



REPUBLIC OF GHANA
MINISTRY OF HEALTH

Final Report

Managing Paediatric Burkitt Lymphoma in Ghana: A Health Technology Assessment

2022



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2 Summary

Background

Burkitt lymphoma (BL) is the most common type of childhood cancer in sub-Saharan Africa, accounting for approximately 35% of all childhood cancers. The endemic type of BL associated with Epstein-Barr virus (EBV) is prevalent in malaria-endemic areas in Africa and Papua New-Guinea, including Ghana. There are an estimated 1,300 new cases of childhood (ages 0-14 years) cancer annually in Ghana, of which close to a third are endemic BL.

Treatment for BL is very effective, consisting of a short and intensive multidrug chemotherapy, including high doses of cyclophosphamide, doxorubicin, and methotrexate. BL is a highly curable cancer, but outcomes for endemic BL in sub-Saharan Africa are poor, with overall survival (OS) of between 40% to 60%, compared to OS in high income countries of 75% to 90%.

The challenges for treating childhood cancer and BL in low- and middle-income countries (LMICs) include a general lack of awareness about childhood cancer, delayed health seeking, limited access to health services, low treatment adherence, insufficiently trained health workers in paediatric cancer management, inadequate diagnostic services, unavailability or irregularity in the supply and unaffordable costs of chemotherapeutic agents. Access to care for paediatric cancer in Ghana is limited and primarily provided at two centres, Korle Bu Teaching Hospital (KBTH) and Komfo Anokye Teaching Hospital (KATH). Approximately 300 out of more than 1,000 paediatric cancer cases are seen at KBTH and KATH annually.

Ghana's paediatric oncology program is primarily financed by the Ministry of Health. The National Health Insurance Authority does not cover treatment for childhood cancer, and thus a significant portion of treatment costs are borne by patients. The high out of pocket costs of care seeking can be catastrophic and are associated with a high treatment abandonment. It is estimated that approximately 90% of paediatric patients with cancer experience treatment delay and up to two thirds of children who start treatment are likely to be lost to follow-up. Due to the aggressive nature of BL, untreated patients lost to follow-up are presumed dead.

Aim

This review sought to establish the clinical and economic impact of extending the coverage of current cancer medicines on the NHIS medicines list to include treatment for childhood cancers (for children under the age of 15 years).

Methods

This health technology assessment (HTA) used mixed methods to generate evidence as follows:

- 1) Desktop reviews and interviews were conducted to develop a situational assessment of the problem in Ghana. A systematic review was undertaken to obtain global evidence on the clinical effectiveness of treatments for BL in children below the age of 15 years. The findings of the systematic review, together with in-depth searches for Ghana-specific data, were used to populate the economic model used in this study.
- 2) A cost-effectiveness analysis was undertaken, using a decision-analytic model developed in Microsoft Excel, to compare the costs and health outcomes of two strategies for managing BL: 1) treatment when coverage for care was provided by NHIS (NHIS-reimbursed treatment); and 2) when insurance coverage was not provided (current practice). The evaluation was taken from a societal perspective. Costs were estimated based on the treatment protocol for BL in Ghana, including only costs of laboratory investigations, confirmatory tests and medications. Health outcomes were measured using Disability-Adjusted Life Years (DALYs). A probabilistic sensitivity analysis was performed to account for uncertainty in the parameters. A budget impact analysis (BIA) was undertaken from the perspective of the NHIS, to estimate the financial impact of adding BL to the NHIS reimbursement list.

Results

Our cost analysis estimated the annual cost per patient to the NHIS for the treatment of BL to be \$524.67 for Stages I, II and III and US\$1076.16 for Stage IV. The annual cost per patient abandoning treatment was estimated to be US\$313.89 for Stage I, II, & III, and US\$580.07 for Stage IV. The cost analysis estimated the societal cost of BL treatment to be \$1,930.33 per patient for Stages I, II and III, and \$2,697 per patient for Stage IV treatment.

The base-case cost-effectiveness analysis showed that the intervention was very cost-effective as it was both more effective and less costly. The current practice was dominated; thus the NHIS-reimbursed treatment is always the preferred option from a societal perspective.

The budget impact analysis projected annual costs of treatment that are likely to be borne by the NHIS for over a period of five years. The five-year treatment costs assuming current NHIS tariff rates are estimated to be US\$951,750. In addition, a scenario analysis and a one-way sensitivity analysis were also performed in order to examine the effect of uncertainty on the results.

Key messages

- Childhood cancers remain a significant challenge in Ghana, despite gains in the last decade.
- A large portion of BL deaths are avoidable, but a multitude of factors ensure the perpetuation of the status quo. Costs to patients are shown to be a contributing factor to treatment abandonment.
- The costs to society are potentially large. Since treatment abandonment is high, and there are no gains when a patient abandons treatment, these resources are described as a resource loss. We estimated annual societal costs for patients abandoning treatment to be US\$1,016.72 at Stages I, II and III, and US\$1,390.59 at Stage IV. Additional, significant resource loss also occurs due to lost productivity from early death.
- Providing treatment to patients is highly cost-effective, but this rests on the assumption that NHIS coverage leads to increased uptake of healthcare services. This is not easy to achieve and other interventions to encourage care-seeking and positive behavioural attitudes should be implemented at the same time.

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5 Background

5.1 Overview of Burkitt lymphoma

Burkitt Lymphoma (BL), a type of non-Hodgkin's Lymphoma (NHL), is the most common type of childhood cancer in sub-Saharan Africa, accounting for approximately 35% of all childhood cancers in the region (1, 2). The disease presents in both adults and children, but is more prevalent in children, accounting for more than 40% of paediatric NHL compared to 5% in adults. Childhood NHL originates in the lymph system and can therefore, affect any organ within the body. There are three major sub-types of childhood NHL: anaplastic large cell lymphoma (ALCL), lymphoblastic lymphoma (LL), and aggressive Mature B-cell NHL (3). BL is a sub-type of Mature B-cell NHL first described by Denis Burkitt in 1958 (4).

In the 2016, the World Health Organization updated the classification for Mature B-cell neoplasms and broadened the definition for BL to include Burkitt-like lymphomas (BLL) with 11q aberration and arguably without changes in the MYC gene (normally used for diagnosis). Existing evidence, though limited, indicates that BL and BLL respond similarly to same treatments (5, 6).

BL can be classified into three clinical groups: endemic, sporadic and immunodeficiency-related BL. Endemic BL is associated with Epstein-Barr virus (EBV) in almost all cases and occurs more frequently in males, with a peak incidence between four and seven years (7, 8). This type of BL mainly occurs in malaria-endemic areas such as Africa and Papua New Guinea and is the most common childhood cancer overall in these areas (9, 10). Common sites for endemic BL include the bones of the jaw and other facial bones, as well as extra-nodal sites (11). Endemic BL accounts for 50% of all childhood tumour diagnoses and up to 90% of lymphoma diagnoses in equatorial Africa (10). The prognosis for endemic BL in sub-Saharan Africa are poor, with an estimated overall survival (OS) of between 40% and 60%, compared to children with sporadic BL in high-income countries, who have an OS of 75% to 90% (12). High cure rates are achievable, but are often not realized due to a multitude of constraints including limited access to health facilities and low treatment adherence (12). From the patient or caregiver's perspective, the biggest challenge is financial, given the high costs of accessing care (13).

Sporadic BL occurs throughout the world, and is the form of BL found in the United States and Western Europe (8). It accounts for less than 1% of B cell NHLs in adults, but more than 30% of all childhood lymphomas (14). The average age of diagnosis in children is three to twelve years, with an annual estimated incidence of four per one million children (11). An abdominal tumour is the most common site of disease occurrence (15). Immunodeficiency-related BL is mainly prevalent in HIV infected individuals (5). It can also occur in patients who have inherited immune deficiencies or those taking immunosuppressive medications (16).

5.2 Staging of Burkitt Lymphoma in children

The St. Jude staging system is routinely used for paediatric patients (11):

Table 1. The St. Jude Staging System

Disease Stage	Criteria
Stage I	<ul style="list-style-type: none"> A single tumor (extranodal) or a single anatomical area (nodal), excluding mediastinum or abdomen A tumor (extranodal) with regional node involvement, on the same side of the diaphragm.
Stage II	<ul style="list-style-type: none"> A single tumour (extranodal) with regional node involvement, lymph node involvement on same side of the diaphragm (two or more nodal areas or two single extranodal tumours, with or without regional node involvement) A primary gastrointestinal tract tumour (usually ileocecal) with or without associated mesenteric node involvement, grossly completely resected.
Stage III	On both sides of the diaphragm: <ul style="list-style-type: none"> (two or more nodal areas or two single extranodal tumours) all primary intrathoracic tumours (e.g., mediastinal or pleural thymic), all extensive primary intra-abdominal disease Or <ul style="list-style-type: none"> unresectable abdominal disease, even if only in one area all primary paraspinal or epidural tumours, irrespective of other sites.
Stage IV	<ul style="list-style-type: none"> Any of the above with initial central nervous system or bone marrow involvement

5.3 Treatment of Burkitt lymphoma

BL is very aggressive, requiring immediate hospitalisation and commencement of therapy on diagnosis. Different combination chemotherapy regimens are used to treat BL in children and adolescents, and the cure rates are high, especially in children (8). The overall cure rate for sporadic BL approaches 90% for children in high income settings (12). The treatment protocol in high income settings is often a short and intensive multidrug chemotherapy, including high doses of cyclophosphamide, doxorubicin, and methotrexate. The side effects and complication of this intense regime requires a high level of supportive care. Treatment in low-resource settings follows a similar, but less intensive protocol (mainly due to unavailability of resources), thus the same outcomes as in high income settings may not be realised (17). The current standard of treatment for BL in sub-Saharan Africa is a short course or single dose of cyclophosphamide. To improve survival rates, cyclophosphamide is used in combination with other agents including vincristine, prednisone, methotrexate and doxorubicin (18, 19). Lymphoma regimens using anthracyclines, vincristine, cyclophosphamide and prednisone were initially recommended for treatment in children; and to improve survival rates, a “pre phase” was introduced, combining low doses of steroids and chemotherapy, followed by high-dose chemotherapy a week later (8).

Treatment depends on patient age and stage. In children with complete surgical resection of disease, patients are given two cycles of chemotherapy of moderate-intensity (i.e., cyclophosphamide, vincristine, prednisolone, doxorubicin) (11). Children with stage III disease, receive a minimum of four cycles of dose-intensive chemotherapy (i.e., two cycles of cyclophosphamide, vincristine, prednisolone, doxorubicin, and high-dose methotrexate); and thereafter two cycles of cytarabine and high-dose methotrexate. Intrathecal therapy is administered concurrently with chemotherapy. Where the central nervous system or bone marrow are affected, it is recommended that children receive up to eight cycles of dose-intensive chemotherapy (i.e., two cycles of cyclophosphamide, vincristine, prednisolone, doxorubicin, and high-dose methotrexate) plus two courses of cytarabine and etoposide, in addition to four courses of maintenance chemotherapy (i.e., vincristine, prednisolone, high-dose methotrexate, cyclophosphamide, doxorubicin, cytarabine, and etoposide). Intrathecal therapy is administered concomitantly with chemotherapy.

5.4 Management of side effects and complications

Chemotherapy is associated with significant side effects, and treatment-related toxicity can be a major barrier to survival among children (12, 20). The most common toxicity of chemotherapy is myelosuppression, which leads to increased susceptibility to infection (12). Another side effect is chemotherapy-induced nausea and vomiting, which can lead to malnourishment if not properly managed. Other chemotherapy-associated toxicities include mucositis, skin necrosis, nephrotoxicity, cardiomyopathy and risk of secondary malignancy. Supportive care is recommended including prevention of tumour lysis syndrome, fever management, and nutrition supplementation (11). Many patients in LMICs do not complete treatment because of the high costs of treating and managing BL.

5.5 Burkitt lymphoma in Ghana

5.5.1 Target population, Incidence and Prevalence

All children younger than 15 years are at risk of developing childhood cancer. Ghana had a total estimated population of approximately 31 million in 2020, of which 11.5 million were below the age of 14 years (21). It is estimated that there are approximately 1,300 new cases of childhood cancer every year in Ghana and approximately 0.01% of all children are affected by NHL (22).

In the age group 0-14 years, endemic BL is the most common childhood cancer. It is further reported to be the leading cause of cancer deaths in children (23-25). Notwithstanding, there are variations in terms of the prevalence of lymphoma in different age categories, with Hodgkin's Lymphoma being the most common in the age group 10-15 years, BL in the 5-10 year age group and Acute Lymphoblastic Leukaemia (ALL) in children under 5 years (25). One study which combined endemic BL data from Ghana, Tanzania and Uganda estimated that the age at diagnoses was 0-2 years for 2.4% of the cases; 3-8 years in 69.1% of cases, and 9-14 years for 28.4% of cases. In younger patients, tumours were more often observed in the face, while older children more often had tumours in the abdomen or another site. Males were more often affected by BL than females (26).

The prevalence of childhood lymphoma in Ghana was reported to have declined in the decade preceding 2013; having reduced to 31% with BL

making up 22% of all childhood cancers (23). However, a more recent study using data from 2012 – 2014 found that the prevalence of BL was around 41% (25).

Approximately 90% of paediatric patients are likely to experience treatment delay mainly as a result of familial financial constraint (13), and treatment abandonment is prevalent (24).

5.5.2 Policy frameworks

Ghana is a priority partner country for the WHO Global Initiative for Childhood Cancer that aims to achieve a global survival rate of 60% by 2030. Until recently, non-communicable diseases and in particular childhood cancer were not a priority. This was due to several factors including limited information on the disease burden and the focus on global and regional health priorities, which have had a strong emphasis on communicable diseases.

The Ghanaian government has developed several policy measures and strategies to address the national cancer burden. The National Strategy for Cancer Care (2012-2016) outlines the country's overall response to cancer (27). It outlines the requirements and specifications for a population-based cancer registry and draws up a broad strategy for cancer control.

The National Policy for the Prevention and Control of Chronic NCDs in Ghana (2012) is a broader policy that captures cancer as a subgroup of NCDs. The Public Health Act (2011) also falls within the broader scope of policy framework that may contribute to cancer control especially from the prevention perspective. It highlights the need to adopt healthy lifestyles including good nutrition, reduced alcohol and tobacco use.

5.5.3 Reimbursement status of medicines and therapeutics

The paediatric oncology program is primarily financed by the Ministry of Health. Although a National Health Insurance Authority (NHIA) exists in Ghana. For medicines to be considered for coverage under the National Health Insurance Scheme (NHIS), it needs to respond to the NHIS benefits package and be listed on the National Essential Medicine List (NEML). However, coverage and availability is not assured even if a drug is listed on the NEML (28). The NHIS currently does not cover childhood cancers, meaning that children with cancer do not benefit from a coverage under the NHIS.

