates compared with those in high-income countries (HICs). These poorer outcomes are due to limited access to supportive care, delayed starting of empirical antibiotics, and inconsistent enforcement of infection control protocols. Many oncology centres lack services like those at RCWMCH.[6,8,11,13] Socioeconomic disparities worsen these outcomes by increasing the frequency of treatment interruptions, delaying accurate diagnoses, and leading to late-stage presentations. Furthermore, overcrowded treatment facilities raise the risk of transmission of multidrug-resistant infections.[13-17] As a result, complications such as febrile neutropenia, which are usually manageable in HICs, often become fatal events in the southern African context.

Spectrum of infectious agents responsible for infectious disease complications in children with cancer

Infectious complications in childhood cancer are associated with a broad spectrum of aetiological agents, as shown in Tables 2 and 3 and Fig. 2.

In comparison of SA findings with international epidemiology, a study conducted in Cameroon reported positive blood cultures in 28.1% of febrile episodes among paediatric oncology patients.[18] Among these, 50.9% of infections were caused by Gram-negative bacilli and 35.1% by Gram-positive cocci. *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pantoea* spp. were the most commonly cultured Gram-negative bacilli. Coagulase-negative staphylococci were the most frequently cultured Gram-positive cocci.

The range of pathogens responsible for infectious complications in paediatric oncology patients in the southern African context remains inadequately characterised. Although most facilities can perform blood cultures, a significant shortage of healthcare professionals often limits the number of samples submitted for pathogen identification. This reduced identification of pathogens hinders the analysis of regional epidemiological trends, which is vital for guiding empirical antibiotic choices and optimising treatment strategies at individual centres.[8]

The role of viral pathogens in febrile neutropenia among paediatric oncology patients remains inadequately documented. The true significance of this inadequate documentation cannot be precisely assessed from the study conducted at Tygerberg Children's Hospital,[19] because a large proportion of febrile episodes were classified as fevers of unknown origin. While some of these febrile episodes may have been viral in origin, the actual incidence of viral infections could be either overestimated or underestimated. Nevertheless, the possibility of viral infection should not delay the prompt initiation of empirical antimicrobial therapy in paediatric oncology patients presenting with fever and neutropenia.

The impact of the COVID-19 pandemic on the epidemiology of viral infections in paediatric oncology patients has been documented in Poland.[20] Between 2020 and 2021, 312 viral infections were diagnosed in 192 children with acute lymphoblastic leukaemia (ALL), representing a significant increase compared with the 72 cases reported in 53 patients with ALL between 2018 and 2019. During the pandemic, SARS-CoV-2, rhinovirus

Table 1. Incidence of infectious complications among paediatric oncology patients in South Africa

	Setting		
Variable	**CHBAH (1991 - 1995)[12]**	**CHBAH (2011 - 2015)[13]**	**RCWMCH (2012 - 2014)[11]**
Duration of study	48 months	60 months	36 months
Patients, *n*	83	131	89
Infectious episodes,* *n*	200	518	150
Infectious episodes per patient, *n* (average)	2.4	4.0	1.7
Deaths, *n*	17	14	3
Infectious mortality rate per patient† (%)	20.5	10.7	3.4

CHBAH = Chris Hani Baragwanath Academic Hospital; RCWMCH = Red Cross War Memorial Children's Hospital.
*The exact definition for infectious episode differed between the studies, but the results remain comparable to illustrate the incidence of infectious complications in different paediatric oncology populations.
†Deaths/patients.

and respiratory syncytial virus emerged as the main viral pathogens. Adenovirus, rotavirus and varicella-zoster virus were more frequently identified in the pre-pandemic period.[20] Data on the effect of the COVID-19 pandemic on viral infections in southern African paediatric oncology populations remain limited.

