BMJ Global Health

Alignment in the registration, selection, procurement and reimbursement of essential medicines for childhood cancers in South Africa

Iris R Joosse ,[1] Hendrika A van den Ham,[1] Aukje K Mantel-Teeuwisse,[1] Fatima Suleman[2]

To cite: Joosse IR, van den Ham HA, Mantel-Teeuwisse AK, *et al*. Alignment in the registration, selection, procurement and reimbursement of essential medicines for childhood cancers in South Africa. *BMJ Glob Health* 2023;**8**:e012309. doi:10.1136/bmjgh-2023-012309

Handling editor Seye Abimbola

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjgh-2023-012309).

Received 15 March 2023
Accepted 30 July 2023

For numbered affiliations see end of article.

Correspondence to
Dr Hendrika A van den Ham; H.A.vandenHam@uu.nl

ABSTRACT

Introduction The effectiveness of a health system in providing access to medicines is in part determined by the alignment of several core pharmaceutical processes. For South Africa's public health sector, these include the registration of medicines, selection and subsequent procurement through national tenders. Registration, selection and reimbursement are key processes in the private sector. This study assessed the alignment of forementioned processes for essential paediatric oncology medicines in South Africa.

Methods A selection of priority chemotherapeutics, antiemetics and analgesics in the treatment of five prevalent childhood cancers in South Africa was compared with those listed in 1) the WHO Essential Medicines List for Children (WHO EMLc) 2021, 2) the registered health products database of South Africa, 3) the relevant South African National Essential Medicines Lists (NEML), 4) bid packs and awarded tenders for oncology medicines for 2020 and 2022 and 5) oncology formularies from the leading Independent Clinical Oncology Network (ICON) and two private sector medical aid schemes. Consistency between these sources was assessed descriptively.

Results There was full alignment for 25 priority chemotherapeutics for children between the NEML, the products registered in South Africa and those included on tender. Due to unsuccessful procurement, access to seven chemotherapeutics was potentially constrained. For antiemetics and analgesics, eight of nine active ingredients included on the WHO EMLc were also registered in South Africa and on its NEML. An exploratory assessment of private sector formularies showed many gaps in ICON's formulary and two medical scheme formularies (listing 33% and 24% of the chemotherapeutics, respectively).

Conclusion Despite good alignment in public sector pharmaceutical processes, access constraints to essential chemotherapeutics for children may stem from unsuccessful tenders. Private sector formularies show major gaps; however, it is unclear how this translates to access in clinical practice.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The alignment of National Essential Medicines Lists with the WHO model List of Essential Medicines has been the topic of several publications. However, these publications studied one source of information on access in isolation from other related processes in the pharmaceutical value chain.

WHAT THIS STUDY ADDS

⇒ This study looked at the interplay of multiple core pharmaceutical processes that together determine accessibility of medicines, combining data from a national and international essential medicines list, a drug registry and procurement data for the public sector, as well as medicine formularies from private sector insurance schemes. The thorough overview obtained led to the identification of potential bottlenecks in access to childhood cancer medicines.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The bottlenecks identified in this study can be used to inform the South African policy agenda while moving towards National Health Insurance. To improve access to medicines for other diseases and across different countries, the approach presented here can guide research efforts in other areas.

INTRODUCTION

Childhood cancer is an emerging challenge in low-income and middle-income countries (LMICs) including South Africa (SA).[1] With reported survival rates of about 52%, SA is lagging behind other better-resourced countries.[2] An important reason for this is the late detection of the cancer and children subsequently presenting late with advanced disease.[2] The aggressive and fast-spreading nature of many paediatric cancers further contributes to this.[3]

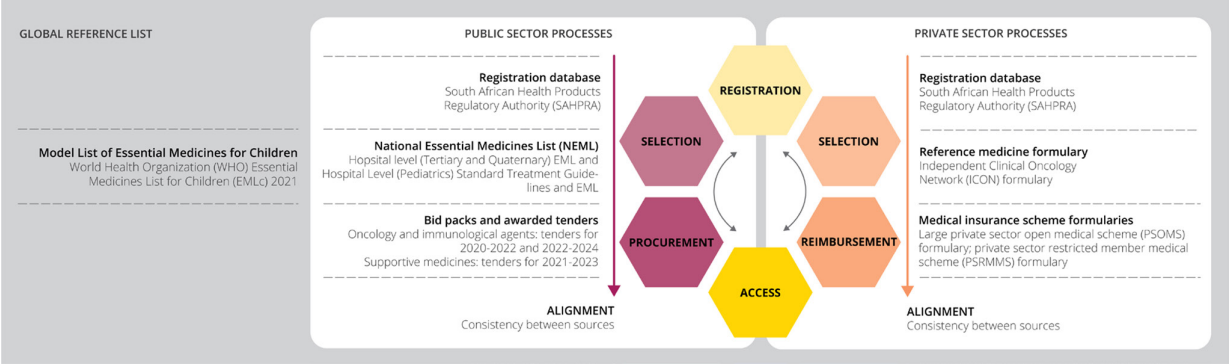

Figure 1 Ideal access pathways through alignment of core pharmaceutical processes and respective resources compared. This figure does not capture loophole arrangement for unregistered access. Core domains *distribution* and *use* not shown.