Private philanthropic sources of funding exist to offset out-of-pocket costs incurred by families; the most prominent are World Child Cancer, an international nongovernmental agency, and the Ghana Parents' Association for Childhood Cancer. Local private and faith-based organizations also play an important role in the day-to-day operation and financing of the paediatric oncology program, including fundraising and providing financial assistance to low-income families for transportation, meals, and medical services.

Similarly, donor funds are currently used by the paediatric oncology unit at Komfo Anokye Teaching Hospital (KATH) to stock and provide vincristine, cyclophosphamide, methotrexate, cytarabine and doxorubicin for free to their patients. Nevertheless, many caregivers still experience high out of pocket costs when seeking care for their children. The high costs incurred by families are associated with high treatment abandonment.

5.5.4 Resources for managing childhood cancer

There are six units in Ghana that provide oncology services: the Korle Bu Teaching Hospital (KBTH) and the Peace and Love Hospital in Accra; the Komfo Anokye Teaching Hospital (KATH) and the Peace and Love Hospital in Kumasi; Tamale Teaching Hospital in Tamale, and the Sweden Ghana Medical Centre in Tema. Only KBTH and KATH have specific centres for paediatric oncology care.

Paediatric patients are mostly seen at KBTH and KATH, two of the largest tertiary centres in the country. KBTH is a 2,000-bed tertiary facility and the largest hospital in Ghana, situated in the capital Accra (29). The hospital serves a catchment area of approximately 19.74 million in the southern half of the country. KBTH also receives patients from other countries in West Africa. The KBTH paediatric cancer unit contains 30 inpatient beds and treats on average 170 new diagnoses annually, with approximately 77 outpatients seen daily.

KATH is situated in Kumasi, the regional capital of Ashanti region which is 250 kilometres north of Accra, the nation's capital (30). With a bed space of 1200, KATH is the second-largest hospital in Ghana and the only tertiary health facility in the Ashanti Region. The hospital receives referrals from all the northern regions (Northern, Upper East and Upper West Regions), Brong Ahafo, Central, Western, Eastern and parts of the Volta Regions. KATH has a paediatric oncology unit that diagnoses approximately 170 new cases of cancer in children (14 years or less) annually.

Access to healthcare services is limited for much of the population, so there remains a large number of children who are currently not diagnosed. Only 300 out of expected 1,000 paediatric cancer cases report to KBTH and KATH (23-25).

As of 2017, there were only 12 oncology nurses practicing in the country's cancer treatment centres (31). Since 2015, the Ghana College of Nurses and Midwives provides oncology nursing in Ghana. The first three cohorts produced 12 oncology nurses in total. Currently, the total number of local formal trained oncology nurses is 45 (12 Nurse Specialists and 33 nurses in training) (32). Locally accredited graduate and postgraduate training programmes for radiation oncologists, medical physicists, radiotherapy technicians and nurses are available through the Ghana College of Physicians and Surgeons, nursing, and University of Ghana Allied Health and Nuclear Sciences Division.

Ghana has three installed radiation therapy machines which includes two conventional simulators, two modern Cobalt 60 tele-therapy machines in KBTH and KATH. Also, a private treatment facility in Accra has a CT simulator and a linear accelerator. These translate into an estimated 0.1 machine per million patients, which is well below the expected 1 – 3 machines per million patients in Africa and 4 – 8 machines per million in developed countries (33).

Basic laboratory tests for cancer diagnostics are readily available at KBTH. However, most of these tests are not covered by the NHIS and pose a serious financial burden for many patients (24). Immunophenotyping and cytogenetic studies are currently unavailable in KBTH and EBV serology is not routinely performed as part of the BL diagnosis (24).

Little routine data can be found on the availability, affordability, and quality of childhood cancer drugs. An assessment of access to essential medicines for children with cancer in Ghana, revealed that there was a 65% alignment between the WHO essential medicine list for children (EMLc) and the Ghanaian national EML (28). The study reported that on average, drugs were out of stock for approximately 101.5 days (median: 70 days, range: 0 to 455 days) during the 15-month study period. The number of stock-out days was also positively correlated to the median price ratio (MPR). In other words, those drugs that were procured inefficiently also experienced longer stock-outs. The key medicine for BL treatments overall had a MPR below 2.5 which can be seen as an efficient private sector procurement. Overall, eleven of the thirty-eight (38) drugs researched had an inefficient procurement with a MPR above 2.5. Stock-

outs or inefficient procurement strategies can be detrimental when providing treatment for BL given its aggressive nature, timely treatment is essential to survival.

5.5.5 Challenges regarding treatment for BL in Ghana

There are only five paediatric oncologists to serve the entire population of 30 million people (34). The current treatment centres for childhood cancers in the country are based in Kumasi and Accra. Despite the availability of Peace and Love Hospital also located in Accra and Kumasi, and the Sweden Ghana Medical Centre in Tema, treatment for childhood cancer is not a main service provided in these facilities. The Tamale Teaching hospital also has a 7-bed capacity paediatric oncology unit housed in the 42-bed capacity paediatric ward. Radiation oncologists are concentrated at KBTH and KATH.

Various challenges including the general lack of awareness about childhood cancer, compounded by adverse socio-cultural practices and limited access to services, with few health workers trained in paediatric cancer management. Other limitations include inadequate diagnostic services, unavailability or irregularity in the supply and unaffordable costs of chemotherapeutic agents, limited access to suitable protocols and inadequate supportive care. One qualitative study from a paediatric oncology unit in Ghana, highlighted the daily challenges of nurses, which included administrative and management issues, staff shortages and limited knowledge on care for unique cases (31). The study highlights the need to improve working conditions in the hospital, educating more nurses and strengthening of their knowledge to ensure (life-long) education to treat patients with the highest standard of care.

5.5.6 Clinical management of BL in Ghana

Figure 1 outlines the diagnostic and treatment process for BL in Ghana, which is typically done in three steps with 1) an initial assessment and baselining, 2) confirmatory testing and initial treatment, and 3) subsequent treatment and follow-up.

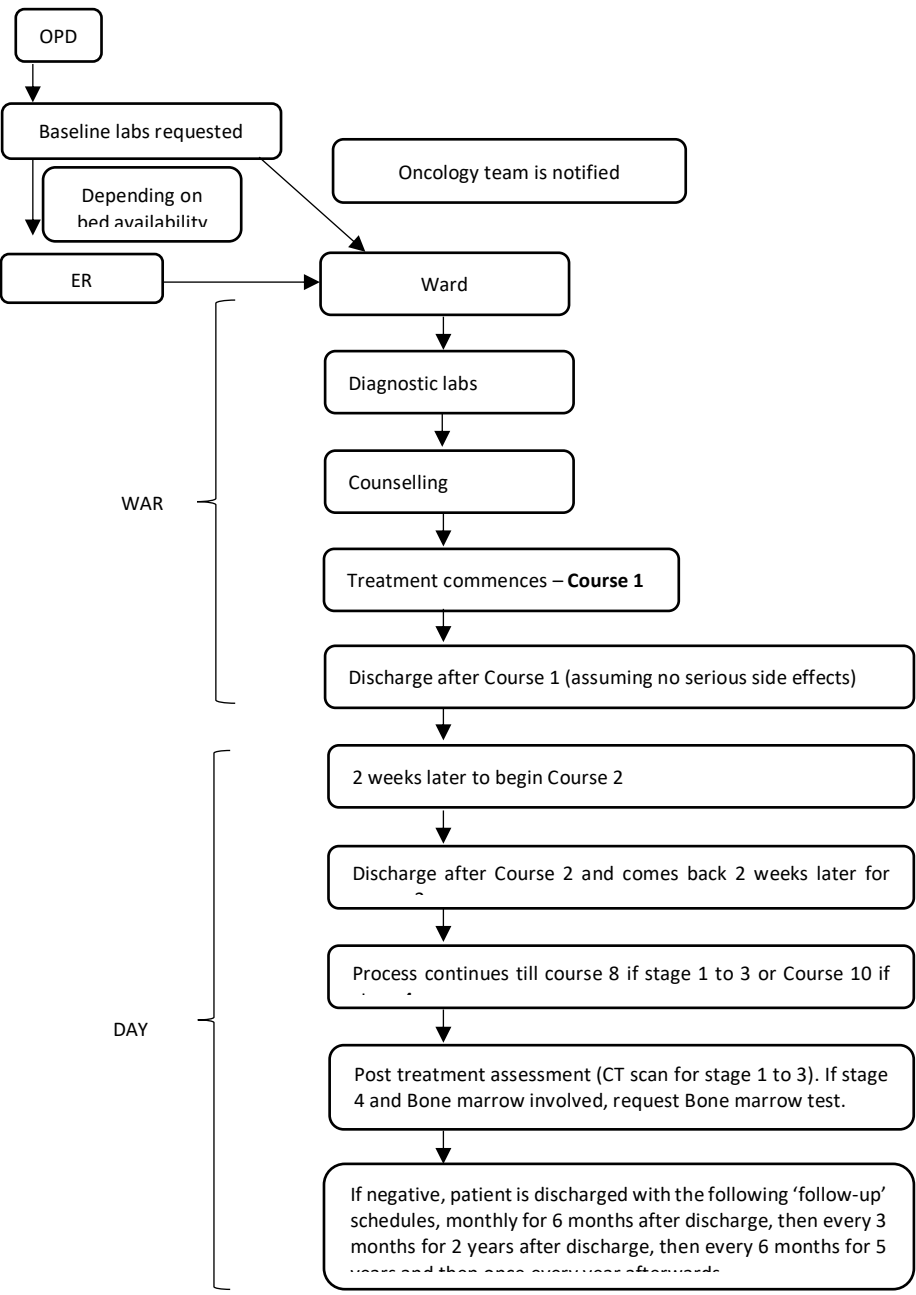
Step 1 is the diagnostic stage where suspected cases are moved on to further treatment. The tests typically included in the baseline laboratory analyses are listed in Table 2.

Table 2. Baseline laboratory investigations

Full Blood Count (FBC)
HB Electrophoresis
BUE Creatinine
Liver Function Test (LFT)
Lactate Dehydrogenase Test (LDH)
Uric acid Test
Calcium, Phosphate (Ca, P0 ₄)
Hepatis B Surface Antigen Test (HBSAg)
Hepatitis C Test
Retro screen (HIV Test)
Urine Routine and Microscopy (R/E)
Stool Routine and Microscopy (R/E)

Source: Korle Bu Hospital

Figure 1. Identification and treatment of Burkitt lymphoma in health facilities in Ghana



Source: Korle Bu Hospital

When baseline laboratory analyses indicate that BL is a possibility, patients are admitted into inpatient care and further confirmatory laboratory analyses are performed. The analyses used to confirm suspected BL are listed in Table 3. BL is confirmed using the Fine Needle Aspiration Cytology (FNAC), considered standard practice in SSA (35) and Ghana (24).

Table 3. Tests conducted to confirm Burkitt lymphoma

Chest X-ray (CXR)
Abdominal Ultrasound (USG)
CT Scan of the site (Jaw)
Bone Marrow Aspiration Test (BMA)
USG Guided Biopsy/Fine Needle Aspiration Cytology (FNAC) comprising: <ul style="list-style-type: none">• Biopsy• Needle• Histology• Gauze + lidocaine

Treatment for BL in Ghana is differentiated from patient to patient based on the patient’s disease stage within the St. Jude staging system. The treatment protocol (Table 4) describes the regimen for a patients based on their disease stage. For treatment for Stages I, II and III disease, a combination therapy is utilized, incorporating cyclophosphamide, vincristine, doxorubicin (adriamycin), cytarabine and low-dose methotrexate. Stage IV treatment involves a modified version of a mature B-cell protocol without rituximab. The notable change in Stage IV treatment is the addition of high-dose methotrexate and associated supportive medications like potassium chloride.

Table 4. BL Treatment protocol in Ghana

Tumor Stage	Course of Treatment
Stages I, II & III	A pre-phase dose of IV cyclophosphamide 1400mg/m2 with IT methotrexate, followed by a combination chemotherapy consisting of 6 cycles (cyclophosphamide, vincristine and doxorubicin alternating with cyclophosphamide, vincristine and cytarabine every 2 weeks) with IT methotrexate given during the first 3 courses
Stage IV	For bone marrow involvement a modified version of a mature B-cell protocol for high income countries without rituximab is used, and inclusive of four cycles of maintenance therapy, following reduction, induction and consolidation phases of therapy. For CNS disease, additional intrathecal therapy is included until cerebrospinal fluid (CSF) cytology is negative

Source: Offor et al. (2018)

See also Appendix 1 for the detailed treatment protocol provided by clinicians in Ghana during this review.

6 Objectives and scope

This assessment was conducted with the Ghana HTA Technical Working Group with technical assistance from the NIPH, to inform national policy on treatment and reimbursement for BL. Despite having a relatively high burden, childhood cancers including BL are presently not listed for reimbursement by the National Health Insurance Scheme (NHIS). Even though essential medicines for childhood cancers such as cyclophosphamide, methotrexate and doxorubicin are included on the NHIS medicines list, they are indicated for treatment of other cancers such as breast cancer. This review thus sought to ascertain the clinical and economic impact of extending the coverage of current cancer medicines on the NHIS list to include childhood cancers.

The objective of this study was to conduct an evaluation of the clinical and economic impact of managing Burkitt lymphoma in Ghanaian children under the age of 15 years, comparing a scenario where NHIS coverage is provided (intervention), to a scenario where children have no insurance cover (standard of care).

7 Methodology

This assessment was guided by the recommendations for producing Rapid Relative Effectiveness Assessments (REA) (36), as well as the HTA Core Model (37) of the European Network for HTA (EUnetHTA). In these guidelines, the HTA report sums the evidence on the technology being assessed in the following key domains: health problem and current use of the technology; description and technical characteristics of the technology; safety; clinical effectiveness; and costs and economic evaluation. Based on this, we collected data on BL, including its burden, management and effects of treatments using the checklist of questions (based on EUnetHTA guidance) in Appendix 2. Information was gathered using: 1) desktop reviews and interviews to develop a situational assessment of childhood cancer in Ghana, 2) a systematic review to obtain evidence on the clinical effectiveness of treatments for BL. Some of this information was used in the economic evaluation. Clinical experts in Ghana were consulted throughout the review and wider stakeholder consultations were also undertaken to develop a deeper understanding of the context.

Most of the information gathered in the situational assessment is used in the background section of this report. Though we collected data on all the elements proposed in the REA framework (health problem, characteristics, safety and effectiveness of technology), we focused this report on the economic evaluation, as the primary question from the commission was understood to be mainly a question of the economic implication of adding BL to the NHIS reimbursement list. Notably during stakeholder engagements, representatives of the NHIS clarified that there was political will to finance childhood cancer and the rationale for this was clear; rather, what was unclear were the costs of such an endeavour.

Thus, the methods of the situational assessment and systematic review are briefly described below; and the detailed methods and findings are included as appendices to this report. The full study methods are also described in the study protocol submitted together with the report.

