BMJ Open  Availability of cytotoxic medicines in the WHO essential medicine list used in treating childhood malignancies in low-income and lower-middle-income countries: a systematic review protocol

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INTRODUCTION
Cancer is a leading cause of death globally with childhood cancers accounting for around 5% of the total incidence. Almost 90% of childhood cancers are recorded from low-income and lower-middle-income countries (LLMICs), where survival rates are comparatively low. The unavailability of essential medicines for childhood cancers is identified as a reason for this observed health inequity. The objectives of this review are to describe the availability of cytotoxic medicines in the WHO essential medicine list (EML) used in treating children with cancer in LLMICs and to determine the enablers and barriers to accessing WHO essential medicines for childhood cancer.

METHODS AND ANALYSIS
A systematic review will be conducted using electronic databases: MEDLINE, EMBASE and CINAHL. Additional articles and grey literature will be searched in Google Scholar and reference list of the selected articles. It will include primary studies, national/regional reports and policy documents. Review questions will be framed into different components according to the ECLIPSe framework. Children less than 19 years of age diagnosed with any malignant disorder in LLMICs will be the client group. Studies that have focused on the availability of EML for adult malignancies and care providers’ knowledge of EML for childhood malignancies will not be considered. Only the studies reported in the English language will be included. Mixed methods Appraisal Tool will be used to assess the quality of included studies. Data will be presented as a narrative synthesis.

Ethics and dissemination
This research is exempt from ethics approval because the work is carried out on published documents. Findings of this review will be disseminated through a peer-reviewed journal for the authorities in LLMICs to understand the magnitude of the problem and to identify enablers and barriers to take evidence based decisions to improve their health system.

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STRENGTHS AND LIMITATIONS OF THIS STUDY
⇒ This systematic review aims to describe the availability of the enablers and barriers that influence availability of the cytotoxic medicines in the WHO essential medicine list (EML) used in treating children with cancer in low-income and lower-middle-income countries.
⇒ The search strategy was developed through an iterative process by a multidisciplinary team including an academic support librarian, paediatric oncologist, a paediatrician and public health specialists.
⇒ Article screening, data extraction and quality assessment will be performed by two independent reviewers with experience in systematic review methodology to minimise the biases.
⇒ The studies/reports from 1977 to 2022 will be included to capture all publications since the introduction of EML list.
⇒ Since only the articles published in English language will be reviewed in this study, this limitation may introduce language bias.

Childhood cancers account for around 5% of total cancer incidence in the world. According to the WHO, it is estimated that around 400 000 children develop cancer worldwide, accounting for the incidence from 70 to 140 occurrences per million yearly. Leukaemia has been common among children below 14 years at 37%; brain and nervous system cancers stand second at 16%, followed by lymphomas at 13%, and other cancers. Around 110 000 deaths of children and adolescents under 14 years old are reported each year equating to around 1% of total cancer deaths. In most developed countries, cancer is the second highest cause of death in children.

Survival rate is an important measure in assessing the progress of efforts made to improve cancer outcomes. The WHO has
recorded an 80% five-year survival rate in children with cancer in high-income countries, including the USA, Japan, Australia, UK and many European countries. However, childhood cancer survival rate is as low as 15% and 40% at best in low-income and lower middle-income countries (LLMICs) where 90% of childhood cancer incidents are recorded. Moreover, it has been rooted out that solid tumours are frequently documented in these low-income countries since most of the children with leukaemia are misdiagnosed with tropical infectious diseases such as malaria and dengue and die of infections or haemorrhage.

Early diagnosis, access to supportive care facilities and availability of different therapeutic strategies play a huge role in improving survival of children with cancer. When identified early, cancers are more likely to respond effectively to treatment resulting in less suffering and improved survival.

Geographical inequality in childhood cancer survival is closely related to access to care, and unfortunately, it is estimated more than 60% of children with cancer worldwide have little or no access to standard care including essential medicines for cancer. Therefore, WHO has identified improving survival rate of children with cancer to at least 60% in six index cancers globally as a key priority in the global health agenda with the launch of the Global Initiative for Childhood Cancer (GICC) in 2019.

**WHO essential drugs for cancer treatments**

The Essential Medicines List (EML) published by the WHO biennially provides each country with guidance in selecting medications, including anticancer drugs, which should be prioritised for public access. Governments of each country develop national formulae according to the guidance of WHO EML, representing specific medications prioritised for its population. A separate model list of Essential Medicines for children (EMLc) was introduced in 2007. After several updates from contributors such as the Essential Medicines Working Group of the International Society of Pediatric Oncology (SIOP), the EML has expanded with more antineoplastic drugs and drugs used for supportive care. However, it is observed that the national formulae of most LLMICs had less than 50% alignment with the cancer section of EMLc.