Chemotherapy is one of the basic modalities of childhood cancer management and a major determinant of outcomes.[4] Although chemotherapy was reported to be 'available for most cancers the majority of the time' in SA,[4] other sources suggest the opposite and care may be compromised due to unaffordable or unavailable medicines.[5 6] Unavailability is reported to arise from inconsistent drug supplies, stock-outs and unregistered medicines.[6 7] Furthermore, treatment is inaccessible for some patients due to long travel distances to specialised treatment facilities, poor knowledge and understanding of cancer and inadequate referral pathways.[8] Besides chemotherapy and other antineoplastics, supportive medicines for the management of pain and nausea are essential for improving adherence and quality of life and humanising care.[9 10]

Access to cancer medicines—as any medicine—is underpinned by several processes in the pharmaceutical value chain that occur at a national level. The first step towards accessible medicines is the *registration*, or market authorisation, of a drug by a national drug regulatory agency.[11] Subsequent *selection* includes the identification of prevalent health problems and corresponding priority medicines, usually in the form of a formulary or national essential medicines list (NEML) and corresponding standard treatment guidelines (STGs).[12] The WHO model Essential Medicines Lists (EML) may be used as a guide for national selection processes. Insurance *reimbursement* is often linked to selection processes. *Procurement* involves the managing of tenders or other procurement strategies, and establishing contract terms and ensuring adherence to these.[12] Those medicines that have been designated as essential should ideally be given priority in procurement as well. *Distribution* and *use* complete the circle. Alignment of these pharmaceutical processes is essential for access, as a disruption in any of these processes leads to failure of the entire system.[12]

In the South African context, *registration* is regulated by the South African Health Products Regulatory Authority (SAHPRA) for both the public and private sector.[13] *Selection* in the public sector entails the South African NEML, which is established according to different levels of care and guided by the principles of the WHO EML.[14 15] Primary and secondary level NEMLs are extracted from STGs, but the tertiary and quaternary levels only have an approved NEML. All medicines on the NEML should subsequently be *procured* through a national tender; alternatively they may be bought out by individual provinces or hospitals if a contract was not awarded following a tender process.[15] Ideal access pathways for medicines, including access pathways in the South African context, are illustrated in figure 1.

For SA's private medical insurance schemes, the *selection* of medicines consists of protocols, guidelines and formularies that are established by each individual scheme and per benefit option (eg, tier).[16] With respect to (paediatric) cancer, guidance is provided by managed care organisations such as Independent Clinical Oncology Network (ICON) and South African Oncology Consortium (SAOC), yet schemes are permitted to adapt if required.[16] ICON guidelines are reportedly used by the majority of medical schemes. *Reimbursement* of cancer medicines and other medical costs directly depends on a member's benefit limit and those services outlined in the respective scheme's protocols and formularies[15] (figure 1). Beyond the benefit limit only Prescribed Minimum Benefits (PMBs, eg, a defined set of benefits that all members of all medical schemes have access to regardless of their benefit option) must be covered. Despite this compulsory cover, medical schemes are reported to use treatment protocols and medicine formularies to control costs, forcing some patients to pay out-of-pocket for PMB conditions if medicines are not on the respective protocol or formulary.[16] Another major structure that determines access to medicines in SA's private sector is the Single-Exit-Price (SEP) legislation that mandates that a single maximum price can be charged for a medicine (excluding dispensing fees). These prices are recorded in the Medicine Price Registry (MPR).[15]

The effectiveness of SA's health system in providing the medicines required for effective management of childhood cancers to a large extent depends on the alignment of the pharmaceutical processes described above.[14] Although the operational policies are in place and theoretical relations defined,[17] the operationalisation of these processes is unclear. Therefore, this study aimed to

evaluate the alignment of these pharmaceutical processes for paediatric cancers in SA, through a comparison of medicines databases, lists and formularies. This study can contribute to a better understanding of barriers and facilitators that determine access to paediatric oncology medicines, and can help identify critical areas for policy development while SA is moving towards National Health Insurance.[18]

METHODS

Selection of medicines

To allow comparison of pharmaceutical processes, a selection of priority active ingredients in the treatment of prevalent cancers in children under the age of 15 years was made. Basis for this selection was the five most prevalent childhood cancers, identified through reports in scientific literature and the South African National Cancer Registry.[2 19] The five childhood cancers selected were acute leukaemias, brain tumours, lymphomas, nephroblastoma and retinoblastoma. Priority active ingredients were subsequently identified for these cancers through a guideline for the management of paediatric cancers in a low-resource context (Paediatric cancer in Africa[9]). An Africa-wide guideline was used since SA's public sector STGs do not include chapters on childhood cancers. Clinical guidelines from managed care organisation SAOC and ICON are not available in the public domain. Other international treatment guidelines fail to reflect SA's resource-limited setting and hence were not deemed compatible. Antineoplastics (including cytotoxic medicines, targeted therapies and hormones) as well as supportive medicines (antiemetics and analgesics) were eligible. The guideline did not specify which formulations should be used.