7.1 Situational analysis of the current context

The assessment involved a desktop review of the local literature and guidelines, stakeholder engagements and interviews with experts. Official documents and reports of the Ministry of Health and other agencies and stakeholders dealing

with childhood cancer in Ghana were reviewed. Data retrieved included burden of disease; diagnosis and monitoring; responses to policy making; treatments; and costs of childhood cancer.

A mapping exercise was undertaken to identify relevant stakeholders and key experts, who were invited to stakeholder meetings and key expert interviews to give insight into the practices and challenges related to management of childhood cancer. The results of the stakeholder mapping are provided in Appendix 3. Stakeholder engagement included a workshop that brought together various actors to gain further insight into issues of childhood cancer in Ghana. The workshop agenda and minutes attached in Appendix 4.

7.2 Review of literature on treatments for Burkitt lymphoma

We searched for systematic reviews, HTA reports and clinical guidelines of treatment options for (endemic) BL in children. The search was conducted in the following databases: Epistemonikos, International HTA Database, Cochrane Database of Systematic Reviews, Global Index Medicus (GIM)-WHO, EMBASE, NHSEED, EUnetHTA POP Database and PROSPERO. An additional search was undertaken for international guidelines in various electronic databases and websites. The resulting hits were screened for inclusion based on titles and abstracts, after which a full text review of the included papers was undertaken. Full-text articles were then assessed for relevance, quality, and data extraction. Data from the final included studies was extracted and summarized in evidence tables. The study PICO is shown in Table 5, and detailed methods and results are provided in Appendix 5.

Table 5. Study PICO

Population:	Children under the age of 15 with Burkitt lymphoma
Interventions/Control:	<ul style="list-style-type: none">• Cyclophosphamide monotherapy versus combination therapy• Any other single drug chemotherapy versus combination therapy• One type of combination therapy versus another combination therapy• Chemotherapy versus radiotherapy• Chemotherapy plus radiotherapy versus radiotherapy• Chemotherapy versus chemotherapy plus immunotherapy• Chemotherapy versus chemotherapy plus surgery
Outcomes:	Overall survival; event-free survival (central nervous system residuals); overall remission rate (complete and partial); relapse rate (> six months); toxicity and adverse events; quality of life.

7.3 Economic evaluation

7.3.1 Purpose

We developed an economic model to evaluate the clinical and economic impact of extending insurance coverage to children with BL. The model was developed in Microsoft Excel and was informed by guidelines for reporting economic evaluation studies (38). The model was used to conduct a cost-effectiveness analysis and a budget impact analysis to inform the cost implications of adding BL to the reimbursement list of the NHIA.

7.3.2 Study perspective

The cost-effectiveness analysis was undertaken from a societal perspective, which was selected to capture the broader spectrum of costs of managing BL. An additional cost-effectiveness analysis from the perspective of the NHIS was done and is included as supplementary material to this report (Appendix 6). The budget impact analysis was undertaken from the perspective of the payer (NHIA), and captured all the costs and outcomes resulting from the NHIS intervention.

7.3.3 Comparators

The comparators were 1) management of BL in children without providing insurance coverage (the standard of care), and 2) extending NHIS coverage to management of children with BL (intervention). The former reflects the current scenario, where costs of treatment and management of BL are borne by the patient. Routine health care services are NHIS reimbursable, but the general costs of BL treatment are paid out-of-pocket. For example, although common generic antibiotics are covered, chemotherapy for childhood cancer is not, nor are diagnostic tests such as computed tomography scans or pathology. These costs must be absorbed by patients and their families (39). When insurance cover is provided, it covers the costs of health services at the point of care, but costs of accessing care such as transportation are not included.

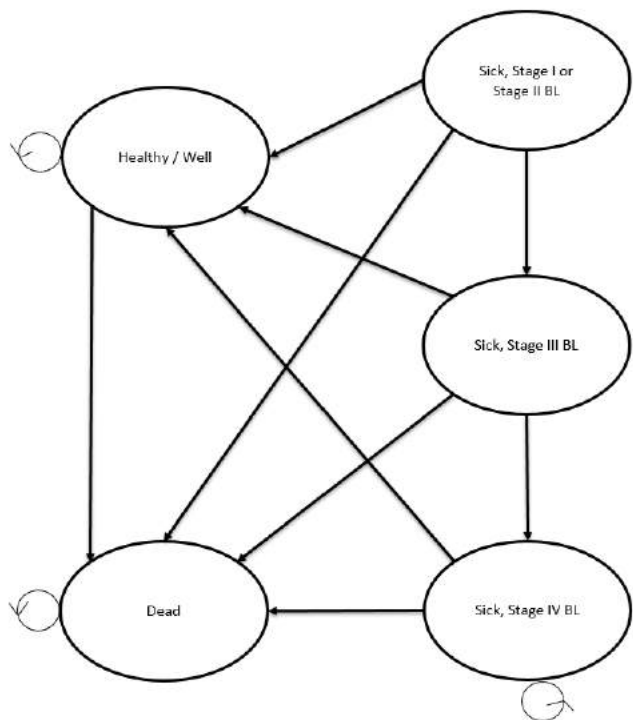
7.3.4 Population

The baseline population used in the model was as all patients below the age of 15 years with a BL diagnosis being treated in a health facility in Ghana. We estimated a cohort of 309 patients, based on the following: 22% of all childhood cancers will be BL; and 30% of these cases will seek treatment in a health facility (23, 24) The majority of cases were estimated to be in Stage III (78%) of BL, 11% in Stage I/II and 10% in Stage IV, according to the St. Jude staging system (REF); this distribution was based on data provided by Oncologists at Korle Bu Teaching Hospital in Ghana and data in the literature (24). The average age of disease onset used was 7 years (10, 24).

7.3.5 Model overview

The analysis was done using a five-state Markov model (Figure 2) to estimate costs and patient outcomes. Patients start in either one of three disease states: Stage I/II, Stage III or Stage IV BL; and then transition to another disease stage, become healthy or die. State transitioning is dependent on the likelihood to abandon treatment, combined with the stage-dependent effectiveness of treatment. Disease progression is unidirectional, with patients transitioning from a lower to higher state. Due to limited data on disease recurrence post successful treatment, we assumed that patients in the well state did not transition back to being sick. The model operates under the assumption that 1-year event-free survival is a valid estimation of long-term overall survival, as BL has very poor survival rates for individuals who progress or relapse (35). All parameters used in the model are provided in Appendix 7.

Figure 2. Markov model of treatment for Burkitt lymphoma



7.3.5.1 Time horizon and cycle length

The model used a cycle length of one year (with half cycle correction). Due to the aggressive nature of BL, we assumed that all health-related outcomes occur within a year (35). Treatment related costs are also incurred within the one-year period, however, according to the protocol, children are followed up for up to two years post treatment. The time horizon for this analysis was a lifetime, based on Ghana’s life expectancy at birth.

7.3.5.2 Treatment modality

The model incorporates the treatment protocol (and related outcomes) shown in Table 4. Treatment for Stages I, II and III involves a low-intensity combination therapy with cyclophosphamide and low-dose methotrexate. Stage IV treatment uses a modified version of a mature B-cell protocol without Rituximab.

7.3.5.3 Treatment abandonment

Treatment abandonment or discontinuation has been shown to be high for childhood cancer in general, with over 25% of children said to discontinue

treatment in Ghana (23, 39). Children who abandon treatment are presumed dead, since they are highly unlikely to survive without treatment (24). We postulated that providing health insurance coverage to BL patients would lead to a reduction in treatment abandonment, as has been shown in a study of paediatric cancer patients in Kenya (40). In our study, we estimated that NHIS coverage would lead to a 50% reduction in treatment abandonment.

7.3.5.4 Cost estimates

We estimated the annual costs per patient associated with treatment and management of BL from a societal perspective and NHIS perspective. The cost of treatment from an NHIS perspective was calculated using cost of diagnostic labs, confirmatory tests, and stage-dependent medication use. The cost of treatment from a societal perspective includes all of these aspects, as well as nonmedical costs to the patient's family during treatment.

Treatment costs

The treatment costs included laboratory/diagnostic and medication costs, based on the Ghana's treatment protocol.

1. Cost of labs and diagnostics

The cost of baseline labs, diagnostic tests and discharge tests were based on hospital fees and NHIS tariffs associated with each individual test given to a patient (Table 6). Baseline laboratory tests undertaken at first diagnosis include full blood count, uric acid, hepatitis C and HIV tests. These are followed by confirmatory tests, which include chest x-ray, abdominal ultrasound, CT scan and bone marrow aspiration tests. During treatment, patients in Stages I, II, and III undergo 6 full blood count lab tests in addition to the baseline labs, while patients in Stage IV have 8 full blood count lab tests in addition to baseline labs. At discharge, patients in Stages I, II, and III undergo a CT scan, while patients in Stage IV have a CT scan and a bone marrow test.

Table 6. Tests undertaken to diagnose and confirm Burkitt lymphoma

Confirmatory tests	# per patient		Cost (Ghana Cedi)	
	Stage I,II,III	Stage IV	Hospital fee	NHIS tariff
Chest X-ray (CXR)	1	1	55.00	19.52
Abdominal Ultrasound (USG)	1	1	55.00	22.91
CT Scan of the site (Jaw)	2	2	666.00	182.15
Bone Marrow Aspiration Test (BMA)*	1	2	321.00	111.80*
USG Guided Biopsy/Fine Needle Aspiration Cytology (FNAC)*	1	1	940.00	37.42*
Baseline labs				
Full Blood Count (FBC)	7	9	39.00	11.33
HB Electrophoresis	1	1	58.00	7.87
BUE Creatinine	1	1	57.00	14.39
Liver Function Test (LFT)	1	1	70.00	19.43
Lactate Dehydrogenase Test (LDH)	1	1	27.00	8.39
Uric acid Test	1	1	39.00	8.57
Calcium, Phosphate (Ca, PO ₄)	1	1	66.00	16.69
Hepatis B Surface Antigen Test (HBSAg)	1	1	31.00	6.00
Hepatitis C Test	1	1	47.00	7.46
Retro screen (HIV Test)	1	1	Free	11.46
Urine Routine and Microscopy (R/E)	1	1	27.00	5.29
Stool Routine and Microscopy (R/E)	1	1	27.00	4.64

*These tests are not currently covered by the NHIS, but will be when childhood BL is included for NHIS reimbursement.

2. Stage-dependent costs of medication

Costs of medication were derived by estimating the total medicines used by patients when completing the entire stage-dependent treatment regimen (Table 7). For height and weight dependent dosing, we used an average height of 118 cm, 20.60 kg for body weight, and 0.822m² for body surface area, based on average height and weights for children aged 7-8 in Nigeria, due to a lack of Ghana-specific data (41).

Table 7. Amount of medication used and associated costs (in Ghana Cedi)

MEDICATIONS	Total dosage required (mg)	Medication unit size (mg)	Number of units	Cost per unit (GHC)	Total medication cost
Dextrose Saline Infusion 500ml	13,057.91	500	27	4.86	131.22
Tablet Allopurinol 100mg	1,500.00	100	15	0.66	9.90
IV Granisetron 1mg/ml	32.00	1	32	25.00	800.00
Tablet Granisetron 1mg	80.00	1	80	0.40	32.00
IV Cyclophosphamide 500mg	6,902.44	500	14	12.00	168.00
IV Vincristine*	8.63	1	9	15.00	135.00
Tablet Prednisolone, 5mg	1,232.58	5	247	0.08	19.76
IT Methotrexate 25mg/ml inn 2ML	49.30	50	1	25.00	25.00
IV Doxorubicin (Adriamycin) 50mg	98.61	50	2	56.50	113.00
*IV Cytarabine	1,972.13	100	20	30.00	600.00
Medicines used at (Stage IV)					
Dextrose Saline Infusion 500ml	19,624.20	500	40	4.86	194.40
Tablet Allopurinol 100mg	1,500.00	100	15	0.66	9.90
IV Granisetron 1mg/ml	40.00	1	40	25.00	1,000.00
Tablet Granisetron 1mg	100.00	1	100	0.40	40.00
IV Cyclophosphamide 500mg	8,545.88	500	18	12.00	216.00
IV Vincristine	11.09	1	12	15.00	180.00
Tablet Prednisolone, 5mg	1,479.09	5	296	0.08	23.68
IT Methotrexate 25mg/ml inn 2ML	4,296.10	50	86	25.00	2,150.00
IV Doxorubicin (Adriamycin) 50mg	123.26	50	3	56.50	169.50
IV Cytarabine	3,079.50	100	31	30.00	930.00
IT Hydrocortisone	150.00	15	10	3.00	30.00
IV Folic Acid	616.29	50	13	0.13	1.69
IV 5% Dextrose infusion	20,542.98	500	42	4.80	201.60
Potassium Chloride	50.00	20	3	3.50	10.50

The NHIS does not currently reimburse cytarabine or vincristine, thus to estimate NHIS prices, data was taken from a study that provided Ghana wholesale supplier prices of cancer treatment drugs, which matched very closely with the NHIS-prices for drugs that are currently reimbursed by the NHIS (28). Further, due to a lack of data, the cost of certain medications and treatment aspects was not able to be captured in this analysis. For example, the costs of blood transfusions were not included.

3. Total annual treatment costs

We estimated annual costs for both patients completing and abandoning treatment. The cost of treatment completion reflected the full array of costs for a patient who went through all cycles from beginning to end. This included cost of baseline labs, diagnostic tests, stage-dependent cost of labs during treatment, stage-dependent cost of discharge tests, and stage-dependent medication costs. For patients abandoning treatment, the following parameters were added together: cost of baseline labs, cost of diagnostic tests, 50% of stage-dependent cost of labs during treatment, and 50% of the stage-dependent medication costs. The cost of discharge tests were ignored, and the medication costs and lab costs during treatment were reduced by 50%.

When converting from US dollars to Ghana Cedi, the exchange rate for 30 July, 2021 according to the US Department of Treasury was used. The exchange rate used was 5.85 Ghana Cedi to 1 US dollars.

Societal costs

Societal costs were estimated by combining treatment and family costs, as well as the productivity losses associated with premature death. The data were based on a study by Dawson et al, estimating the costs associated with informal caregiving for children with lymphoma attending a tertiary hospital in Ghana, see parameters included in Table 8 (13). The study considered the family costs and physician time used for cancer treatment, including post-treatment follow-up visits as suggested in the treatment protocol. Dawson et al also estimated productivity losses using the human-capital approach (the daily minimum wage in Ghana multiplied by the number of working days in a year).

Table 8. Direct and indirect family costs

Average costs per year	Cost
Direct family costs	
Transportation costs	\$209.51
Food costs	\$179.83
Average indirect family cost during treatment	
Time spent on personal care	\$47.78
Time spent on travel	\$37.25
Time spent in waiting	\$18.62
Time spent on treatment	\$51.13

Source: Dawson et al (2020)

Post-treatment costs

We included the costs of follow-ups after the initial treatment (Table 9), which include physician and patient costs (13). Follow-ups are conducted monthly for six months after initial discharge, then every three months for two years, thereafter every six months for five years; and then once a year afterwards.