The incidence of fungal infections in paediatric oncology patients is lower than that of bacterial infections; however, invasive fungal infections (IFIs) are linked to a higher risk of mortality.[21] A retrospective study in Greece reported a crude mortality rate of 33.3% due to IFIs.[22] In Cameroon, fungal pathogens were found in 14% of blood samples from febrile children with cancer, with *Candida* species responsible for 87.5% of these infections.[18]

Risk factors for an immunocompromised state in children with cancer

Effect of malignancy on the immune system

Malignancy itself causes significant immune dysregulation, characterised by impaired innate and adaptive immune responses that enable tumour immune evasion and weaken host defence mechanisms, thereby increasing the risk of infections.[23]

Leukaemia-derived exosomes (LEXs) represent a key mechanism of malignancy-induced immunosuppression. In a study from Iran, LEXs isolated from paediatric patients with ALL were co-cultured with healthy T lymphocytes.[24] The introduction of LEXs into healthy T lymphocytes led to increased FOXP3 expression, a transcription factor that plays a crucial role in the differentiation and development of regulatory T cells, resulting in increased production of transforming growth factor-beta (TGF-β) and interleukin-10 (IL-10) by regulatory T cells. This study delineates a precise molecular pathway through which LEXs impair adaptive immunity, facilitating immune evasion in ALL.

Hillinger and Herzig[25] studied 23 patients with Hodgkin's disease and observed impaired lymphocyte proliferation *in vitro*, mediated by suppressor monocytes and suppressor T cells. These patients had not received treatment for at least 6 weeks prior to their participation. The degree of suppression correlated with the number of suppressor mononuclear cells, with no soluble inhibitory factors identified. Neither disease stage nor prior treatment influenced this suppression, suggesting an intrinsic immune dysregulation associated with Hodgkin's disease.

The mechanisms behind malignancy-induced immune dysregulation are not yet fully understood in southern African paediatric oncology populations. Future research is needed to develop better diagnostic and therapeutic approaches. Such studies should clarify the immunopathological processes involved, helping to create targeted diagnostic tools and improved treatment options.

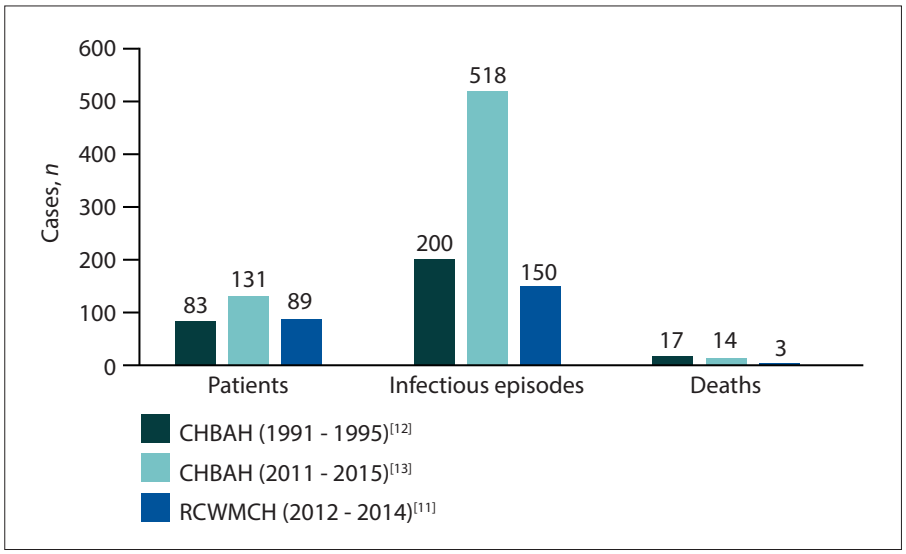

Fig. 1. Incidence of infectious complications among paediatric oncology patients in South Africa. (CHBAH = Chris Hani Baragwanath Academic Hospital; RCWMCH = Red Cross War Memorial Children's Hospital.)