Data sources and characteristics

The basket of active ingredients was compared with those medicines listed in or on:

A. **The WHO's Essential Medicines List for Children (EMLc) 2021.** SA's NEML process is reported to align well with the WHO process,[14] yet it remains unclear how the active ingredients on the NEMLs align to the WHO EMLc.[20] We, therefore, included this category to assess the NEML's alignment to WHO's model list for international reference. Besides active ingredients, information on child-appropriate dosage forms and strengths was also extracted from the WHO EMLc.
B. **The database of the South African Health Products Regulatory Authority.** Medicinal products approved for use in SA are recorded in this database.[13] We sought for active ingredients in the database on non-proprietary name and brand name(s) if necessary on 16 June 2022. Registered dosage forms and strengths were extracted.
C. **NEMLs.** As cancer management predominantly takes place in specialised tertiary and quaternary hospitals, antineoplastic medicines are listed on SA's Tertiary and Quaternary Level Essential Medicines List updated in 2022.[21] This NEML is intended for both adults and children and lists active ingredients and approved indications. Supportive medicines were sought for in the 2017 (Paediatrics) Hospital Level STGs and Essential Medicines List for SA.[22] As the NEMLs (and STGs) do not specify formulations, only data on active ingredients was extracted.
D. **Antineoplastic medicines tendered for and awarded in SA's national tenders.** Oncology and immunological agents are tendered for in a separate tender. Tender round HP04-2020ONC for the period 1 July 2020 to 30 June 2022 and the additional tender round HP04-2020ONC/01 for products not awarded in the first round were included, as well as tender round HP04-2022ONC for 1 July 2022 to 30 June 2024.[23] The additional tender round for 2022–2024 (HP04-2022ONC/01) was excluded, as this tender was sent out for bidding but results had not been published by January 2023. Supportive medicines were procured through other tenders, mostly the tender for oral solid dosage forms (HP09-2021SD and HP09-2021SD/01).[23] Data on active ingredients and dosage forms and strengths included on bid packs and whether or not products were subsequently awarded were extracted. If products were not awarded in the main tender for 2020 but the additional round was successful, the procurement was still deemed successful in our analyses.

Besides an assessment of the public sector lists and databases described above, an exploratory comparison of processes in SA's private sector was conducted. Therefore, the basket of active ingredients was also compared with those medicines listed on:

E. **The ICON formulary.** Managed care organisation ICON provides protocols and guidelines, including an oncology formulary that is used as a reference in SA's private sector.[24] As the clinical guidelines and protocols created by ICON and SAOC are not publicly available, ICON's oncology formulary is used as a reference for SA's private sector. This formulary does not include supportive medicines. Formularies from October 2020, April 2021 and July 2022 were compared. Data on active ingredients and dosage forms were extracted.
F. **Private sector medical aid scheme formularies.** The formularies from a large private sector open medical scheme (PSOMS) and the Medicines Price List (MPL) of a private sector restricted member medical scheme (PSRMMS) for oncology were obtained and compared.[25 26] The PSOMS's formularies, which included supportive medicines, for quarters 1 and 2 of 2020, 2021 and 2022 were included. PSRMMS's oncology MPLs from October 2020, December 2021 and September 2022 were compared. Data on active ingredients and dosage forms were extracted.

Consistency between sources and consequent accessibility of childhood cancer medicines was assessed

descriptively on active ingredient level. Public (data sources A-D) and private sector (data sources A, E and F), as well as antineoplastic vs supportive medicines were examined separately (see figure 1). Medicines were considered accessible if no barriers were found in the national pharmaceutical processes/sources.

An additional examination into the marketing status of solid oral dosage forms was performed (both antineoplastic and supportive medicines) since these formulations are generally more difficult to manipulate (eg, dose adjustments through breaking, crushing) than injectable medicines. Additionally, solid oral dosage forms increase the possibility for treatment closer to the patient's home, whereas injectable medicines must be administered in a hospital setting. This makes the accessibility of specific age-appropriate formulations essential for improving access. Data sources A, B and D were compared, as well as source G:

G. **MPR.** The SEP of all medicinal products to be sold in SA's private sector must be recorded in the MPR.[27] Inclusion of a product in the MPR indicates that the medicine is for sale on the private market, where inclusion in the SAHPRA database only indicates regulatory approval. We sought for active ingredients in the registry on non-proprietary name and brand name(s) if necessary as at 17 November 2022. Registered dosage forms and strengths were extracted.

Patient and public involvement

There was no patient or public involvement in the design or conduct of this study. The findings of this study and recommendations will be disseminated to policymakers and public health researchers in SA.

RESULTS

A total of 25 priority antineoplastics were identified from the guideline for the 5 selected cancers (table 1), as well as 19 active ingredients (including within-class alternatives) for general supportive care (table 2). This basket of 44 active ingredients was used as a reference for comparing SA's pharmaceutical processes. WHO's model EMLc listed 21 (84%) of the antineoplastic medicines in the basket and 9 (47%) of the supportive drugs.

Antineoplastics in SA's public healthcare sector

Of the 25 antineoplastics in the basket, 19 (76%) were found in the SAHPRA database (table 1). Although chlorambucil and mercaptopurine could not be identified in the database despite the use of several different search terms, these active ingredients were found in the private sector's MPR. This implies that these products are in fact registered in SA and that the SAHPRA database is incomplete.

All 21 medicines registered in the country were also found on the NEML, showing perfect alignment between the registration and selection step. Agreement between the two essential medicine lists was 90%, with only 2 out of 21 active ingredients that were included on the WHO EMLc missing from the NEML (ie, dactinomycin and procarbazine).

At the procurement level, we found almost full agreement between medicines on the NEML and those active ingredients included in the bid pack for the national tenders (results not shown). Of notice, the two glucocorticoids (ie, dexamethasone and predniso(lo)ne) were not included in the oncology tender (but may have been included in other tenders) and the procurement step could therefore not be assessed for these drugs. Of the remaining 19 drugs on the NEML, 12 (63%) were successfully procured in both 2020 and 2022.