Table 9. Average cost per follow-up visit per patient

Cost type	Cost
Cost 1 year post-treatment	\$262.75
Cost 2 years post-treatment	\$80.36
Cost 3 years post-treatment	\$60.27
Cost 4-7 years post-treatment	\$40.18
Cost 8 years post-treatment	\$20.09

Source: Own costing based on patient costs (Dawson et al, 2020) and average cost of outpatient visits

7.3.5.5 Health outcomes

Health outcomes in the cost-effectiveness analysis were measured using Disability-Adjusted Life Years (DALYs). The DALY consists of two parameters: the years of life lost (YLL) from a disease, and the quality-adjusted years lived with disease (YLD). DALYs are calculated by adding these parameters together (42).

In the model, YLD for a given state is calculated by multiplying the number of people in a given state with the disability weight associated with being in that state, as well as the number of years of life spent in that state. YLD for all individuals in the cohort throughout the entire model is calculated by summarizing these aspects across all states in all cycles. The YLL is the years lost due to early death from BL.

To calculate YLLs and YLDs, we assumed the following: mean disease duration was one year; the average age at onset of BL was 7 years; life expectancy at birth of 64.1 years; we used the following disability weights – 0.288 for BL Stages I and II, and 0.451 for BL Stages III and IV. The probability of death from BL was estimated to be 0.25 for Stages I and II, and 0.2857 for Stages III and IV. DALYs were not age-weighted.

7.3.5.6 Discounting

Future values for costs and health effects were discounted to present values at a discount rate of 3% (43).

7.3.5.7 Determining cost-effectiveness

Cost-effectiveness was determined by means of the incremental cost-effectiveness ratio (ICER) calculated as cost per DALY averted. The WHO-CHOICE threshold measures for determining cost-effectiveness were used as follows: a cost per DALY averted less than three times the GDP per capita of Ghana is “cost-effective”; a cost per DALY averted less than one times the GDP per capita of Ghana is “very cost-effective” (43). The GDP per capita of Ghana in 2019 according to the World Bank was \$2202.

7.3.5.8 Sensitivity analysis

A probabilistic sensitivity analysis was performed, with parameter estimates assigned a probability distribution. Beta distributions were fitted for probability parameters using point estimates and standard errors. Lognormal distributions were fitted for relative risks using point estimates and their confidence intervals. The gamma distribution was used for costs and DALYs. The full list of parameters used in the model is provided in Appendix 7.

7.3.5.9 Budget impact analysis

A budget impact analysis (BIA) was undertaken from the perspective of the payer (NHIS), to estimate the financial impact of adding BL to the NHIS reimbursement list. We performed a dynamic cohort analysis based on our Markov model. The same baseline cohort of 309 patients was used. We estimated that there would be approximately 1,000 new cases of BL every year in the general population (22) (with 30% seeking treatment). We further assumed that the treatment seeking would increase by 5% annually as a result of insurance coverage. The analysis used a five-year time horizon for cost estimation, and accounted for a 5% annual inflation rate.

The BIA costs are estimated using in the following three scenarios:

- 1) Using the current NHIS tariff rate for the cost of labs and tests (assuming BMA & FNAC are reimbursed on the ratio of NHIA to hospital-fee)
- 2) Using only fees charged by KBTH for the cost of labs and tests;
- 3) Using 65% of the fees charged by KBTH for the cost of labs and tests.

A one-way sensitivity analysis was performed for selected parameters to explore the effects of uncertainty. The following parameters were examined in this analysis: percent reduction in assumed treatment-related resource use in treatment abandonment, proportion of patients who abandon treatment, proportion of BL patients who seek treatment, annual rate of increase in

treatment seeking due to NHIS-reimbursement, and proportion of patients diagnosed with Stage IV disease. The base-case values and the values used for the sensitivity analysis of these parameters can be seen in Table 10.

Table 10: Values used in the sensitivity analysis for budget impact

Parameter	Base-case value	Values used in sensitivity analysis		
		Low	Medium	High
% abandoning treatment	25%	0%	10%	68%
% seeking treatment	30%	10%	50%	100%
Annual increase in treatment seeking NHI	5%	0%	10%	15%
% patients in BL Stage IV	10%	5%		20%
Resources used when a patient abandons treatment	50%	0%	25%	75%

8 Findings

8.1 Cost analysis

Table 11 shows the total cost per patient per year of treatment for Stages I-IV from both an NHIS perspective and a societal perspective. The cost per-patient from an NHIS perspective for Stages I, II and III is \$524.67 per year, while the cost of treatment in Stage IV is \$1076.16 per year. The cost per-patient from a societal perspective for Stages I, II and III is \$1,930 per patient and \$2,697 per patient for Stage IV treatment. The addition of high-dose Methotrexate in Stage IV treatment, as well as the addition of additional treatment cycles, are among the factors leading to the higher cost for the treatment of Stage IV patients.

Table 11. Cost analysis

Stage of Treatment	Cost to the NHIS of treatment with NHIS coverage	Cost to society of treatment with NHIS coverage
Stages I, II and III	\$524.67	\$1,930
Stage IV	\$1076.16	\$2,697

**All costs presented in USD were derived with an exchange rate of 5.85 cedi to 1 USD*

In Table 12, we show the cost for patients who abandon treatment. As there are no health gains when a patient abandons treatment, these resources are described as a resource loss. Therefore, the net resource loss to the NHIS per patient abandoning treatment is US\$314 at Stages I, II and III and US\$580 at Stage IV. From a societal perspective, these net losses are estimated to be US\$1,017 at Stages I, II and III and US\$1,390 at Stage IV per patient.

Table 12. Estimated cost of treatment abandonment

Stage of treatment	Cost to NHIS	Cost to society
Stages I, II and III	\$314	\$1,017
Stage IV	\$580	\$1,390

Table 13 breaks down the cost composition of the treatment costs (in Tables 11 and 12). As a percent of total cost, diagnostic tests are consistently the highest cost at all stages, for both patients who complete or abandon treatment. The

share of diagnostic tests and baseline labs declines as disease stage progresses, but that for medication increases. The share of medication costs at Stage IV is five times that at Stage I. The trends are similar for treatment abandonment.

Table 13. Composition of treatment costs

Aspect of treatment	Stage I & II		Stage III		Stage IV	
	Comple ^t ion	Abandonment	Comple ^t ion	Abandonment	Comple ^t ion	Abandonment
Baseline labs	6.9%	7.2%	5.4%	6.3%	4.4%	5.6%
Diagnostic tests	84.7%	88.4%	66.2%	77.1%	53.7%	67.9%
Medication	8.3%	4.3%	28.4%	16.6%	41.9%	26.5%
Total cost of treatment	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

8.2 Base-case cost-effectiveness analysis

Table 14 presents the base-case cost-effectiveness analysis. As the NHIS-reimbursed treatment is both more effective and less costly, the NHIS-Reimbursed treatment is always preferred.

Table 14. Results of the cost-effectiveness analysis

Strategy	Cost per patient	DALYs per patient	ICER (incremental cost per incremental DALY averted)
Current practice	\$9,558	23.33	- \$219
NHIS-reimbursed treatment	\$8,302	17.60	

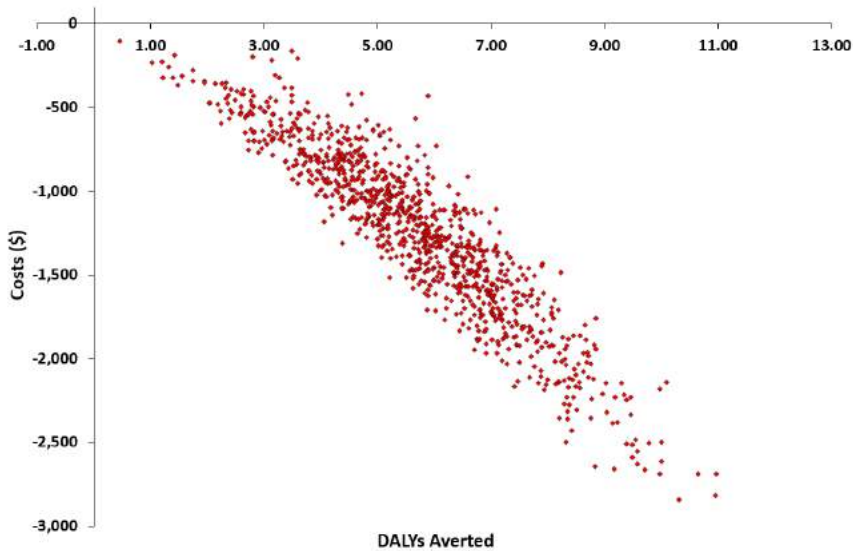
NHIS-reimbursed treatment dominates. The results presented in Table 10 are based on the societal perspective. For analyses using the NHIS perspective, see Appendix 6

8.3 Probabilistic cost-effectiveness analysis

Figure 3 presents a scatter plot of incremental cost-effectiveness ratios (ICERS) derived by running 1,000 simulations of the cost-effectiveness analysis. All ICERS plotted on the graph fall below the horizontal axis (DALYs averted) and

to the right of the vertical axis (\$ costs), implying that the intervention (NHIS-reimbursed treatment) is both cheaper and more effective than the standard of care (current practice). In other words, the NHIS-reimbursed treatment dominates treatment with Current Practice in 100% of the 1,000 simulations, and can thus be considered to be very cost-effective.

Figure 3. Treatment with NHIS reimbursement compared to current practice



8.4 Budget impact analysis

8.4.1 Base-case results

Figure 4 presents the results of the base-case Budget Impact Analysis. The cost to the NHIS estimated in years 1 through 5 are as follows: \$83,871 in year 1, \$185,001 in year 2, 215,800 in year 3, \$227,822 in year 4, and \$239,256 in year 5. This leads to an estimated total budget impact to the NHIS of \$951,750 in the first 5 years should BL be added to the NHIS reimbursement list.

Figure 4. Base-Case results of Budget Impact Analysis

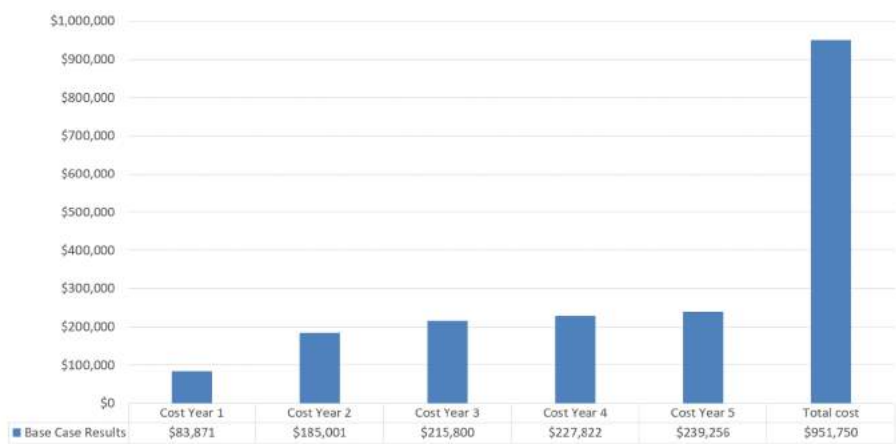
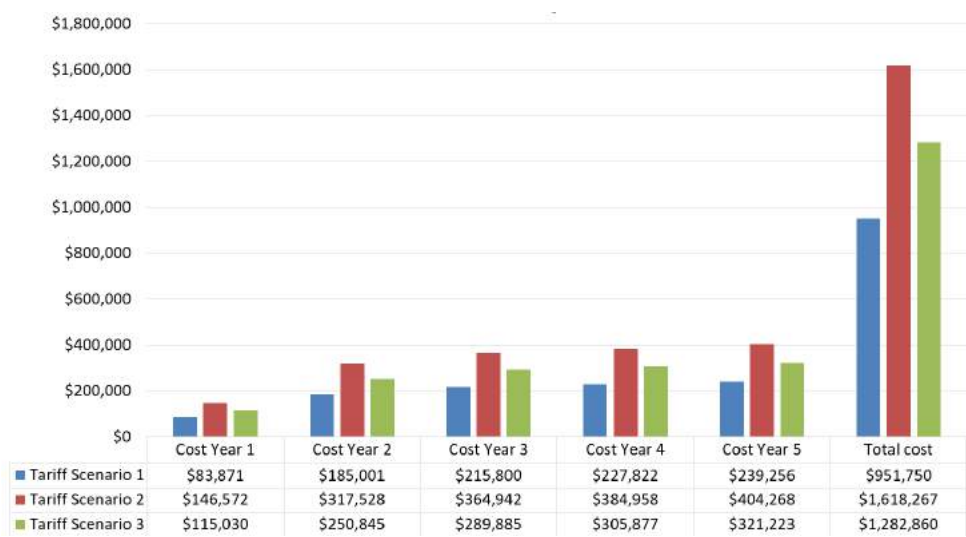


Figure 5 presents the results of the scenario analysis, showing the projected annual costs of treatment that are likely to be borne by the NHIS at three coverage scenarios over a period of five years:

- 1) Using the current NHIS tariff rate for the cost of labs and tests (assuming BMA & FNAC are reimbursed on the ratio of NHIA to hospital-fee),
- 2) Using 100% of the fees charged by KBTH for the cost of labs and tests as the tariff rate;
- 3) Using 65% of the fees charged by KBTH for the cost of labs and tests as a tariff rate.

The results showed a total expected NHIS budget impact of \$951,750 under Tariff scenario 1 (base-case scenario), \$1,618,267 under Tariff scenario 2, and \$1,282,860 under Tariff Scenario 3. Compared to Tariff Scenario 1, Tariff Scenario 3 poses an incremental difference of \$331,110. Scenario 2 poses an incremental difference of \$335,407 compared to scenario 3. All of the Tariff scenarios show the lowest cost in the first year and an increasing cost in each subsequent year.

Figure 5. Results of the scenario analysis



The results of the one-way sensitivity analysis for all Tariff scenarios can be seen in Table 15. The sensitivity analysis showed whether change in these parameters leads to a decrease or increase of total cost.