Table 2. Aetiological agents responsible for infectious complications in paediatric oncology patients in South Africa

	Setting			
Variable	**CHBAH (1991 - 1995),[12] *n* (%)***	**Tygerberg Children's Hospital (2000 - 2001),[19] *n* (%)***	**CHBAH (2011 - 2015),[13] *n* (%)***	**RCWMCH (2012 - 2014),[11] *n* (%)***
Duration of study	48 months	14 months	60 months	36 months
Infectious episodes,† *n*	200	102	518	150
Bacterial infections	180 (90.0)	24 (23.5)	442 (85.3)	157 (104.7)
Gram-positive, *n*	140	11	249	85
Gram-negative, *n*	40	13	193	72
Fungal infections	19 (9.5)	-	47 (9.1)	16 (10.7)
Viral infections	-	31 (30.4)	-	-
Polymicrobial infections	-	6 (5.9)	98 (18.9)	21 (14.0)
Other/unknown aetiologies	1 (0.5)	53 (52.0)	-	-

CHBAH = Chris Hani Baragwanath Academic Hospital; RCWMCH = Red Cross War Memorial Children's Hospital.
*Except where otherwise indicated. Percentages are % of the total infectious episodes.
†The exact definition for infectious episode differed between the studies, but the results remain comparable to illustrate the aetiological agents responsible for infectious complications in paediatric oncology patients in South Africa.

Table 3. Bacterial and fungal species responsible for infectious complications in paediatric oncology patients in South Africa

Variable	Setting			
	CHBAH (1991 - 1995),[12] *n* (%)*	Tygerberg Children's Hospital (2000 - 2001),[19] *n* (%)*	CHBAH (2011 - 2015),[13] *n* (%)*	RCWMCH (2012 - 2014),[11] *n* (%)*
Duration of study	48 months	14 months	60 months	36 months
Bacterial infections, *n*	180	24	442	157
Gram-positive bacterial infections, *n*	140	11	249	85
Coagulase-negative staphylococci	-	4 (36.4)	180 (72.3)	40 (47.1)
Staphylococcus aureus	27 (19.3)	2 (18.2)	19 (7.6)	5 (5.9)
Streptococcus pneumoniae	4 (2.9)	1 (9.1)	9 (3.6)	6 (7.1)
Streptococcus viridans	13 (9.3)	-	38 (15.3)	23 (27.1)
Enterococcus species	5 (3.6)	-	38 (15.3)	9 (10.6)
Gram-negative bacterial infections, *n*	40	13	193	72
Escherichia coli	5 (12.5)	2 (15.4)	64 (33.2)	19 (26.4)
Klebsiella species	6 (15.0)	4 (30.8)	28 (14.5)	18 (25.0)
Enterobacter species	5 (12.5)	-	15 (7.8)	7 (9.7)
Pseudomonas species	5 (12.5)	1 (7.7)	28 (14.5)	6 (8.3)
Haemophilus influenzae	3 (7.5)	-	2 (1)	3 (4.2)
Fungal infections, *n*	19	-	47	16
Candida parapsilosis	8 (42.1)	-	-	5 (31.3)
Candida albicans	7 (36.8)	-	-	4 (25.0)

CHBAH = Chris Hani Baragwanath Academic Hospital; RCWMCH = Red Cross War Memorial Children's Hospital.
*Except where otherwise indicated. Percentages are % of infections within the respective Gram-positive, Gram-negative or fungal categories.

Cytotoxic chemotherapy

Cytotoxic chemotherapy shows limited selectivity between cancerous and normal dividing cells. This limited selectivity causes unintended damage to rapidly dividing normal tissues such as bone marrow and mucosal epithelium. This cytotoxicity appears as both a dose-limiting toxicity and an intentional therapeutic effect aimed at destroying malignant cells.[26]

Myelosuppression-induced neutropenia is a primary mechanism through which cytotoxic chemotherapy weakens the host's innate immunity. Adekunle *et al.*[6] established a significant link between severe neutropenia and increased risk of infectious morbidity and intensive care unit admission, thereby outlining the pathophysiological connection between chemotherapy-induced myelosuppression and infectious complications in paediatric oncology patients.

In addition to causing myelosuppression, cytotoxic chemotherapy damages the physical barriers of the innate immune system, especially through the development of mucositis. In a prospective cohort study of 140 paediatric oncology patients in Hong Kong receiving cytotoxic chemotherapy, 41% developed oral mucositis.[27] Neutropenia was linked to a higher risk of mucositis, with a hazard ratio of 3.08.