Ultimately, we found no barriers in access for 56% of the basket (14/25), intermittent access for 2 antineoplastic agents (8%) and constrained access for 9 (36%) products, 5 of which due to procurement restraints only (table 1).

When looking in more detail at the procurement step of antineoplastic medicines (table 3), we noticed that a very low proportion of medicines was successfully tendered for in the main tender round of 2020, with 7 (33%) of the 21 that was tendered for getting awarded. In the additional tender that was finalised over 5 months later, seven active ingredients were additionally awarded (including a second formulation of folinic acid) but the tender remained unsuccessful for another seven products. The 2022 tender round was considerably more successful, with only 6 of 21 (29%) products not getting awarded. No new tender contracts were awarded yet following an additional tender round by SA's Department of Health (DoH).

Supportive medicines in SA's public healthcare sector

Table 2 shows a variety of medicines that may be used in the management of (anticipatory) nausea and vomiting and nociceptive pain. A large majority of 17 of 19 (89%) of these supportive care medicines is registered for use in SA. Potential barriers in access due to medicines not being listed on the NEML were found for 10 (53%) supportive medicines. Compared with the WHO EMLc, we identified no barriers in access for 8 of 9 (89%) active ingredients, the one exception being the antiemetic aprepitant.

Antineoplastics in SA's private healthcare sector

In an exploratory assessment of private sector alignment, table 4 shows that there may be many gaps in access. The ICON formulary that can be used as guidance by the private sector medical schemes in establishing their own formulary shows many gaps as compared with the WHO EMLc and NEML, including for medicines such as the glucocorticoids, cytarabine and mercaptopurine. From 2020 to 2021, several products seem to be removed from the formulary, for which the reasons are unknown. No new products were added to the formulary during this time. In contrast, the PSOMS seems to have added more products to their formulary in 2021. Despite that, the scheme still shows major gaps as compared with ICON

Table 1 Comparison of antineoplastics in South Africa's public sector core pharmaceutical processes

Active ingredient	WHO EMLc	SAHPRA	NEML	Procurement	Accessibility
H02Ab Glucocorticoids					
Dexamethasone	✓	✓	✓!		✓!
Predniso(lo)ne	✓	✓	✓!		✓!
L01A Alkylating agents					
Chlorambucil	✗	!	✓	✓	✓
Chlormethine					
Cyclophosphamide	✓	✓	✓	✓	✓
Ifosfamide	✓	✓	✓	✓	✓
Lomustine	✗	✗	✗	✗	✗
L01B antimetabolites					
Cytarabine	✓	✓	✓	✗	✗
Mercaptopurine	✓	!	✓	✓	✓
Methotrexate	✓	✓	✓	✓	✓
L01C Plant alkaloids and other natural products					
Etoposide	✓	✓	✓	✓	✓
Vinblastine	✓	✓	✓	✓	✓
Vincristine	✓	✓	✓	✓	✓
L01D Cytotoxic antibiotics and related substances					
Bleomycin	✓	✓	✓	✗	✗
Dactinomycin	✓	✗	✗	✗	✗
Daunorubicin	✓	✓	✓	✗	✗
Doxorubicin	✓	✓	✓	✓	✓
Idarubicin	✗	✓	✓	✗	✗
L01X Other antineoplastic agents					
(L-)Asparaginase	✓	✓	✓	✗	✗
Carboplatin	✓	✓	✓	✓	✓
Cisplatin	✓	✓	✓	✓	✓
Procarbazine	✓	✗	✗	✗	✗
Tretinoin	✓	✓	✓	✓	✓
V03AF detoxifying agents for antineoplastic treatment					
Calcium folinate	✓	✓	✓	✓	✓
Mesna	✓	✓	✓	✓	✓

Continued

Table 1 Continued

Active ingredient	WHO EMLc	SAHPRA	NEML	Procurement	Accessibility

Inclusion of childhood oncology medicines on essential medicines lists and the South African registration database; whether successfully procured in 2020 and 2022 national tenders for oncology and immunological agents; and consequences for perceived access.

=yes/always

=sometimes;

=no/never;

=corticosteroids are not included in the tertiary and quaternary level essential medicines list but rather included on the 2017 (Pediatrics) Hospital Level Standard Treatment Guidelines and Essential Medicines List for South Africa. Corticosteroids were not part of the tender for oncology and immunological agents.

=Not found in SAHPRA database, but can be found in Medicines Price Registry.

NEML, National Essential Medicines List; SAHPRA, South African Health Products Regulatory Authority; WHO EMLc, WHO model Essential Medicines List for children.

and the EMLs. Of the 21 active ingredients on the NEML, only 7 (33%) were on the formulary in 2022. For members of a restricted medical scheme, a meagre 5 (24%) active ingredients were listed between 2020 and 2022.

Solid oral dosage forms in SA's public and private healthcare sector

An exploratory assessment of pharmaceutical policy processes specifically for solid oral dosage forms was performed (online supplemental annex S1), containing all (child-appropriate) solid oral dosage forms as listed in the WHO EMLc for the registered active ingredients in our basket. Where the WHO EMLc generally listed several dosage strengths for oral solids, not all of these strengths were registered in SA. Additionally, although some products are registered in the country, not all of them seem to be accessible in both the public and private sector (eg, (successfully) tendered for or found in MPR). For example, dexamethasone 4 mg tablets and morphine 10 mg immediate release tablets do not seem to be accessible in either sector.