For the parameters “Resources used when a patient abandons treatment” and “proportion of patients who abandon treatment”, the total cost decreases when we assume values greater than the base-case scenario, and the total cost increases when we assume values less than the base-case scenario. The type of relationship between these parameters and the total cost, where a decrease in one value leads to an increase in the other and vice versa can be defined as a negative relationship

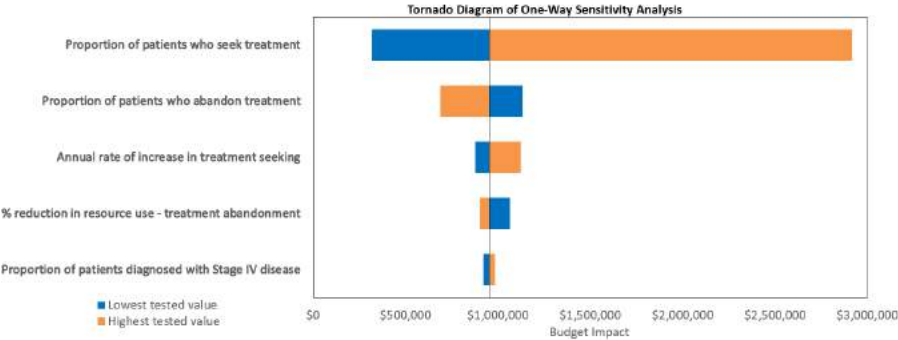
For the parameters “Proportion of patients who seek treatment”, “Annual rate of increase in treatment seeking”, and “Proportion of patients diagnosed with Stage IV disease”, the total cost increases when we assume values greater than the base-case scenario, and the total cost decreases when we assume values less than the base-case scenario. The type of relationship between these parameters and the total cost, where an increase in one value leads to an increase in the other and vice versa can be defined as a positive relationship.

Table 15. One-way sensitivity of the results to selected parameters under three Tariff scenarios

Model Parameter	Value in Model	Sensitivity Analysis	Tariff Scenario 1 (base case)	Tariff Scenario 2	Tariff Scenario 3
Resources used when a patient abandons treatment	50%	0%	\$1,066,144	\$1,620,360	\$1,420,588
		25%	\$1,001,402	\$1,671,201	\$1,334,174
		75%	\$902,099	\$1,565,333	\$1,231,545
Proportion of patients who abandon treatment	0.255	0.000	\$1,132,383	\$1,873,974	\$1,501,511
		0.100	\$1,059,610	\$1,771,187	\$1,413,541
		0.682	\$687,234	\$1,239,624	\$960,505
Proportion of patients who seek treatment	0.3	0.1	\$317,250	\$539,422	\$427,620
		0.5	\$1,586,250	\$2,697,112	\$2,138,100
		1.0	\$2,917,045	\$4,956,935	\$3,930,406
Annual rate of increase in treatment seeking	0.05	0.00	\$875,114	\$1,487,080	\$1,179,122
		0.10	\$1,034,886	\$1,760,662	\$1,395,437
		0.15	\$1,124,914	\$1,914,947	\$1,517,390
Proportion of patients diagnosed with Stage IV disease	0.1				
		0.050	\$923,346	\$1,590,309	\$1,254,733
		0.150	\$982,366	\$1,648,401	\$1,313,177

Figure 6 further presents the results of the one-way sensitivity analysis through a visual medium via a tornado diagram. This figure illustrates the degree of sensitivity of the results to each individual selected parameter. The total cost is most sensitive to change in “proportion of patients who seek treatment”, followed in descending order by “proportion of patients who abandon treatment”, “the annual rate of increase in treatment seeking”, “resources used when a patient abandons treatment”, and “proportion of patients diagnosed with stage IV disease”.

Figure 6. Tornado diagram of the one-way sensitivity analysis of selected parameters



9 Discussion

This assessment was commissioned to evaluate the costs and impacts of adding BL to the NHIS reimbursement list. We performed an economic evaluation to present the cost effectiveness of extending insurance coverage to children with Burkitt lymphoma; in addition, we undertook a cost analysis to estimate the budgetary implications for the payer (NHIS).

The costs of managing childhood cancer have been documented in Ghana and in other settings, and have been shown to be substantial. We estimated a cost to the NHIS of \$580 per patient per year for management of advanced stage disease, and an average cost of US\$1,390 from the societal perspective. This is similar to what has been shown in other studies of childhood cancer. A study in Ghana assessing medicines for treating childhood cancer estimated that it would cost on average US\$900 to treat a 30 kg child (44). In a cost-of-illness study, Dawson et al estimated an average cost of US\$440 for treating lymphoma in children (13). Similar to our finding, the average costs of treating BL in Uganda were estimated to be US\$1,350 (45). Another study in four African countries found that the cost per new diagnosis of childhood cancers ranged between US\$2400 and US\$31,000 (46). Differences in cost estimates were attributed to variations in among other things admission practices, drug prices and the rate of treatment abandonment.

In general, the costs of treating and managing childhood cancer have been shown to be highly cost-effective across several settings in sub-Saharan Africa (45-47). One of the reasons for this is that a high number of life years are potentially gained from saving a young life (e.g. more than 50 life years gained per child on average). This shows the importance of supporting effective treatments and mechanisms for managing childhood cancer. In our study, we evaluate the impact of providing health insurance, so that affected children can have access to much needed care. This has been advocated by many groups who point to the fact that the costs of childhood cancer are prohibitive and lead many families to either delay care or abandon it once treatment has commenced (13, 39, 48). Financing healthcare for childhood cancer has been shown to be effective in increasing access to care, limiting treatment abandonment, leading to an increase in overall survival (40). This assumption that we made about the success of insurance coverage in our study did improve the overall effect and cost-effectiveness of the intervention. However, the

sensitivity analysis showed that this assumption was not highly sensitive to changes.

Our analysis has shown that providing insurance cover to BL patients is potentially highly cost-effective in Ghana. This intervention can help to achieve desirable treatment outcomes and prevent avoidable deaths of children by increasing access to care and treatment retention. However, increasing access to care may not always be as easy in real world settings and several factors must be taken into consideration. In Ghana for example, there are not many facilities providing cancer treatment. Care is mainly provided at two health facilities which may not be easily accessible to patients from remote areas of the country. Patients have to travel long distances to access treatment and this contributes to high costs to the family. Providing insurance cover may thus only partially alleviate patient costs.

Further, much needs to be done to generate awareness among patients, teaching them about cancer and to generally improve treatment seeking behaviour. These 'awareness raising' costs can be high, but have not been considered in this study. However, in all likelihood, the intervention is still likely to be cost-effective, due to the increased overall survival of children being treated for cancer. In additional analyses, we showed that even if the study perspective was restricted to the NHIS only, the intervention would still most likely be very cost-effective.

The costs to the NHIS are expected to be between US\$951,000 and US\$1,620,000 over a five-year period, i.e. between US\$0.03 and US\$0.05 per capita (based on the total population of Ghana).

9.1 Limitations

There are some limitations with our study. Firstly, data is triangulated from various sources including on the effect of health insurance on treatment abandonment, some population characteristics and treatment effects, for which data was not available in Ghana. We tried to use locally available data as far as possible and tested the uncertain parameters in sensitivity analyses; these assumptions were shown to be robust. In addition, we performed probabilistic sensitivity analyses with microsimulation, which randomized parameter estimates and showed that the result would always favour the intervention.

The costs of treating and managing childhood cancer presented in this study could be an underestimate. Even though we endeavoured to provide costs from a societal perspective, there are a lot of other costs beyond access to care that families could incur that are not considered here, for example the funeral expenses. In addition, the intangible costs related to grief and human loss cannot be quantified. These issues could be investigated in future research. We are confident however, that we have provided an acceptable cost estimate, which fall within the range of what has been shown to be the costs of managing childhood cancer in sub-Saharan Africa.

The study considers the overall economic impact of providing health insurance, but does not consider whether such an endeavour would be affordable to Ghana. The actuarial past, present and future financial risks to the NHIS have also not been considered. These issues should be taken into consideration in future assessments.

Only one childhood cancer was considered in this evaluation and thus both the costs and benefits highlighted are minimal. However, BL accounts for a significant proportion of childhood cancers and the findings given in this report can be extended to other cancers. However, to better inform the government and the NHIS, further analyses should be conducted to outlay the full cost implications of changing the financing policy for childhood cancer in general.

9.2 Policy implications

Our study provides useful information that can inform policy on managing childhood cancer in Ghana and other sub-Saharan African countries. The study supports increasing calls from stakeholders for funding to childhood cancers, which are often overlooked in comparison to adult cancers and other non-communicable diseases. This is despite the increasing attention that is paid to non-communicable diseases and cancer in general. Indeed, while treatments for childhood cancer are available on the essential medicines list of the NHIS in Ghana, childhood cancer treatment is not considered for reimbursement. Stakeholders who participated in this current assessment indicated that there was political will to effect financing of childhood cancer, and the findings we have provided will give impetus for increased attention to paediatric cancer.

In many ways, the findings of this assessment also point to the need for overall improvement in the health system. Treatment seeking appears to be a

challenge that needs to be urgently addressed. A lot of cancers are detected at advanced stages, which negatively impacts survival. Thus, policy should encourage both early treatment and retention. The role of stakeholders, particularly at the community level should be taken into consideration, especially in relation to the governments expanding strategy for cancer control.

10 Conclusion

This evaluation demonstrates the cost-effectiveness and financial implication of extending health insurance to Burkitt lymphoma in Ghanaian children. The treatment of childhood cancers in general has been shown to be cost-effective across various settings in sub-Saharan Africa, including Ghana. However, access to essential cost-effective care is a significant challenge for many patients and their families. Consequently, there are many preventable deaths of children with cancer. Our analysis shows that the government and society in general can benefit from investment in childhood cancer.

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12 Study team

The following persons worked on various aspects of this report, either as core members or technical partners co-opted into Ghana HTA Technical Working Group for this task.

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A report of the Ghana HTA Technical Working Group

13 Budget and funding

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14 Appendices

Appendix 1: The treatment protocol for Burkitt lymphoma in Ghana

Stages I, II and III

First course of chemotherapy

Pre-hydration – 2.5l/m for 24 hrs

Allopurinol 100mg tds x 5 days

Chemotherapy after 24 hrs of prehydration

Antiemetic required Metoclopramide 8 hourly or Granisetron (mostly used here) 12 hourly

Course 1

1. IV Cyclophosphamide 1400mg/m² (or 40mg/kg) over 30 mins in 100ml fluid (Normal Saline). (The 1400mg/m² can be given as follows – 300mg/m² stat, then 400mg/m² after 72 hrs, then 700mg/m² after 7 days)
2. Tabs Prednisolone 60mg/m² in 2 divided doses x 5 days
3. IT Methotrexate dose by age CSF for cytology repeat day 5

Continue with post-hydration for at least 48 hrs after last dose of Chemotherapy (CTX).

Second and subsequent courses (two weeks intervals)

Check FBC and ensure neutrophils > 1.0 before giving chemo.

Course 2, 4, 6, 8

1. IV Vincristine 1.5mg/m² bolus
2. IV Doxorubicin (Adriamycin) 30mg/m² 250ml fluid over 2 hrs.
3. IV Cyclophosphamide 1000mg/m² in 100ml fluid over 30 mins (pre-hydration at 125ml/m² for 1 hour and post-hydration at 125ml/m² hourly x 4 hours)
4. Tab Prednisolone 60mg/m² in 2 divided doses x 5 days
5. IT Methotrexate dose by age (course 2 only)

Repeat this at two weekly intervals alternating with:

Course 3, 5, 7

1. IV Vincristine 1.5mg/m² bolus
2. IV Cytarabine (cytosine arabinoside) 400mg/m² in 500ml fluid over 24 hrs daily x 2 days.

3. IV Cyclophosphamide 1000mg/m² in 100ml fluid over 30 mins (pre-hydration at 125ml/m² for 1 hour and post-hydration at 125ml/m² hourly x 4 hours).
4. IT Methotrexate dose by age (course 3 only)

IT Methotrexate is given for only the first three courses if no CNS disease

NOTE: Stage IV (Bone marrow/CNS) to receive maintenance of the above on completion of 8 cycles alternating at 4 weekly intervals to a total of 10 cycles.

Type of staging method	St Jude's
Average number of Patient's per year	Not too clear (yet to be provided)
MEDICATIONS	
Pre-hydration before chemotherapy	IV Fluids (Dextrose Saline 2.5Litres/metre squared over 24 hours)
Prevention of tumour lysis syndrome	Allopurinol
Antiemetics	IV ondansetron and upon discharge oral IV Granisetron and upon discharge oral
How many Treatment cycles	Refer to Protocol. Stage 1 to 3 require 8 cycles whilst stage 4 goes to 10 cycles
Treatment medications	IV Cyclophosphamide. IV Vincristine, Tab Prednisolone, IT Methotrexate, IV Doxorubicin, IV Cytarabine
Pain medications used	Oral Morphine, Oral Paracetamol
Fee for preparation of cytotoxic	No fee
Consultation fee	No fee

NOTE

BSA Equation

- In addition to the use of the nomogram, BSA may be determined through use of the following formula:

$$BSA, m^2 = \sqrt{\frac{Ht (cm) \times Wt (kg)}{3600}}$$

- Calculate the BSA for a patient measuring 165 cm in height and weighing 65 kg.

$$BSA, m^2 = \sqrt{\frac{165 (cm) \times 65 (kg)}{3600}}$$

$$BSA = 1.73 m^2, answer.$$

INTRATHECAL METHOTREXATE: AGE RELATED DOSING STANDARD

Age in years	Intrathecal methotrexate dose in mg
< 1	8
1 to 2	10
2 to 3	12
3+	15

Stage IV Treatment Protocol

Chemotherapy after 24 hrs of prehydration

Antiemetic required Granisetron (every 12 hours)

First course of chemotherapy

Pre-hydration – 2.5l/m for 24 hrs

Allopurinol 100mg tds x 5 days

Course 1

1. IV Cyclophosphamide 1400mg/m² (or 40mg/kg) over 30 mins in 100ml fluid (Normal Saline). (The 1400mg/m² can be given as follows – 300mg/m² stat, then 400mg/m² after 72 hrs, then 700mg/m² after 7 days)
2. Tabs Prednisolone 60mg/m² in 2 divided doses x 5 days
3. Triple IT: IT Methotrexate 12.5mg, IT Hydrocortisone 15mg, IT Cytarabine 30mg CSF for cytology

Continue with post-hydration for at least 48 hrs after last dose of Chemotherapy (CTX).

Note: Weekly Triple IT as above until CSF clear of blasts and for two extra weeks

Second and subsequent courses (two weeks intervals)

Check FBC and ensure neutrophils > 1.0 before giving chemo.

Note: High-dose methotrexate (HdMTX) to be given only up to course 6 and not for maintenance. Total number of courses is 10.

Course 2, 4, 6

Day 1) IV Vincristine 1.5mg/m² bolus

Tabs Prednisolone 60mg/m² in two divided doses daily x5

IV Methotrexate (HdMTX) 1000mg/m² with hydration pre and post as per protocol

IV/Oral Folinic acid 25mg/m² (start exactly 24 hrs from start of IV HdMTX) 6hrly x 6 doses

Day 2) IV Doxorubicin (Adriamycin) 30mg/m² 250ml fluid over 2 hrs.

IV Cyclophosphamide 1000mg/m² in 100ml fluid over 30 mins (pre-hydration at 125ml/m² for 1 hour and post-hydration at 125ml/m² hourly x 4 hours)

Triple IT as in Course 1, for each cycle on day 2 and day 6.