Cytotoxic chemotherapy also disrupts adaptive immune function, mainly through causing lymphopenia. In a Nigerian study involving 80 chemotherapy-naive adult oncology patients, CD4 lymphocyte counts were measured before and during a chemotherapy cycle.[28] The results showed a statistically significant decrease in CD4 lymphocyte levels during treatment, indicating chemotherapy-induced suppression of cell-mediated immunity.

Collectively, these studies highlight the multifaceted immunosuppressive effects of cytotoxic chemotherapy. These combined effects significantly increase susceptibility to infections.

Corticosteroids

Corticosteroids are often included in paediatric oncology treatment protocols owing to their strong anti-inflammatory and lymphocytic effects, especially in haematological malignancies.[29] However, their use raises the risk of infection.

A study by Naidu *et al.*[30] enrolled 169 children with cancer and found a strong link between high-dose corticosteroid exposure and tuberculosis (TB) incidence. Among TB-positive patients, the rate of high-dose corticosteroid courses was 350 per 100 child-years, significantly higher than the 29.4 per 100 child-years in the TB-negative group. These findings suggest a significant correlation between corticosteroid-induced immunosuppression and increased susceptibility to TB.

The selection of glucocorticoid agents in paediatric oncology can significantly influence infection-related morbidity and mortality. Prednisone and dexamethasone are commonly used in treatment protocols. Although dexamethasone has demonstrated superior antileukaemic efficacy, particularly in ALL,[31] its use is linked to more severe infectious complications compared with prednisone. In a multicentre randomised controlled trial conducted in Europe, Möricke *et al.*[31] reported 80 severe and 29 lethal infections in patients who received dexamethasone, v. 33 severe and 13 lethal infections among those treated with prednisone. These findings emphasise the importance of balancing therapeutic

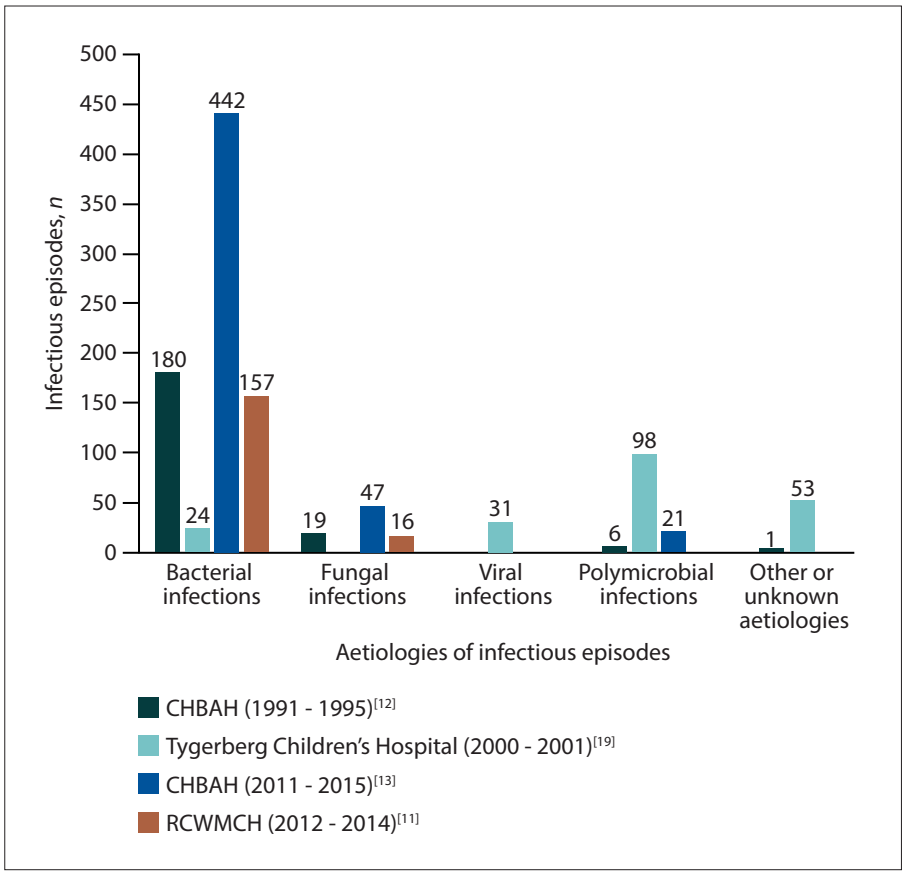

Fig. 2. Aetiological agents responsible for infectious complications in paediatric oncology patients in South Africa. (CHBAH = Chris Hani Baragwanath Academic Hospital; RCWMCH = Red Cross War Memorial Children's Hospital.)