DISCUSSION

The key pharmaceutical processes of registration, selection and procurement of medicines for five major childhood cancers seem to be aligned in SA's public healthcare system, indicating good operationalisation of SA's policies and processes. The bottleneck seems to lie in the procurement of essential medicines through national tenders. Private sector formularies listed a limited selection of priority chemotherapeutics, indicating potential restrictions in what may be reimbursed to their beneficiaries.

While our findings also indicate alignment with international processes, the few gaps in comparison to the WHO EMLc may have a big impact. In fact, in a 2022 cross-sectional survey to determine priority essential childhood cancer medicines, dactinomycin was in the top 10 of most frequently selected drugs by paediatric oncologists when asked what medicines would achieve greatest benefit in children.[28] Thus, the lack of market authorisation for dactinomycin in SA indicates that deficiencies in therapeutic care exist. Although certain legislative loophole arrangements—in SA's case in the form of Section 21 access—can still allow the use of unregistered drugs after named-patient approval, this access pathways is associated with a range of challenges.[29] These include the obtaining of hospital and/or provincial approval and the associated administrative burden on clinicians, the universally limited budgets to buy products outside of the NEML, and considerable delays in supply when products need to be imported. In SA's private sector, medical schemes are under no obligation to reimburse section 21 medicines.[16]

Procurement issues potentially constraint access to some of the key chemotherapeutics in the management of childhood cancers such as cytarabine and etoposide.[25] From the evidence obtained in this study, it cannot be deduced whether submitted bids were not awarded by the DoH or whether companies are not submitting any bids, but anecdotal evidence suggests that the DoH's price expectations are too low to make bidding profitable.[29] Additionally, even if some products were eventually successfully awarded in an additional tender for 2020–2022, this supplementary round brings a considerable delay of about 4 months based on the tender documents. These delays also affected core chemotherapeutics such as doxorubicin and vincristine.[28] Noteworthy, DoH's price expectations were unchanged for the additional tender round. In the meantime products must be bought out by provincial governments or individual hospitals to meet the demand, putting considerable strain on hospital pharmacists and continuous supply cannot be guaranteed during this time.[30]

Although our findings indicate potential difficulties in procurement, actual accessibility remains hard to predict based on these tender documents alone: medicines can be procured through buy-outs if contracts were not awarded, or medicines may be in short supply despite a contract. With regimens generally consisting of four or five active ingredients, even intermittent supply issues for one drug can negatively impact care for these aggressive cancers; omitting or switching of drugs is undesirable and could have detrimental effects.[2 7] Surveys on the ground are required to get a more complete picture of supply and availability issues and how these impact patient outcomes.

Table 2 Comparison of supportive care medicines in South Africa's public sector core pharmaceutical processes

Active ingredient	WHO EMLc	SAHPRA	NEML	Accessibility
Paracetamol	✓	✓	✓	✓
NSAIDs				
Ibuprofen*	✓	✓	✓	✓
Niflumic acid*	✗	✗	✗	✗
Diclofenac*	✗	✓	✗	✗
Weak opioids				
Codeine*	✗	✓	✗	✗
Tramadol*	✗	✓	✗	✗
Nalbufine*	✗	✗	✗	✗
Buprenorphine*	✗	✓	✗	✗
Strong opioids				
Morphine*	✓	✓	✓	✓
Fentanyl*	✗	✓	✗	✗
5-HT3 antagonists				
Granisetron*	✓	✓	✓!	✓
Ondansetron*	✓	✓	✓	✓
Benzodiazepines				
Lorazepam*	✓	✓	✓	✓
Alprazolam*	✗	✓	✓!	✓
Dopaminergic antagonists				
Metoclopramide	✓	✓	✓	✓
Prochlorperazine	✗	✓	✗	✗
Other antiemetic agents				
Aprepitant*	✓	✓	✗	✗
Dexamethasone	✓	✓	✓	✓
Fosaprepitant*	✗	✓	✗	✗

Inclusion of childhood oncology medicines on essential medicines lists and the South African registration database and consequences for perceived access.
✓=yes; ✗=no; !=not included on pediatric hospital level standard treatment guidelines and essential medicines list, but rather on the 2022 Tertiary and Quaternary Level Essential Medicines List.
*Within-class alternatives.[9]
NEML, National Essential Medicines Lists; NSAID, Non-Steroidal Anti-Inflammatory Drug; SAHPRA, South African Health Products Regulatory Authority; WHO EMLc, WHO Essential Medicines List for Children.

Notwithstanding the considerable number of red crosses for access to supportive medicines, we have identified no major issues in accessibility of these active ingredients based on the *registration* and *selection* step alone. Not only are the gaps in registration status and NEML selection largely in line with international guidelines,[20] but also not all within-class alternatives are required to be accessible if another from the same therapeutic class is (also stipulated in guideline[9]). It is, however, relevant that at least one alternative can be accessed if the medicine of first choice is not well tolerated. In this South African case study, we find that at least one active ingredient per class should be accessible—except for weak opioids. This gap does not seem problematic, since there is no international consensus on their use due to a lack of evidence.[31] In the *other antiemetics* group, the inclusion of aprepitant on the NEML could be an important future addition, since aprepitant or analogues may be used as a further escalation in care if other antiemetics are insufficient.[7 10]

Table 3 Details of public sector procurement of oncology medicines in 2020 and 2022