A study by Barr and Robertson found that listing 18 preidentified antineoplastic drugs in the EMLc in National Essential Medicines Lists (NEMls) or National Reimbursable Medicine lists of 135 countries varied from 27% to 95%. Not surprisingly it was lowest in low-income countries, suggesting that this variability was associated with the Gross National Income of the country.

Even if a medicine is included in an NEMl, that does not guarantee the on-the-ground availability of such medicine. This is because economic conditions and the prevalence of certain cancer risk factors highly influence decisions related to cancer drug access in these countries. Furthermore, it has been positively associated with the gross domestic product, Human Development Index and health expenditures of each country. Therefore, it is crucial to understand on the ground availability of medications in order to improve benefits for children and reduce the survival gap between children with cancer globally.

The Pediatric Oncology in Developing Countries committee of SIOP has created a working group to help identify essential paediatric cancer medications in LLMICs, and to identify obstacles in the way of achieving equity of access and affordability to these medicines after considering public health, resource limitations, cost considerations, health disparities and ethics in addition to biomedical evidence. To date, systematically synthesised literature on WHO essential medicine availability and accessibility in LLMICs is scarce to generate evidence informed recommendations.

In this backdrop, the current review aims to identify and summarise literature that has assessed/described the availability of WHO essential medicines for childhood cancers in LLMICs and to describe barriers/enablers to access such medicines.

**Objectives**

The objectives of this review are as follows.

1. To describe the availability of WHO essential medicine for childhood malignancies in LLMICs.
2. To determine the enablers and barriers to access WHO essential medicines for childhood cancer in LLMICs.

**METHODS AND ANALYSIS**

This protocol was registered in PROSPERO registry on 31 May 2022 (CRD42022334156). Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines will be followed in conducting and reporting of this systematic review.

**Eligibility criteria**

Review question was broken into different components according to ECLIPSE framework.

**Expectations**

To describe availability of WHO essential medicine for childhood malignancies in LLMICs and to determine the factors associated with medicine availability/non-availability.

**Client group**

Children with diagnosed malignancy.

**Location**

LLMIC.

**Impact**

Reduce cost and more equitable access to EMLc with malignancy (enablers and barriers).
Professionals involved:
Healthcare professionals, policy-makers, hospital administrators.

Service
Availability of essential medicine for childhood malignancy free of charge.

Study characteristics
This systematic review will include primary studies (cross-sectional studies and mixed-methods studies) and national/and or regional reports, and policy documents on availability of WHO essential medicine for childhood malignancies in LLMICs and also studies on enablers and barriers to their access. Studies on availability of EML for adult malignancies and studies which focus on assessing care providers’ knowledge of EML for childhood malignancies will be excluded.

Definitions
The term ‘WHO essential medicines’ included all medicines listed in the WHO Model List of EMLc in any version from 1997 to 2021. This review will be limited to availability of cytotoxic medicines used in treatment of children with cancer. ‘Childhood malignancies’ describes any malignant disorder diagnosed in children less than 19 years of age. The term LLMIC was defined according to the World Bank categorisation 2021.12

Time frame
We will be including studies/reports from 1977 up to 2022 since the EML list was first started in 1977 and is revised every 2 years and last being in 2021. An update search of the same databases will be carried out just before the completion of data extraction for the current review. The expected time frame between last search performed and submission for publication is 3 months.

Report characteristics
We will only include studies reported in the English language due to resource constraints. However, the searches carried out without language filters will allow us to gauge the volume of potentially relevant non-English literature excluded by this criterion.

Information sources
Our sources of information for this review will include published literature in electronic databases, different types of grey literature and personal communication. An electronic search will be performed through the following databases without language filters: MEDLINE, EMBASE and CINAHL. In addition, Google Scholar and reference searching of all included studies will be done to identify any additional literature. Moreover, we will also include the national and/or regional published documents of best practices related to WHO essential medicine availability in childhood malignancy.

Search strategies
The search strategy will be developed through an iterative process by a multidisciplinary team including an academic support librarian, paediatric oncologist, a paediatrician, public health specialists and a nursing officer. In addition to Medical Subject Headings (MeSH) terms, popular and commonly used phrases stated in related literature will be utilised to identify appropriate keywords to capture constructs of the availability of EML for childhood malignancies and its enablers and barriers. First, the search strategy will be developed for MEDLINE search and then the same strategy will be applied with relevant modifications to the other databases. Our initial search strategy for MEDLINE is as follows:
1. exp Drugs, Essential/ or essential medicine*.mp.
2. essential drug*.mp.
3. 1 or 2
4. cancer*.mp.
5. exp Neoplasms/
6. (tumor* or tumour* or malignanc*).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7. 4 or 5 or 6
8. 3 and 7
9. child*.mp. or exp Child/
10. 8 and 9