efficacy with toxicity, especially in settings with a high burden of infectious diseases. In the southern African context, where background infection rates (e.g. TB, HIV) are high, the choice of corticosteroid should be carefully tailored to optimise treatment outcomes while minimising infection-related risks.

Indwelling catheters

Indwelling central venous catheters are routinely employed in paediatric oncology to facilitate the administration of chemotherapy. While these devices are integral to modern treatment protocols, various complications related to the device have been reported, including catheter-related bloodstream infections.[32] These devices compromise the integrity of the skin, a crucial physical barrier of the innate immune system, thereby increasing the likelihood of microbial entry and systemic infection.[33]

A retrospective study reviewed 293 Hickman line insertions over a period of 26 years and 3 months. While 62.5% of catheter placements had no complications, 13.3% of cases developed sepsis directly caused by the indwelling device.[34] These findings are supported by Mvalo *et al.*'s[11] study, which showed that 44.7% of patients with a central vascular access device experienced at least one episode of a bloodstream infection, compared with only 15% among those without such devices. These data emphasise the increased risk of catheter-associated infections among paediatric oncology patients and underscore the importance of strict infection prevention and catheter care protocols.

Furthermore, Naidu *et al.*[13] found that the use of indwelling central venous catheters increased the risk of sepsis by 2.87 times, as confirmed through microbiological testing, compared with patients without such devices.

A study conducted in South Korea found that prolonged hospitalisation (≥60 days) was a significant risk factor for the earlier development of central line-associated bloodstream infection (CLABSI), with a reported hazard ratio of 8.40 (95% confidence interval 5.14 - 13.73; $p<0.01$).[35] Similar studies in the southern African context are needed to clarify region-specific risk factors affecting the timing and occurrence of CLABSI among children receiving cancer treatment.

Malnutrition

Malnutrition is a pathological state that results from an imbalance of energy and nutrients, leading to compromised physiological integrity.[36] This deterioration encompasses impaired immune function, increasing the susceptibility of affected individuals to infectious diseases.[37]

In Nicaragua, the effect of malnutrition on morbidity and mortality in children with cancer was studied.[38] A noteworthy association between malnutrition and severe infection was established ($p=0.033$).

Malnutrition is strongly linked to profound neutropenia in paediatric oncology populations. In a cohort study of 84 paediatric cancer patients in Malawi, Israëls *et al.*[39] demonstrated a statistically significant association between malnutrition and the occurrence of severe neutropenia, with malnourished children showing a 14-fold higher odds compared with their well-nourished peers. Similarly, Mvalo *et al.*[11] reported that 23.3% of paediatric oncology patients with confirmed bloodstream infections were classified as moderately or severely underweight for age, a measure used as an indicator of poor nutritional status. This finding emphasises the strong connection between poor nutritional status and increased vulnerability to infectious complications in childhood malignancy.

Contrasting findings were reported in a retrospective study at Inkosi Albert Luthuli Central Hospital, which evaluated the impact of malnutrition on infection rates and other outcomes in 139 paediatric oncology patients over a period of 18 months.[40] Infection rates did not differ significantly between malnourished and well-nourished patients. The authors attributed this to comprehensive nutritional assessment and early intervention strategies employed during treatment, which may have mitigated the harmful effects of malnutrition on immune function and infection risk. The postulated effectiveness of such interventions emphasises the potential for targeted nutritional management to lower the risk of infection.