Repeat this at two weekly intervals alternating with:

Course 3, 5,

Day 1) IV Vincristine 1.5mg/m² bolus

IV Methotrexate (HdMTX) 1000mg/m² with hydration pre and post as per protocol

IV/Oral Folinic acid 25mg/m² (start exactly 24 hrs from start of IV HdMTX) 6hrly x 6 doses

Day 2) IV Cyclophosphamide 1000mg/m² in 100ml fluid over 30 mins (pre-hydration at 125ml/m² for 1 hour and post-hydration at 125ml/m² hourly x 4 hours)

IV Cytarabine (Cytosine Arabinoside) 400mg/m² in 500mLs over 24 hrs days 2 and 3.

Triple IT as in Course 1, for each cycle on day 2 and day 6.

High-Dose Methotrexate administration protocol

T=-2 Prehydrate with 125ml/m²/hr (dextrose or dextrose saline with, NaHCO₃, 25mmol/500mls) for a minimum of 2 hours. Urine pH ≥7 and Urine output ≥100 mLs/m²/hr.

T=0 High-dose Methotrexate in 5% dextrose (with NaHCO₃ 25mmol/500mLs) at 1000mg/m² over 3 hours.

T=+3 Posthydration with 5% dextrose (with NaHCO₃ 25mmol/500mLs) and KCl (10mmol/500mL) at 3L/m²/day to maintain urine pH ≥7 for 48 hours. Continue normal hydration for 24 hours more.

T=+24 Folinic Acid 15mg/m² orally or IV, every 6 hours for a total of 6 doses

*Alternative to IV NaHCO₃ is oral at 1mmol/kg 6hrly to maintain urine pH ≥7.

Appendix 2: Checklists and questions to guide data collection and analysis

Assessment elements and translating research questions

Topic	Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'Critical' elements	Answered	Who	Deadline
Description and technical characteristics of technology						
Features of the technology and comparators	What is the technology and the comparator(s)?	Yes	What is the standard of care for treatment of BL and what are the comparators?	draft		
Regulatory Status	For which indications has the technology received marketing authorisation or CE marking?	Yes	What are the approved indications?	No		
Features of the technology and comparators	What is the claimed benefit of the technology in relation to the comparators?	Yes	What is the claimed benefit of standard of care in relation to the comparators in BL?	No		
Features of the technology	What is the phase of development and implementation of the technology and the comparator(s)?	No		No		
Features of the technology	Who administers the technology and the comparators and in what context and level of care are they provided?	Yes		No		
Investments and	What kind of special	No				

tools required to use the technology	premises are needed for the technology and the comparator (s)?					
Investments and tools required to use the technology	What supplies are needed for the technology and the comparator (s)?	Yes		No		
Regulatory Status	What is the reimbursement status of the technology?	Yes		No		
Health problem and current use of technology						
Target Condition	What is the disease or health condition in the scope of this assessment?	Yes	<i>What is BL and natural course of the disease?</i>	<i>draft</i>		
Target Condition	What are the known risk factors for the condition?	Yes	<i>What are the known risk factors for BL?</i>	No - draft		
Target Condition	What is the natural course of the disease or health condition?	Yes	<i>What is the natural course of BL?</i>	<i>draft</i>		
Target Condition	What are the symptoms and the burden of disease or health condition for the patient?	Yes	<i>What are the symptoms and the burden of the disease or health condition for the patient?</i>	No		
Target Condition	What is the burden of disease for society?	Yes		<i>no</i>		
Current Management of the Condition	How is the disease or health condition currently diagnosed according to published guidelines and in practice?	Yes ?	<i>How is BL currently diagnosed according to WHO and other internationally published guidelines? And also according to Ghanaian guidelines?</i>			

Current Management of the Condition	How is the disease or health condition currently managed according to published guidelines and in practice?	Yes	<i>How is BL currently managed according to WHO and other internationally published guidelines? And also according to Ghanaian guidelines?</i>	<i>no</i>		
Target Population	What is the target population in this assessment?	Yes	<i>What is the target population in this assessment?</i>	<i>no</i>		
Target Population	How many people belong to the target population?	Yes	<i>How many people belong to the target population?</i>	<i>no</i>		
Utilisation	How much are the technologies utilised?	No				
Clinical effectiveness - from scoping review, extra information welcome						
Mortality	What is the expected beneficial effect of the intervention on mortality?	Yes	<i>What is the expected effect of treatments on overall survival?</i>			
Morbidity	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition or disease?	Yes				
Morbidity	How does the technology affect progression (or recurrence) of the disease or health condition?	Yes	<i>What is the effect of treatments on disease progression, treatment response and relapse rate?</i>			
Function	What is the effect of the technology on patients' body functions?	No				

Function	How does the use of technology affect activities of daily living?	No				
Health-related quality of life	What is the effect of the technology on generic health-related quality of life?	Yes				
Health-related quality of life	What is the effect of the technology on disease-specific quality of life?	Yes				
Patient satisfaction	Was the use of the technology worthwhile?	No				
Safety - from scoping review, extra information welcome						
Patient safety	How safe is the technology in relation to (the) comparator(s)?	Yes				
Patient safety	Are the harms related to dosage or frequency of applying the technology?	Yes				
Patient safety	How does the frequency or severity of harms change over time or in different settings?	No				
Patient safety	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?	No				
Patient safety	Are the technology and comparator(s) associated	No				

	with user-dependent harms?					
Investments and tools required to use the technology	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?	Yes				

Appendix 3: Mapping of stakeholders in childhood cancer in Ghana

Stakeholder	Sector	Interest stakes in Burkitt Lymphoma management	Contribution to successful outcomes in BL management (knowledge, time, money, labour etc.)	Decision making power (Influence)
National Health Policy, 2020				
Ministry of Health	Governmental	+++	+++	+++
Ghana Health Service	Governmental	+++	+++	+++
Healthcare providers – (Teaching hospitals)	Public Health	+++	++	+
National Health Insurance Authority	Governmental	++	+++	++
Pharmaceutical companies	Pharmaceutical sector	+	++	+
World Health Organization	Non-governmental	+++	+++	+
NGOs for childhood cancer - Burkitt Lymphoma (e.g. Childhood cancer international, World child cancer)	Non-governmental	++	+	+
Ghana Parents Association for Childhood cancer (GHAPACC)	Patient group	+++	+	+
National Health Insurance Act, 2012 (Act 852)				
Ministry of Health	Governmental	+++	+++	+++
Ghana Health Service	Governmental	+++	+++	+++
Healthcare providers – (Teaching hospitals)	Public Health	+++	++	+++
National Health Insurance Authority	Governmental	+++	+++	+++
Pharmaceutical companies	Pharmaceutical sector	+++	+	++
World Health Organization	Non-governmental	++	++	+
NGOs for childhood cancer - Burkitt Lymphoma (e.g.	Non-governmental	++	+	+

Childhood cancer international, World child cancer)				
Ghana Parents Association for Childhood cancer (GHAPACC)	Patient group	+++	+	+
Essential Medicines List, 7th Edition, 2017				
Ministry of Health	Governmental	+++	+++	+++
Ghana Health Service	Governmental	+++	+++	+++
Healthcare providers – (Teaching hospitals)	Public Health	+++	+++	+++
National Health Insurance Authority	Governmental	++	++	++
Pharmaceutical companies	Pharmaceutical sector	++	+++	++
World Health Organization	Non-governmental	+++	+	++
NGOs for childhood cancer - Burkitt Lymphoma (e.g. Childhood cancer international, World child cancer)	Non-governmental	+	+	+
Ghana Parents Association for Childhood cancer (GHAPACC)	Patient group	+	+	+
NHIS Medicines List, 2021				
Ministry of Health	Governmental	+++	+++	+++
Ghana Health Service	Governmental	+++	+++	+++
Healthcare providers – (Teaching hospitals)	Public Health	+++	++	++
National Health Insurance Authority	Governmental	+++	+++	+++
Pharmaceutical companies	Pharmaceutical sector	+++	++	++
World Health Organization	Non-governmental	++	++	+
NGOs for childhood cancer - Burkitt Lymphoma (e.g. Childhood cancer international, World child cancer)	Non-governmental	+	+	+

Ghana Parents Association for Childhood cancer (GHAPACC)	Patient group	+++	+	+
National Policy for the Prevention and Control of Chronic Non-Communicable Diseases in Ghana				
Ministry of Health	Governmental	+++	+++	+++
Ghana Health Service	Governmental	+++	+++	+++
Healthcare providers – (Teaching hospitals)	Public Health	+++	++	++
National Health Insurance Authority	Governmental	+++	+	+
Pharmaceutical companies	Pharmaceutical sector	++	+	+
World Health Organization	Non-governmental	+++	++	++
NGOs for childhood cancer - Burkitt Lymphoma (e.g. Childhood cancer international, World child cancer)	Non-governmental	+++	+	+
Ghana Parents Association for Childhood cancer (GHAPACC)	Patient group	+++	+	+
Standard Treatment Guidelines, 2017				
Ministry of Health	Governmental	+++	+++	+++
Ghana Health Service	Governmental	+++	+++	+++
Healthcare providers – (Teaching hospitals)	Public Health	+++	+++	+++
National Health Insurance Authority	Governmental	+++	+	+
Pharmaceutical companies	Pharmaceutical sector	+++	+++	+++
World Health Organization	Non-governmental	+++	+++	+++
NGOs for childhood cancer - Burkitt Lymphoma (e.g. Childhood cancer international, World child cancer)	Non-governmental	+	+	+
Ghana Parents Association for Childhood cancer (GHAPACC)	Patient group	+	+	+

National Strategy for Cancer Control in Ghana (2012 -2016)				
Ministry of Health	Governmental	+++	+++	+++
Ghana Health Service	Governmental	+++	++	+++
Healthcare providers – (Teaching hospitals)	Public Health	+++	+++	++
National Health Insurance Authority	Governmental	+++	+	+
Pharmaceutical companies	Pharmaceutical sector	+	+	+
World Health Organization	Non-governmental	+++	++	+
NGOs for childhood cancer - Burkitt Lymphoma (e.g. Childhood cancer international, World child cancer)	Non-governmental	+++	++	+
Ghana Parents Association for Childhood cancer (GHAPACC)	Patient group	+++	+	+
Public Health Act, 2012				
Ministry of Health	Governmental	+++	+++	+++
Ghana Health Service	Governmental	+++	+++	+++
Healthcare providers – (Teaching hospitals)	Public Health	+++	++	+++
National Health Insurance Authority	Governmental	+++	++	++
Pharmaceutical companies	Pharmaceutical sector	+++	++	+++
World Health Organization	Non-governmental	+++	++	++
NGOs for childhood cancer - Burkitt Lymphoma (e.g. Childhood cancer international, World child cancer)	Non-governmental	++	+	+
Ghana Parents Association for Childhood cancer (GHAPACC)	Patient group	+	+	+

+++ = High
 ++ = Moderate
 + = Low

Appendix 4: Stakeholder engagement and workshop



Ministry of Health

HTA Secretariat

#8 Meeting of the Ghana HTA Technical Working Group

Date: 17th August 2021

Stakeholder engagement on HTA for Burkitt Lymphoma

Preamble

Ghana has setup structures for HTA in within the health system. Technical work has started. This review will seek to assess the impact of adding childhood cancers to the NHIS list of reimbursable morbidities.

The focus of this work will be to use provide evidence from HTA analysis to guide the possible extension of current anti-cancer medicines on the NHIS list to cover childhood cancers.

Objectives

The objectives of this HTA for Burkitt Lymphoma project is as follows:

1. To conduct HTA comparing treatments for Burkitt Lymphoma, with NHIS coverage vs no NHIS coverage, in Ghanaian children under the age of 15 years.
2. To build capacity within the current HTA country structures alongside HTA analysis

Meanwhile the objectives of this stakeholder workshop is to garner inputs from stakeholders on the above context, as well as build consensus on the analytical pathways and expected outputs. The HTA questions is framed as below:

Population	• Children under the age of 15 years with endemic Burkitt lymphoma
Intervention	• All treatments found on the NHIS essential medicines list (with NHIS coverage)
Control	• Standard of care regimen (with no NHIS coverage)
Outcome	• Survival, mortality, DALYs, costs, cost per DALY

Schedule

Activity	Lead
Arrival and registration, Lunch	1:30 am

Opening		2:00 pm
1.	Opening prayer and Introductions	[10 mins]
2.	Opening Remarks	Joycelyn Azeez, Director Pharmaceutical Services, HTA TWG Co-Chair [5 mins]
3.	Purpose of the meeting and introduction of the agenda	Justice Nonvignon, HTA TWG Co-Chair [5 mins]
4.	Presentation of the context for Burkitt Lymphoma and the role of HTA	Brian Asare, HTA Coordinator [10 mins]
5	Moderated discussion on BL in Ghana	Dr Richmond Owusu [60 min]
5. Coffee Break		3:30 - 4:00 pm
6.	Next steps and the role of various stakeholders	Ivy Amankwah, HTA Secretariat [10 mins]
7.	Summary of key inputs from Stakeholders	Dr Emmanuella Abassah-Konadu, HTA Secretariat [10 mins]
8.	Closing	4:30 pm

Meeting details

Mode	Hybrid meeting
Participants	<ol style="list-style-type: none"> HTA TWG members and HTA Secretariat ADP-PATH representation NIPH representation Selected Stakeholders in Paediatric Oncology
Co-Chairs	Justice Nonvignon-SPH, Ghana HTA TWG Chair Joycelyn Azeez, Director Pharmaceutical Services-MOH, HTA TWG Co-Chair

Questions used in breakout sessions and plenary

Important: In preparation for the meeting, participants are encouraged to review the questions in advance.

- What is the current burden of paediatric Burkitt lymphoma in Ghana (morbidity, prevalence, mortality, distribution, and risk groups etc)?

2. What is the current protocol, guideline, or practice for management of childhood cancer in Ghana?
3. Is there a specific protocol/guideline for management of Burkitt and Burkitt-like lymphoma?
4. What are the perceived benefits and challenges of the overall response to childhood cancers and Burkitt lymphoma in particular?
5. What ethical, social, or legal aspects specific to childhood cancer should be taken into consideration in the assessment?
6. What is the status of financing of treatment for Burkitt lymphoma patients? Who is responsible for paying for treatment – out-of-pocket by patients? Or NHIS or co-payment?
7. Are the existing policies on cancer control and management (e.g., National strategy for cancer control, Public Health Act, Standard Treatment Guidelines, etc.) achieving their goals? If yes, what are the facilitators if no what are the challenges of implementation?
8. What would you like to see changed in the childhood cancer control and management space, in terms of policy, protocols/guidelines? Why?
9. What other key issues should the analysis team consider?