Study records
Selection process
Title and abstract of the studies identified by the initial search will be screened by two independent investigators for relevance after duplicates are removed. The initial screening of manuscripts will be as inclusive as possible to identify relevant studies within the eligibility criteria to capture the breadth of the literature. The reference lists of retrieved articles will also be manually assessed for further studies for inclusion. Studies and reports that appeared to meet the eligibility criteria will be retrieved and the full text will be assessed for relevance by two independent investigators. The results will be compared and any disagreement between the two reviewers on eligibility of a study will be resolved through consensus. In the event of a dispute, a third investigator will be consulted to arrive at a decision.

Data items
From each selected article or report the following information will be extracted: author, country, objectives of the study, study period, study setting, study design, study population, sample size and sampling technique, inclusion and exclusion criteria, reported drug availability, barriers/facilitators for availability of EML.

Data extraction
The data will be extracted from each selected article by two independent reviewers with experience in conducting
systematic reviews and will be entered into the extraction sheet developed and pretested by the review team (online supplemental file 1). These two sheets will be compared and any inconsistencies will be discussed and adjudicated by a third reviewer if required. In case further information or clarification is needed, the corresponding authors will be contacted. The study selection process will be detailed in a PRISMA flow chart.

**Risk of bias assessment**

Mixed Methods Appraisal Tool (MMAT) will be used to assess the quality of included studies. Risk of bias assessment will be undertaken independently by two reviewers who are experienced in risk of bias assessment using MMAT. Disagreements will be resolved by discussion between reviewers or consulting a third member of the review team for arbitration. Studies will not be excluded based on the quality, instead will be presented.

**Data synthesis**

**Strategy for data synthesis**

A high level of heterogeneity is expected of the studies to be included in the review, based on the broadness of the review question, the scope for meta-analysis is limited. Therefore, a narrative synthesis of the included studies will be conducted and presented as follows:

- Studies will be grouped based on type of reports. For best practices, the underlying theory of change will be described.
- Findings of each included study will be presented with key characteristics such as first author, year of publication, country/region, study design, sample size and sampling method, etc (online supplemental file 1).
- Results will be reported according to the review questions.
- Risk of bias assessment will be presented based on the MMAT.
- Limitations of the synthesis method will be discussed.

**Analysis of subgroups or subsets**

If reported, variations in essential drug availability among subgroups defined by different characteristics (including but not limited to those listed below) within individual studies will be examined (country or region, income level: low-income/middle income, health system in operation (Beveridge, Bismarck Model, National Health Insurance, Private Insurance System)).

**Expected outcomes**

Availability of WHO essential medicine for childhood malignancies will be described as follows:

- Percentage of cytotoxic medicines from the WHO EMLc included in the National EMLs.
- Cytotoxic medicines from the WHO EMLc reported stockouts and shortages.
- Number of unexpired cytotoxic medicines from the WHO EMLc in a health facility compared with the total expected number of drugs on the list defined by the WHO.

To determine the barriers and enablers for WHO essential medicine availability

1. Funding arrangements for the WHO essential medicine.
2. Health policy.
3. Role of Health Technology Assessment.

The PRISMA-Protocols reporting guidelines were followed when this manuscript was prepared.

**Patient and public involvement**

Patients and/or public were not involved in the design of this scoping review protocol.

**DISCUSSION**

Childhood cancer is highly curable as evidenced by the outcomes in high-income countries. However, in LLMICs where the vast majority of childhood cancer patients live, have far inferior outcomes. One of the major reasons for this global inequality is due to barriers in accessing quality care including access to essential medicines. A key first step in addressing this problem is understanding its magnitude. Therefore, this comprehensive review sets out to describe the availability of WHO essential medicines in LLMICs. The shortages and stockouts of these medicines will be discussed with reference to the economic status of the countries, impact on the WHO GICC index cancers, temporal variation on the availability and global trends, etc.

Many countries have recognised the need to improve availability of WHO EML medicines for childhood cancers and implemented a number of interventions in this regard. This review will also attempt to describe such interventions and their success as well as identified barriers and enablers for improving access to WHO EML medicines in LLMICs.

Therefore, findings of our review would fill the knowledge gap in availability of essential cytotoxic medicines used in treating childhood malignancies in LLMICs to influence evidence-based policy decisions. Furthermore, findings of this review, especially the identification of enablers and barriers will help to address the same problem existing in countries belonging to higher income categories.

However, limiting to English language publications and adhering to the scientific review methods which might not capture some technical reports, policy briefs, inter-department communications of Ministries of Health, etc. would be limitations of the current review.

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Supplemental material

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Supplemental material
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