HIV infection

SA bears the highest global burden of HIV infection, a challenge that significantly affects the paediatric population. In 2023, ~160 000 children aged 0 - 14 years were living with HIV, of whom 63% were on antiretroviral therapy (ART) and only 47% had achieved viral suppression.[41] HIV infection causes a severe

depletion of CD4 T lymphocytes, resulting in a weakened adaptive immune system and increased susceptibility to opportunistic infections.[42]

HIV infection, as an immunocompromising condition, is associated with an elevated risk of malignancies in paediatric populations. Davidson *et al.*[43] conducted a retrospective study across six paediatric oncology units and one satellite centre in SA from 1995 to 2009. They demonstrated a progressive increase in both AIDS-defining and non-AIDS-defining malignancies concurrent with the expanding HIV epidemic.[43] Complementing these findings, Bohlius *et al.*[44] analysed data from 11 707 children living with HIV enrolled in ART programmes in Cape Town and Johannesburg, reporting a 71% reduction in malignancy risk among children receiving ART. Collectively, these studies underscore the increased oncogenic risk conferred by HIV infection and highlight the protective effect of effective ART-mediated viral suppression in reducing cancer incidence.

The concomitant presence of HIV infection and malignancy synergistically exacerbates immunosuppression, thereby increasing susceptibility to infectious complications. In Davidson *et al.*'s[43] cohort, 28.5% of paediatric patients with both cancer and HIV had active TB co-infection. Similarly, Naidu *et al.*[30] reported a TB incidence rate of 19.3 cases per 100 child-years in patients with concurrent HIV and malignancy, markedly higher than the 6.4 cases per 100 child-years reported in the HIV-negative oncology population. These data emphasise the compounded immunodeficiency in children living with HIV and malignancy, significantly increasing their vulnerability to opportunistic infections such as TB.

Adherence to ART, chemotherapy and corticosteroid regimens is a significant concern. In adults with comorbid HIV and cancer in Uganda, adherence was influenced by the patients' awareness of their cancer staging, their cancer type (AIDS defining v. non-AIDS defining), where they received ART, and treatment cost.[45] In paediatric populations, parental perceptions of these factors may have an even greater impact. The high pill burden associated with these regimens further complicates adherence. Potential drug interactions between therapies remain understudied, highlighting the need for research to optimise treatment in patients with comorbid conditions.[45,46]

Multifactorial risk for infectious disease complications in children with cancer

Most paediatric oncology patients are likely to experience many, if not all, of the risk factors outlined in the section above on risk factors for an immunocompromised state. Fig. 3 illustrates the multifactorial risk factor profile of a child with cancer in the southern African context and its potential causal effects on the development of infectious complications. The individual risk factors are discussed in the section on risk factors, and their mechanistic actions will not be repeated here.

Although prolonged hospitalisation was not addressed as a separate subsection in the section on risk factors, it is included in Fig. 3, as it has been reported to result from infectious complications.[6]

Conclusion

This review provides a comprehensive overview of the epidemiology and pathophysiology of infectious complications in paediatric oncology patients. Considering the high morbidity and mortality linked to infectious events, early detection and targeted management of predisposing factors, including neutropenia, mucosal barrier injury,