Notes from the Stakeholder meeting held on 17th August

Question & Answers

*questions during the second part of morning session

** questions during the afternoon session with TWG and stakeholders

Questions from NIPH towards role/vision of TWG:

- *Situational assessment is used to gather information for the economic evaluation. The primary question is not a treatment effect, but an economic effect. Not the treatments and how effective they are. We have assumed that the question is what coverage scenarios and what system should be in place coverage vs. no coverage; is this correct?*
- *What should be the perspective of the economic evaluation, societal or payer (either government or NHIS)? What is the appropriate time horizon for the BL economic evaluation?**

- *Should the underlying model from economic evaluation be a full markov model or hybrid?*
- *Are our outcomes chosen outcome measures appropriate, e.g. US dollars and DALYs?*
- *If NHIS will cover treatment of BL, is the protocol going to be different?**
- *What are the consequences on treatment abandonment? Assumption every will die, is this correct?** *Should we assume that if NHIS is covered, does this ensure that abandonment does not happen?**

Q&A TWG and NIPH

- *Various question on why the cost of treatment on NHIS is lower than the cost of treatment without NHIS coverage*
 - Answer: (1) depends on perspective; (2) tariffs NHIS (aka government reimbursement) will never match the cost charged by healthcare provider – e.g. waste; (3) some diagnostics are not covered by NHIS
 - Answer continued: For NHIS question is not CE. The budget impact analysis, is most important in this case for NHIS. We should also consider, what is going to convince the NHIS to reimburse treatment.”
 - Answer continued*: We do not have value for unit cost (of diagnostic tests, etc.), we used user fees as proxy for the unit costs.
- *Cost template to understand the cost for municipal hospitals, teaching hospitals, etc. What is the role for the private sector?*
 - Answers: Stakeholder mapping, and looking at gap analysis for childhood cancers in general. There is a separate report, which we not have pended to this report. Who are the stakeholders, who is doing what, interview government, ngo, private sector.
- *How where the numbers on abandonment retrieved?**
 - Answer: ... We do not have indication on what this rate will be. We have used estimates from similar studies, if you have insurance coverage it can help to stop abandonment up to 80% (assumption we have made)

Local stories provided by stakeholders**

- **Childhood cancers**

- Lymphoma 30-35% of all cancers cases in children; Leukaemia cases (commonest cancer) are now catching up, as well as liquid blood cancers are catching up with lymphoma.
- Lymphoma is uniformly deadly if not treated, because fastest growing lymphoma when present and within 6 weeks large tumour.
 - We have endemic type (located on the jaw), but see more and more sporadic type
 - Aggressive but very treatable – use chemotherapy and melts in front of you; diagnosis should be early, it needs to be treated early and if further harder to cure and need more intensive treated. Many children have survived if getting adequate treatment.
- NHIS indicated 2500 children with (childhood OR BL) cancers per year
 - We [participants] agree which centers [those five highlighted in the meeting] can do these treatments
- **Treatment**
 - Currently using an adapted version treatment protocol which fits the context. *E.g. a “high” dose of methotrexate is still lower in Ghana than in the West, treatment is there to prevent relapse, treat child, while not emptying the pockets...*
 - High dose methotrexate (now BL HTA said to be only given IT); but when provided in high dose than it is provided IV. Methotrexate IV is added in stage 4.
 - The interval between courses is two weeks, cover between certain extend and do next schedule.
 - Patients can become resistant, so therefore we use several drugs. Therefore, we alternate them and give up to eight cycles. Sometimes we extend depending on the advancement of the disease.
- **Supportive treatment**
 - Supportive care, is more expensive than the cancer treatment itself. You need certain facilities, when you use certain facilities.

- Dietitians and nutrition does not come at extra cost, but this consult cannot even afford consult. They cannot get a dietitian ... sometimes necessary in the treatment dietitians and nutrition does not come at extra cost, but this consult cannot even afford consult. They cannot get a dietitians while this is sometimes necessary in the treatment

- **Relapse**

- Risk depends on how advanced the disease is, three categories: local, locally advanced, static disease in bone marrow or brain (high relapse risk).
- Occurrence every time you get advanced disease (metastatic cancer), not necessarily high, provide more aggressive treatment to lower risk on relapse.
 - *E.g. if disease diagnosed in stage III it is locally advanced and not metastatic, aggressive treatment should lower the metastatic burden.*

- **Abandonment / disrupted treatment**

- Typical example case *I have a child who I discovered with Burkitt's in Ashanti who was being treated at Agogo(?) Hospital. I hear she has absconded once the tumour size went down after about 6 months of treatment. If we get her back, what is the prognosis now?*
- Challenges with traditional medicine; patients gotten assurance they can be cured. When they come to hospital they still want to go back home, two weeks later the child does not come back for appointment leading to risk of relapse. ... We need to ensure patients come back to treatment center, even when treatment is not possible provide palliative care.

- **Catastrophic pay**

- No money for treatment, goodwill individuals will support – various stories
- It is not just chemotherapy which is expensive, cost to be considered are transportation to treatment center, parents having to stop work ... Shelter in Accra is expensive, parents might have impossible choice this [sick]

child is only one of the children, when symptoms are better parents go back home to family.

- If we cover the medicine, uptake will increase. But we have to be ready for the additional cost parents still have to pay for.

- **Tariffs NHIS**

- If HIS rate is too low and that leads to hospitals still charging. Understand pricing to reduce wastage. However, at the level of implementation to lead the child actually get the service full reimbursement required... People are covered but still paying.
- People are covered but still paying

- **Early detection**

- No need for screening, but need for early detection and early warning – solution education and training.

- **Policy issues**

- Need for attention to palliative care
- Need to look at care holistically, e.g. including supportive care as nutrition during treatment
- We need all these specialties, we need to educate and we need money

- **NHIS Remarks**

- We cannot do immunotherapies, but some of the treatments now already on medicine list how much does it cost, how much courses do we need.
- How do we diagnosis, what do we do , intervals, when secure, when in remission, etc.
- let's get it done

Feedback on our HTA/model

- NHIS will need to verify the values
- What is the true cost of BL
- What are the reasons to abandon treatment, can we investigate (?)
- TWG member: The budget impact should be the total cost to us bearing in mind that if the NHIS does cover the condition it will be intended to be

comprehensive and so there should be no gap to allow for illegal top-up payments.

- For policy purposes it will be a great idea to assess the scenarios for different settings or system perspective; tertiary, private, other settings.
- 5 pediatric doctors, on 30 million population; it's not only pediatric doctors how treat BL, but also standard oncologist are doing this, hematologist – should be taken into account in recommendations
- Add recurrence/relapse of patients with BL * to markov model
- Need for two perspectives*
 - NHIS is not interested in productivity of patients, all indirect costs are intangibles are not part of NHIS costing – look at payer perspective
 - Societal perspective is important to explain why; shows that they are saving and population costs
- NHIS: HTA should not be about if we should cover BL treatment, but we need to understand what is required for diagnoses, what should be in benefit package, etc.

Promises, next steps to keep in mind

Promise of the research team

- Research team will look into the protocol of cytarabine use (feedback, it is only used in stage IV)
- Research team will look in the assumptions made for treatment per stage of the disease
- Research team will work with NHA/NHIS to investigate how tariffs are made and what are the cost templates.
- Research team will add extra arrow / relapse rates in the markov model (if data is available)*

Promise stakeholders

- One hospital (colleague Prof. Renner) indicated that they could share current data on abandonment rate. Indication already now less than 10%.

Appendix 5. Results of the systematic review of the literature on treatments for Burkitt Lymphoma

Characteristics included systematic reviews

Two systematic reviews that assessed the effectiveness of treatment for BL were included in this overview, (1, 2) no clinical guidelines or HTAs met our pre-defined eligibility criteria.

The review by Okebe et al. included Randomized Control Trials (RCTs) or quasi-RCTs for populations aged younger than 20 diagnosed with BL. The last search occurred in January 2011(1). In 2008 and 2016, the WHO updated the classification of hematologic malignancies, including BL. The review by Della Rocca et al. (2) was recently published, but only included primary intervention studies that diagnosed BL according to the 2008 classification of the WHO. Further, the primary studies included could be any type of intervention with either adults or children with any type of BL as participant. Only four of the nine included studies, reported on the treatment effect in children. We only discuss the outcomes from these four studies (See, table 2).

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Table 1. Participant characteristics of included systematic reviews

Review ID	Included studies	Setting	Age	Staging Method
Okebe, 2011	10	Uganda (3-6) Kenya (7, 8) Ghana (9) Europe (10) North America (11, 12)	Range: 6 months to 25 years (Three studies did not report specific ages (9-11))	Murphy/St. Jude's staging system (10-12) Zielger (4, 5, 7, 8) WHO staging method (6)
Della Rocca, 2021	4	Malawi (13, 14) Cameroon (15) Russia & Belarus (16)	Range: 2 to 18 years	Murphy/St. Jude's staging

There was no overlap between the two included systematic reviews and their respective underlying primary studies. The reason is that the date of last search, included primary studies, and population criteria differed considerably (Appendix 5).

The interventions in the systematic review by Della Rocca et al. were classified as follows: Firstly, the three African studies all used chemotherapy protocols without rituximab, but dosages schemes and or inclusion of various other medicine varied widely. Depani et al. used the Malawi 2010 chemotherapy protocol, which provided the patients with one chemotherapy cycle per week for 4 weeks. Hesselning et al. used the Cameroon 2008 BL protocol. The treatment consisted of two phases: an induction phase with 1 chemotherapy cycle per week for 3 weeks, followed by a consolidation phase with 1 cycle of chemotherapy per week for 1 to 3 weeks depending on the risk group. Thirdly, Molyneux et al. used the Malawi 2012 to 2014 chemotherapy protocol. This was the only study from the other two to use doxorubicin for stage III and IV cancers. All chemotherapies included cyclophosphamide, vincristine (both intravenous), methotrexate and hydrocortisone (both intrathecal). The Cameroon protocol included oral prednisolone, which is a medicine to suppress the body's immune response and used for treating various haematological (blood) cancers. Lastly, the study by Maschan et al. used the Berlin-Frankfurt-Münster (BFM) protocol. This usually uses dexamethasone, cyclophosphamide, vincristine, ifosfamide, cytarabine, etoposide, doxorubicin, and methotrexate, and here was also used in combination with rituximab.

Relevant effectiveness and safety outcomes from the systematic reviews

The interventions and comparators from the underlying primary studies in the two systematic reviews were rather heterogeneous, limiting possibilities for statistical or meta-analysis by their respective authors. Therefore, we report the effectiveness results as given in the systematic reviews.

Okebe et al. (2011) Therapeutic interventions for Burkitt lymphoma in children

The ten trials included were separated in two categories, first those studies that aimed to induce remission and, second, those studies that aimed to maintain remission. Remission of cancer refers to the reduction or complete disappearance of the signs and symptoms. Tables 2 and 3 present a summary of the findings, including the assessment of risk of bias determined by Okebe et al.

Table 2. Overview studies that aim to induce remission

Study	Control vs. Intervention	overall survival (death percentage)	two years event-free survival (percentage)	Remission n (percentage)	Relapse (percentage)	Toxicity (percentage)	Risk of bias
Olweiny 1976	Cyclophosphamide monotherapy vs. combination therapy	Rx 1: 58% vs. Rx 2: 33%	nr	Rx 1: 87% vs. Rx 2: 89%	Rx 1: 53% vs. Rx 2: 62%	nr	Low risk Low risk Unclear risk Low risk
Ziegler, 1972a	Cyclophosphamide monotherapy vs. combination therapy	Rx 1: 50% vs. Rx 2: 28%	nr	nr	Rx 1: 80% vs. Rx 2: 61%	nr	Unclear risk Unclear risk Unclear risk Low risk
Brecher, 1997	Pre-specified duration vs. duration determined by clinical response	Rx 1: 29% vs. Rx 2: 21%	Rx 1: 35% vs. Rx 2: 21% (p=0.027)*	Rx 1: 81% vs. Rx 2: 89%	Rx 1: 15% vs. Rx 2: 15%	Rx 1: 74% vs. Rx 2: 96%**	Unclear risk Unclear risk Unclear risk Unclear risk
Patte, 1991	Long-duration chemotherapy vs. short-duration chemotherapy	Rx 1: 10% vs. Rx 2: 12%	Rx 1: 11% vs. Rx 2: 13% average two arms: 88%	Rx 1: 83% vs. Rx 2: 84%	Rx 1: 11% vs. Rx 2: 10%	Rx 1: 0% vs. Rx 2: 4%	Unclear risk Unclear risk Unclear risk Unclear risk

Study	Control vs. Intervention	overall survival (death percentage)	two years event-free survival (percentage)	Remission (percentage)	Relapse (percentage)	Toxicity (percentage)	Risk of bias
Sullivan 1991	Two-month vs. six-month maintenance chemotherapy	nr	Rx 1: 6% vs. Rx 2: 10%	nr	nr	nr	Low risk Low risk Unclear risk Low risk

nr = not reported, CNS = central nervous system, Rx 1 = intervention, Rx 2 = comparator

*risk of bias are reported in the following order: selection bias (random sequence), selection bias (allocation concealment), performance bias and detection bias (blinding), attrition bias (incomplete outcome data).

*Brecher et al., Patte et al., and Sullivan et al. (4-6) conducted their trials in resource-rich areas where sBL is more common.

**In the trial of Brecher et al. four toxic deaths were recorded, two in each of the compared groups.

The studies that aimed to induce remission (see Table 2) did not find any significant differences between the intervention and comparator arms for overall survival, relapse, and toxicity. The trial results in the study by Olweny et al., that compared two chemotherapies which differed in components of drugs, reported on overall survival. Here, in the control group 58% of patients died, while in the intervention groups that administered a more complex treatment this was only 33% of the patients (49). Similar findings were observed by Ziegler et al., again comparing two chemotherapies, with a death percentage of 50% in the control group and 28% in the intervention group with the more complex treatment (50). Remission was induced in most patients (above 85%) for both the intervention and comparator group.

Table 3. Overview of studies that aimed to maintain remission

Study	Intervention vs. control	Overall survival (death percentage)	Two years event-free survival (percentage)	Relapse (percentage)	Toxicity (percentage)	Risk of bias
Magrath, 1973	Chemotherapy (lomustine) vs. no treatment	nr	nr	Rx 1: 38% vs. Rx 2: 38% Type: CNS	nr	Unclear risk Unclear risk Unclear risk Unclear risk

Study	Intervention vs. control		Overall survival (death percentage)	Two years event-free survival (percentage)	Relapse (percentage)	Toxicity (percentage)	Risk of bias
Olweny, 1977	Radiotherapy vs. no treatment		Rx 1: 27% vs. Rx 2: 9%	nr	Rx 1: 54% vs. Rx 2: 36% Type: CNS	nr	Unclear risk Unclear risk High risk Low risk
Ziegler, 1971	Chemotherapy (methotrexate) vs. no treatment	nr		nr	Rx 1: 50% vs. Rx 2: 40% Type: CNS	nr	Unclear risk Unclear risk Unclear risk Low risk

*nr = not reported, CNS = central nervous system, Rx 1 = intervention, Rx 2 = comparator *risk of bias are reported in the following order: selection bias (random sequence), selection bias (allocation concealment), performance bias and detection bias (blinding), attrition bias (incomplete outcome data).**Margrah, et al. and Neequaye et al. do not compare a treatment, but if patients had BCG vaccination vs. no vaccination*

The studies that aimed to maintain remission (see Table 9) all originated from the African continent. The trial results in the study by Olweny et al. reported on overall survival, two patients in the intervention group who received radiotherapy were reported to have died and one was presumed dead (i.e. a death percentage of 27%). In the non-radiation group one patient died equivalent to 9% death-percentage (this result was however not significant). Relapse was reported by all studies, with mixed results. Overall, when patients relapsed the diseases were most often associated with the central nervous system.