	2020		2022
Active ingredient	Main tender	Additional tender	Main tender
Chlorambucil	✓	–	✓
Cyclophosphamide	✗	✓	✓
Ifosfamide	✗	✓	✓
Cytarabine	✗	✗	✗
Mercaptopurine	✓	–	✓
Methotrexate	✓✗	✗	✓
Etoposide	✗	✗	✓
Vinblastine	✓	–	✗
Vincristine	✗	✓	✓
Bleomycin	✗	✗	✗
Daunorubicin	✗	✗	✗
Doxorubicin	✗	✓	✓
Idarubicin	✗	✗	✗
(L-)Asparaginase	✗	✗	✗
Carboplatin	✗	✓	✓
Cisplatin	✗	✓	✓
Tretinoin	✓	–	✓
Folinic acid	✓✗	✓	✓
Mesna	✗	✓	✓
Granisetron	✓	–	✓
Ondansetron	✓	–	✓

Contracts awarded for oncology agents in national tender rounds HP04-2020ONC, HP04-2020ONC/01 and HP04-2022ONC. All products were included on the bid pack, unless indicated with '–'. Additional tender round for 2022 (HP04-2022ONC/01) has not been finalised at the time of writing and is therefore not include above. Note: products not registered in South Africa are not shown in table.
✓=yes; ✓✗=at least one of multiple dosage forms; ✗=no.

Although minimum coverage in the private sector (eg, PMB level) is supposed to be similar to the care as provided in the state sector and across all medical schemes,[15] major gaps are visible as compared with the WHO EMLc and the public sector's NEML. This misalignment already starts in the ICON formulary and is further exacerbated for the two medical scheme formularies. Although the large PSOMS is reported to take guidance from ICON,[16] the inconsistencies between both formularies rather imply that other resources and factors also play a role in the establishment of their formularies. With that, the role of ICON in the private healthcare system is unclear.[16]

The rather large number of red crosses for the ICON formulary and two private sector medical schemes must, however, be interpreted with caution. Reimbursement of cancer therapy for many medical aid plans depends on monetary benefit limits: a predetermined amount from which consultation fees, various investigative scans and treatments including medicines are initially funded.[16] It is only after this limit has been reached that patients may be restricted to formularies to avoid co-payments, especially if their diagnosis is not one of the 270 PMB covered indications (including some paediatric cancers). With that, the gaps identified may be of particular relevance to those without additional oncology benefits and PMB-level insured members. In addition, schemes may opt to use specific oncology protocols to define processes in care and access to medicines, but these are not publicly available. Nonetheless, it is difficult to predict what these results mean for individual medical schemes and insured members. This lack of transparency in what will be—or will not be—covered and when these formularies apply, creates challenges for members when having to navigate the system.[16]

In the interpretation of all of our findings, we acknowledge that even when no major barriers seem to exist on the active ingredients level, access may be more constrained for specific finished pharmaceutical products (FPPs). This is of particular importance for oral dosage forms in paediatrics, since different dosage strengths are required for children of different ages and manipulation of products could introduce quality issues and errors.[32] An exploratory assessment of solid oral dosage forms was conducted with this in mind, but the lack of data in the NEML and ICON's formulary on specific (required) FPPs prevented more comprehensive comparisons. The absence of accurate guidance on required FPPs in these sources constitutes a significant gap in itself, particularly as these documents guide subsequent procurement. A more detailed NEML, potentially complemented by STGs, could address this deficiency. Alternatively, making SAOC's and ICON's treatment guidelines publicly available could play an important role in addressing this gap.

Nevertheless, the fact that some products were not found in either the tender bid packs nor the MPR in the exploratory assessment implies that these common products may no longer be marketed in SA. With that, this exploratory assessment confirmed anecdotal reports that products are disappearing from the market.[29] Similarly, ICON referred to bleomycin access through a section 21 exemption, despite a bleomycin product having market authorisation in SA. This again implies that the registered product is not widely available in SA, and alternative, equivalent products may be accessed via this loophole arrangement.

A limitation of this study is that an Africa-wide treatment guideline from 2017 was used to inform our basket, due to a lack of a South African equivalent. This may have resulted in active ingredients of local importance being missed, particularly some of the innovative medicines

Table 4 Comparison of antineoplastics in South Africa's private sector formularies

Active ingredient	WHO EMLc	NEML	ICON medicine formulary			PSOMS formulary			PSRMMS MPL oncology		
			2020	2021	2022	2020	2021	2022	2020	2021	2022
H02Ab Glucocorticoids											
Dexamethasone	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗
Predniso(lo)ne	✓	✓	✗	✗	✗	✓	✓	✓	✗	✗	✗
L01A alkylating agents											
Chlorambucil	✗	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗
Chlormethine	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Cyclophosphamide	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✗
Ifosfamide	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✗
Lomustine	✗	✗	!	!	!	✗	✗	✗	✗	✗	✗
L01B antimetabolites											
Cytarabine	✓	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗
Mercaptopurine	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗
Methotrexate	✓	✓	✓	✓	✓	✓	✓	✓	✗	✗	✗
L01C plant alkaloids and other natural products											
Etoposide	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓
Vinblastine	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✗
Vincristine	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓
L01D cytotoxic antibiotics and related substances											
Bleomycin	✓	✓	!	!	!	✗	✗	✗	✗	✗	✗
Dactinomycin	✓	✗	!	!	!	✗	✗	✗	✗	✗	✗
Daunorubicin	✓	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗
Doxorubicin	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓
Idarubicin	✗	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗
L01X other antineoplastic agents											
(L–)asparaginase	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗
Carboplatin	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓
Cisplatin	✓	✓	✓	✓	✓	✗	✗	✓	✓	✓	✓
Procarbazine	✓	✗	!	!	✗	✗	✗	✗	✗	✗	✗
Tretinoin	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗
V03AF detoxifying agents for antineoplastic treatment											
Calcium folinate	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗
Mesna	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗