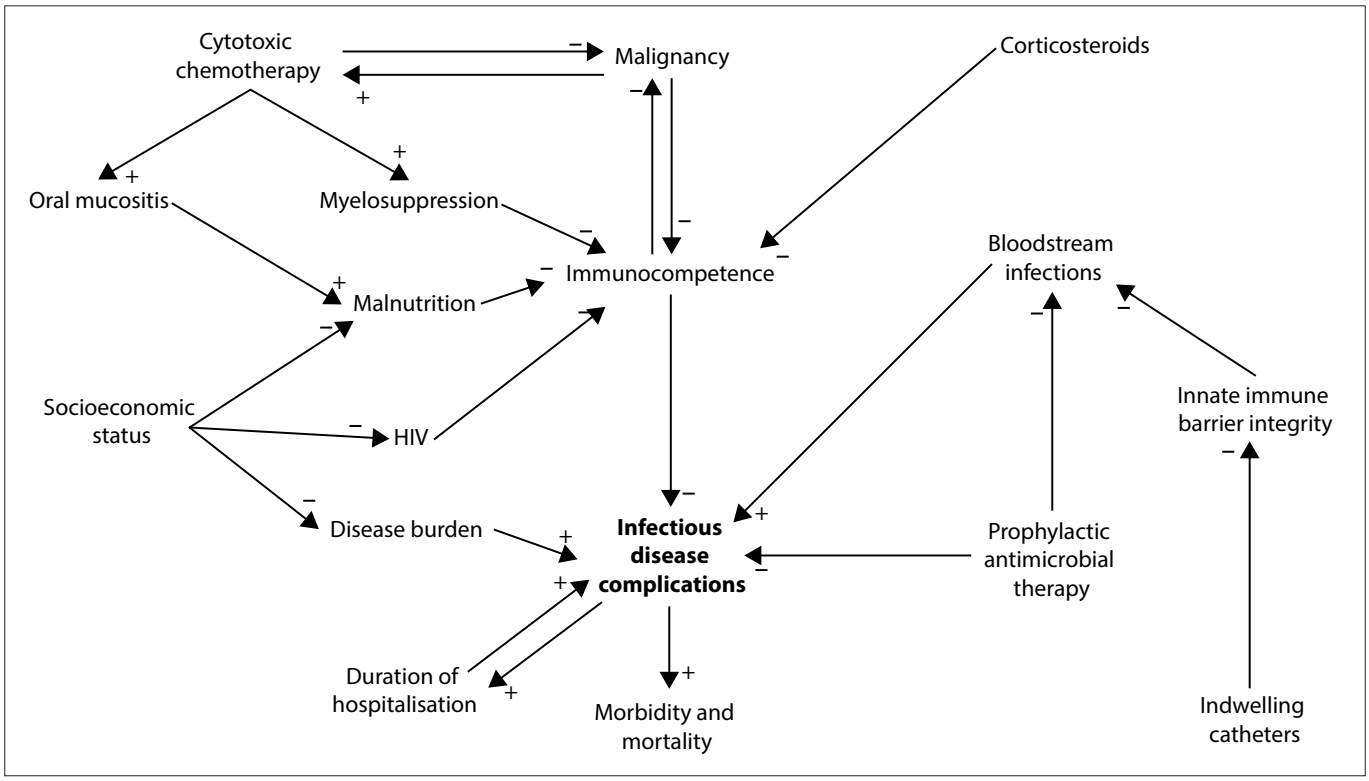

Fig. 3. Multifactorial risk for infectious disease complications in children with cancer. Arrows with a positive sign indicate a direct causal relationship, while arrows with a negative sign indicate a balancing (negative) relationship.

malnutrition, HIV co-infection and indwelling device use, are essential for optimising clinical outcomes.

Despite existing global literature, significant gaps remain in the southern African context, especially with regard to paediatric oncology patients, mechanisms of malignancy-induced immune dysregulation, and aetiology. Furthermore, the relationship between malnutrition and immune competence in this population warrants further investigation.

Future research focused on these areas is crucial to produce region-specific data that can guide evidence-based clinical guidelines. Such guidelines would improve infection prevention, nutritional strategies, and immunomodulatory approaches tailored to the paediatric oncology population in southern Africa, thereby increasing survival rates and enhancing quality of life. We highlight a significant disparity in outcomes of infectious disease complications among children with cancer in the southern African context, and advocate for a co-ordinated global effort to strengthen the entire cancer treatment pathway in a manner that is appropriate for the local setting.

Declaration. This research did not form part of the academic requirements for the authors' 3rd-year medical studies.

Acknowledgements. None.

AI declaration. The authors acknowledge the journal policy on the use of AI, and the requirement to disclose the use of any AI tools in manuscript preparation. For this manuscript, AI tools were used solely for grammatical editing. All intellectual contributions were made by the authors, who take full responsibility for the content of this manuscript.

Author contributions. All authors contributed to the conceptualisation of the study. FV, CD, TG, KG, NK, OP, TTM, IW and JW drafted the various subsections. FV edited the collective manuscript. GN edited and reviewed the manuscript.

Funding. None.

Data availability statement. Not applicable.

Conflicts of interest. None.

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Received 30 June 2025. Accepted 16 October 2025.