Continued

Table 4 Continued

Active ingredient	WHO EMLc	NEML	ICON medicine formulary			PSOMS formulary			PSRMMS MPL oncology		
			2020	2021	2022	2020	2021	2022	2020	2021	2022

Inclusion of childhood oncology medicines on the WHO and South Africa's national essential medicines list; compared with the ICON medicine formularies, a large PSOMS' formularies and a PSRMMS Oncology MPLs for 2020, 2021 and 2022.
✓=yes; ✗=no; !=indicated as essential and accessible through section 21 legislation.
ICON, Independent Clinical Oncology Network; MPL, Medicines Price List; NEML, National Essential Medicines List; PSOMS, private sector open medical scheme; PSRMMS, private sector restricted member medical scheme; WHO EMLc, WHO model Essential Medicines List for children.

that may not be available in most of the other countries on the African continent. Additionally, treatment protocols, clinical insights and available therapies may have changed since then. For example, chlormethine, tramadol and niflumic acid do not seem to be medicines of first choice anymore, also explaining their absence from the WHO EMLc and national sources. Nonetheless, most of the priority medicines were also identified as such in a recent international survey among paediatric oncologists and paediatricians in LMICs,[28] showing general representativeness of our sample. Additionally, details on FPPs were not provided in this resource—nor in some of the other data sources—limiting our analyses to active ingredient level and hence limiting the accuracy of our findings. Despite its limitations, the present basket allowed us to study the alignment of pharmaceutical processes, as was the primary aim of this study. Furthermore, we were limited to the use of publicly available data for this study. This also restricted us to the use of data on tenders as a proxy for *procurement* as a whole. The SAHPRA database was used to assess *registration* status, but it is unclear as to how often this database is updated. To mitigate the risk of incomplete data, the MPR was used to verify whether medicines were on the private market meaning they must have been registered. Finally, in the interpretation of these findings we must stress that even though we have not identified any barriers in access to the majority of these active ingredients via database evaluation, this does not guarantee that a medicine is indeed available on the shelf. The conduct of longitudinal availability surveys would be of particular complementary value to our findings.

The novelty and significance of this study lie in the scope of pharmaceutical processes studied. Where previous studies in other countries have compared national EMLs with the WHO model list[33–35] or with national drug registries,[11] this study is the first to include data on *procurement* and potential *reimbursement* in addition to (international) *selection* and *registration*. By studying these steps together, a more comprehensive picture of potential gaps was obtained and specific bottlenecks could be identified. With that, this study also emphasises the need for making information publicly available, including treatment guidelines, procurement documents and outcomes. Finally, the exploratory assessments performed highlight the importance of checking multiple sources to validate findings and enable the placing of results in the often complex context of a health system.

CONCLUSION

Fundamental pharmaceutical processes in SA's public health system showed extensive alignment for medicines used in the treatment of five major childhood cancers, but access to priority antineoplastic and supportive medicines in the management of these cancers is threatened due to unsuccessful procurement of drugs in national tenders, or an absence of active ingredients or specific formulations on the South African market. Private sector formularies showed major gaps, but it is unclear how oncology benefits/formularies align to international guidelines as these are not transparent. Additionally qualitative research or quantitative surveys are needed to get a better understanding of the challenges in accessing childhood oncology medicines.

Author affiliations
[1]Utrecht WHO Collaborating Centre for Pharmaceutical Policy and Regulation, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands
[2]WHO Collaborating Centre for Pharmaceutical Policy and Evidence Based Practice, School of Health Sciences, University of KwaZulu-Natal, Durban, South Africa

Contributors All authors were involved in conception and study design. IRJ drafted the article, HAvdH, AKM-T and FS were involved in critical revision of the article. FS is guarantor for this work and accepts full responsibility for the finished work and the conduct of the study. All authors approved the final article.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The data that support the findings of this study are publicly available through the cited sources.

ORCID iD

Iris R Joosse http://orcid.org/0000-0001-7677-8589

REFERENCES

1 Magrath I, Steliarova-Foucher E, Epelman S, *et al*. Paediatric cancer in low-income and middle-income countries. *Lancet Oncol* 2013;14:e104–16.
2 Stones DK, De Bruin GP, Esterhuizen TM, *et al*. Childhood cancer survival rates in two South African units. *S Afr Med J* 2014;104:501–4.
3 CANSA. Types of Chilhood cancer. Available: https://cansa.org.za/types-of-childhood-cancer [Accessed 20 Apr 2022].
4 Geel JA, Challinor J, Ranasinghe N, *et al*. Pediatric cancer care in Africa: SIOP global mapping program report on economic and population indicators. *Pediatr Blood Cancer* 2021;68:e29345.
5 Mattila PO, Babar Z-U-D, Suleman F. Assessing the prices and affordability of oncology medicines for three common cancers within the private sector of South Africa. *BMC Health Serv Res* 2021;21:661.
6 Hadley LGP, Rouma BS, Saad-Eldin Y. Challenge of pediatric oncology in Africa. *Semin Pediatr Surg* 2012;21:136–41.
7 Lopez Gonzalez L. South Africa faces paediatric cancer drug shortage as suppliers fail to meet demand. 2016. Available: https://mg.co.za/article/2016-08-01-00-south-africa-faces-paediatric-cancer-drug-shortage-as-suppliers-fail-to-meet-demand [Accessed 4 Jan 2023].
8 Poyiadjis S, Wainwright L, Naidu G, *et al*. The saint Siluan warning signs of cancer in children: impact of education in rural South Africa. *Pediatr Blood Cancer* 2011;56:314–6.
9 Stefan DC, Harif M. *Pediatric Cancer in Africa: A Case-Based Guide to Diagnosis and Management*1st ed. New York: Springer, 2017.
10 Van de Wetering MD, Schouten-van Meeteren NYN. Supportive care for children with cancer. *Semin Oncol* 2011;38:374–9.
11 Lyus R, Pollock A, Ocan M, *et al*. Registration of antimicrobials, Kenya, Uganda and United Republic of Tanzania, 2018. *Bull World Health Organ* 2020;98:530–8.
12 Management Sciences for Health. In: *MDS-3: Managing Access to Medicines and Health Technologies*. Arlington, VA: Management Sciences for Health, 2012.
13 South African health products regulatory authority. Available: https://www.sahpra.org.za/ [Accessed 4 Jan 2023].
14 Perumal-Pillay VA, Suleman F. Selection of essential medicines for South Africa - an analysis of in-depth interviews with national essential medicines list committee members. *BMC Health Serv Res* 2017;17:17.
15 SulemanF, Gray A. Pharmaceutical policy in South Africa. In: Babar Z, ed. *Pharmaceutical Policy in Countries withDeveloping Healthcare Systems*. Springer International Publishing, 2017.
16 Meyer S, Tsotetsi N, Nqabeni G, *et al*. Analysis of oncology benefits offered by 10 medical schemes in South Africa. 2022. Available: https://cancerallliance.co.za/wp-content/uploads/2022/07/Oncology-benefits-from-medical-schemes-in-South-Africa_02.pdf
17 GrayA, Suleman F, PharasiB. South Africa's National drug policy: 20Yearsand still going? *S Afr Health Rev* 2017;2017:49–58.
18 Schneider H, Kredo T, OdendaalWA, *et al*. What are health policy and systems research priorities for universal health coverage in South Africa? *S Afr Med J* 2023;113:61–4.
19 National Cancer Registry. 2019 National cancer Registry report. Available: https://www.nicd.ac.za/centres/national-cancer-registry/cancer-statistics/ [Accessed 4 Jan 2023].
20 World Health Organization. World health organization model list of essential medicines for children. Geneva World Health Organization; 2021.
21 National Department of Health. Hospital level (tertiary and Quaternary) essential medicines list. Pretoria National Department of Health; 2022.
22 National Department of Health. Hospital level (Paediatrics) Standard treatment guidelines and essential medicines list for South Africa, 4th edition. Pretoria National Department of Health; 2017.
23 National Department of Health. Tenders. Available: https://www.health.gov.za/tenders/ [Accessed 4 Jan 2023].
24 Icon Oncology. Clinical quality cancer care. Available: https://iconsa.co.za/about/clinical-quality-resources/ [Accessed 4 Jan 2023].
25 Discovery. Medical aid: chronic illness benefit. 2023. Available: https://www.discovery.co.za/medical-aid/chronic-illness-benefit [Accessed 16 Jan 2023].
26 Government Employees Medical Scheme (GEMS). Formulary lists. Available: https://www.gems.gov.za/en/Healthcare-Providers/Formularies-List [Accessed 16 Jan 2023].
27 South African Medicine Price Registry. Database of medicine prices. Available: http://www.mpr.gov.za/ [Accessed 17 Nov 2022].
28 Denburg AE, Fundytus A, Khan MS, *et al*. Defining essential childhood cancer medicines to Informprioritizationand access: results from anInternational, cross-sectional survey. *JCO Glob Oncol* 2022;8:e2200034.
29 Meyer S, Nqabeni G, Tsotetsi N. Access to cancer medicines inSouth Africa: cancer alliance report CA03/2021. 2021. Available: https://cancerallliance.co.za/wp-content/uploads/2021/05/Access-to-Cancer-Medicines-SA-April-2021-v2.pdf
30 Modisakeng C, Matlala M, Godman B, *et al*. Medicine shortages and challenges with the procurement process among public sector hospitals in South Africa; findings and implications. *BMC Health Serv Res* 2020;20:234.
31 Guidelines on the management of chronic pain in children. Geneva World Health Organization; 2020.
32 Promoting safety of medicines for children, Geneva. World Health Organization; 2007. Available: https://www.who.int/medicines/publications/essentialmedicines/Promotion_safe_med_childrens.pdf
33 Boateng R, Petricca K, Tang B, *et al*. Determinants of access to childhood cancer medicines: a comparative, mixed-methods analysis of four Caribbean countries. *Lancet Glob Health* 2021;9:e1314–24.
34 Tang B, Bodkyn C, Gupta S, *et al*. Access to WHO essential medicines for childhood cancer care in Trinidad and Tobago: A health system analysis of barriers and Enablers. *JCO Glob Oncol* 2020;6:67–79.
35 Boateng R, Renner L, Petricca K, *et al*. Health system determinants of access to essential medicines for children with cancer in Ghana. *BMJ Glob Health* 2020;5:e002906.