We did not report on two studies that compared the use of immunotherapy, specifically having had the BCG-vaccine against tuberculosis with no treatment (6, 9). The observations indicate that vaccines have limited to no protective effect, but the evidence is very uncertain.

Della Rocca et al. (2021) Chemotherapy Treatments for Burkitt Lymphoma: Systematic Review of Interventional Studies

The outcomes reported in the four underlying primary studies were either overall survival, deaths, remissions, relapse, and safety as adverse events or discontinuation (See table 6). From the three studies conducted in the African continent, the study by Depani et al. found the best survival outcomes, reporting the lowest number of deaths (n=4) while Hesseling et al. reported most deaths (n =13) approximately 24% (13, 15).

The interventions in Della Rocca et al. were classified as follows: Firstly, the three African studies all used chemotherapy protocols without rituximab, but dosages schemes and or inclusion of various other medicine varied widely. Depani et al. used the Malawi 2010 chemotherapy protocol, which provided the patients with one chemotherapy cycle per week for 4 weeks. Hesseling et al. used the Cameroon 2008 BL protocol, which was administered in two phases: first an induction phase with 1 chemotherapy cycle per week for 3 weeks, followed by a consolidation phase with 1 cycles of chemotherapy per week for 1 to 3 weeks depending on the risk group. Thirdly, Molyneux et al. used the Malawi 2012 to 2014 chemotherapy protocol. This was the only study to use doxorubicin for stage III and IV cancers. All chemotherapies included cyclophosphamide, vincristine (both intravenous), methotrexate and hydrocortisone (both intrathecal). The Cameroon protocol included oral prednisolone, which is a medicine to suppress the body's immune response and used for treating various haematological (blood) cancers. Lastly, the study by Maschan et al. used the Berlin-Frankfurt-Münster (BFM) protocol. This usually uses dexamethasone, cyclophosphamide, vincristine, ifosfamide, cytarabine, etoposide, doxorubicin, and methotrexate, and here was also used in combination with rituximab

Both the study by Depani et al and Hesseling et al. reported that treatments were most effective in the early stages of disease. Overall, treatment regime by Depani resulted in a 62% (95% Confidence Interval (CI), 44-80%) one-year survival rate. The one-year event free survival rate (EFS) for all stages was 45% (95% CI 33-57%), but broken down per stage the EFS was 100% (stage I), 83% (stage II), 24% (stage III), and 32% (stage V). Hesseling et al. reported an overall EFS for all stages, estimated to be 61% (no CI provided): and when broken down by stage, the EFS was 100% (stage I), 85% (stage II), 60% (Stage III) and 27% (stage IV).

Molyneux et al. reported one-year survival rates by stage as follows: stage I 100%; stage II 60% (95% CI, 29.6-90.4), and stage III-IV 72.2%, (95% CI 57.5-86.9). This was the only (African) treatment regime to include doxorubicin for patients in stage III-IV (14).

The three studies reported varying adverse events. Depani et al. reported hematologic adverse events of which neutropenia (78%) was most common, as well as one case of intestinal obstruction due to vincristine toxicity. Hesseling

et al. had fever and vomiting as the most common adverse events. Molyneux et al. only reported leukopenia as adverse event.

Table 4. Overview studies that aimed to treat Burkitt lymphoma

Study		Overall survival rate (Confidence interval)	Deaths Number n (percentage)	Remission n (percentage)	Relapse n (percentage)	Safety* Discontinuation (percentage)	Quality
Depani, 2015	Malawi 2010 protocol	1y, 62% (44-88%)	4 (6%)	57 (81%)	20 (29%)	10 (14%)	moderate quality
Hesseling 2012	Cameroon 2008 protocol	nr	13 (24%)	nr	nr	nr	low quality
Molyneux 2017	Malawi 2012 to 2014 protocol	1y, 73% (61-85%)	7 (12%)	nr	11 (19%)	nr	low quality
Maschan, 2019	BFM with modification ^{s*}	3y, 90% (BFM)	18 (10%) (BFM)	57 (100%)	5 (3%) (BFM)	0 (0%) (BFM)	moderate quality
		3 y, 88% (RG3)		RG1&2			
		3 y, 83% (RG4)		RG3&4			

nr = not reported,

**BFM with modifications refers to the treatments being used being adapted to the risk group the patient was in. RG refers to the staging with RG1 = low risk, RG3= RG4 = high risk

The study from Maschan et al. was conducted in Belarus and Russia. The modified BMF-treatments provided by Maschan et al. were adapted depending on the risk group a patient was in. It included various medicine which the African protocols did not include, most noticeable was the use of Rituximab. The overall three-year survival rate was high at 90%, but also those for the two advanced risk groups (respectively, 88% RG3 and 83% RG4). There were 17 deaths among those patients in the high-risk group, while one death occurred in the intermediate risk group (16).

Discussion

The systematic reviews in this assessment (and the primary studies therein) show that the most used treatment regimens for BL include multidrug chemotherapy. Interventions with more complex and intensive treatments resulted in little to no difference in the outcomes as more basic regimens. These standard and less aggressive regimes were shown to also decrease the number of adverse events. This is supported by Hesseling et al. (15), which shows that more toxicity events were likely when using aggressive treatment regimens

(those including, vincristine and methotrexate). However, this evidence is very uncertain.

Della Rocca et al. concluded that the simplified treatment protocols used in the studies from Africa without rituximab have worse health outcomes than the treatments provided in high income countries. This difference in health outcomes is more apparent when comparing the results from the African studies to the highly effective treatment in the study by Maschan et al., which used rituximab and reported a 90% overall survival rate. However, Della Rocca et al. did not recommend using more intensive treatment protocols in low resource contexts due to the lack of supportive patient care.

Another, important finding highlighted by the study from Della Rocca and specifically the three studies from the African continent is that, when BL is diagnosed early and treated in the early stage, first-year survival is more likely to be high (2).

The systematic review by Okebe et al. also reported on trials that used BCG-vaccines or radiation therapy, but the evidence suggested the effect of these treatments may again have little to no effect on the outcomes. The evidence is, however, very uncertain due to high risk of bias (1). Overall, radiation therapy is not used to treat BL, because chemotherapy regimens have a better effectiveness and are more relevant when the BL has spread to various parts of the body. Nevertheless, radio therapy does play a key role in diagnoses (17).

The real challenges for low resource settings to achieve better health outcomes, most likely is not solely in updating the treatment protocols for BL. The reasons eBL is currently still fatal for the majority of children can also be explained by diagnosis in advanced stage, lack of supportive care to be able to receive intensive chemotherapy treatments, malnutrition and ability to pay (18) negatively affecting access to care.

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Appendix 6. Results of the Cost-Effectiveness Analysis from the NHIS Perspective

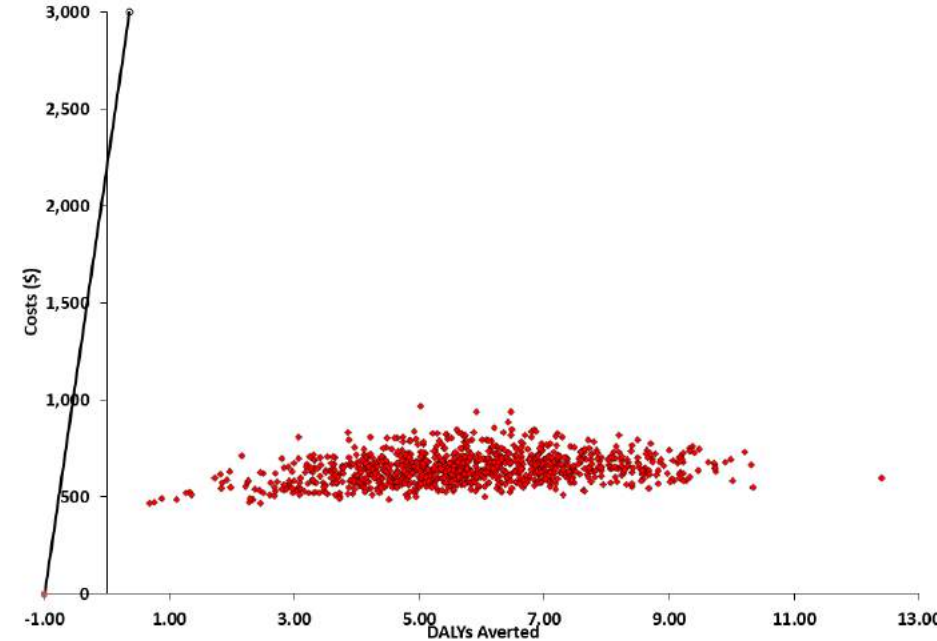
Base-Case Results

Discounted Results

Strategy	Cost per patient	DALYs per patient
Current Practice	\$0	23.32
NHIS-Reimbursed Treatment	\$647	17.60

ICER: \$113 per DALY averted

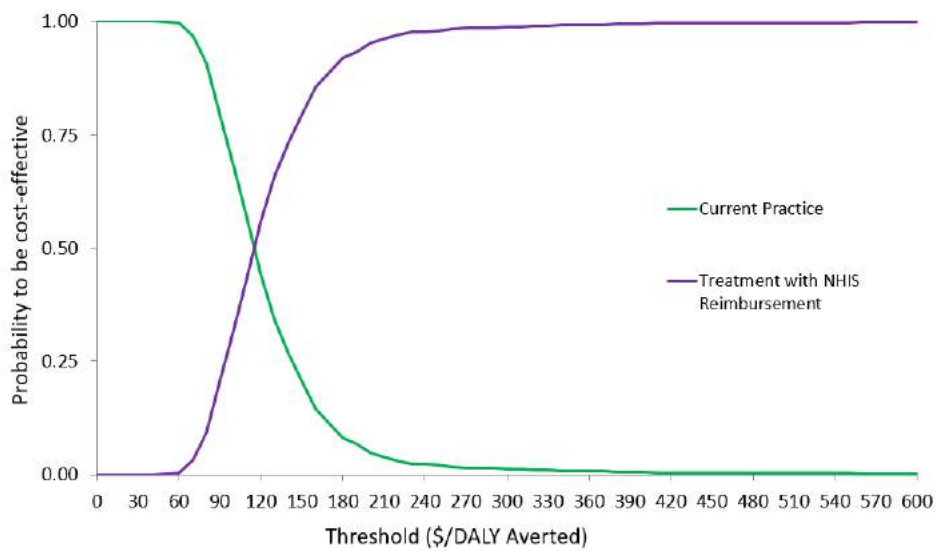
PSA Results: Scatterplot



PSA Results: Cost-Effectiveness Acceptability Curve

Presented below is the Cost-Effectiveness Acceptability Curve for the results from the Probabilistic Sensitivity Analysis from the NHIS’s perspective. This figure shows the likelihood of an intervention to be considered cost-effective at a given Willingness-to-Pay per DALY averted Threshold. As seen in the figure, treatment with NHIS-reimbursement is more likely to be considered the cost-

effective intervention at Willingness-To-Pay thresholds of \$66 per DALY averted and all values above.



Appendix 7. Parameters used in modelling cost effectiveness

Parameters common to both interventions

Parameter	Value	Source
Discount rate of costs	0.03	Tan-Torres Edejer et al, (2003)
Discount rate of effects	0.03	Tan-Torres Edejer et al, (2003)
Size of starting cohort	309	
Starting age of cohort	7	Offor et al. (2018)
Life Expectancy	64.1	World Bank
GDP per Capita of Ghana	\$2202.20	World Bank
Probability of being diagnosed with Stage I BL	0.0578	Offor et al. (2018)
Probability of being diagnosed with Stage II BL	0.0578	Offor et al. (2018)
Probability of being diagnosed with Stage III BL	0.7861	Offor et al. (2018), Information from Oncologists at KBTH
Probability of being diagnosed with Stage IV BL	0.0983	Offor et al. (2018), Information provided from Oncologists at KBTH
Probability of becoming well following Stage I or II BL treatment	0.4211	
Probability of disease progression following Stage I or II BL treatment	0.2632	
Probability of death following Stage I or II BL treatment	0.3158	Molyneaux et al (2016)
Probability of becoming well following Stage III BL treatment	0.4783	Molyneaux et al (2016)
Probability of disease progression following Stage III BL treatment	0.2174	Molyneaux et al (2016)
Probability of death during Stage III BL treatment	0.304	Molyneaux et al (2016)
Probability of becoming well following Stage IV BL treatment	0.6667	Molyneaux et al (2016)
Probability of remaining sick following Stage IV BL treatment	0.0476	Molyneaux et al (2016)
Probability of death during Stage IV BL treatment	0.2857	Molyneaux et al (2016)
Disability factor associated with Stage I or II BL treatment	0.288	Salomon et al (2015)
Disability factor associated with Stage III or IV BL Treatment	0.451	Salomon et al (2015)

Parameter	Value	Source
Probability of treatment Abandonment when insurance is not provided	0.6821	Offor et al (2018)
Probability of treatment Abandonment when insurance is provided	0.2554	Martijn et al. (2017)

Appendix 8. Resource-use treatment maps

Stages I, II and III Disease

	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8
Cyclophosphamide	1400mg*BSA	1000mg*BSA	1000mg*BSA	1000mg*BSA	1000mg*BSA	1000mg*BSA	1000mg*BSA	1000mg*BSA
Prednisolone	300mg*BSA	300mg*BSA	X	300mg*BSA	X	300mg*BSA	X	300mg*BSA
Methotrexate	15mg*BSA*2 courses	15mg*BSA	15mg*BSA	X	X	X	X	X
Vincristine	X	1.5mg*BSA	1.5mg*BSA	1.5mg*BSA	1.5mg*BSA	1.5mg*BSA	1.5mg*BSA	1.5mg*BSA
Doxorubicin	X	30mg*BSA		30mg*BSA		30mg*BSA		30mg*BSA
			400mg*BSA*2 courses		400mg*BSA*2 courses		400mg*BSA*2 courses	
Cytarabine	X	X		X		X		X
Granisetron Oral	1mg*10	1mg*10	1mg*10	1mg*10	1mg*10	1mg*10	1mg*10	1mg*10
Granisetron IV	1mg*4	1mg*4	1mg*4	1mg*4	1mg*4	1mg*4	1mg*4	1mg*4
				250ml+100ml+125ml				
Saline 500ml	2500ml*BSA+5000ml+100ml	250ml+100ml+125ml*BSA+500*BSA	500ml+100ml+125ml*BSA+500*BSA	5ml*BSA+500*BSA	500ml+100ml+125ml*BSA+500*BSA	250ml+100ml+125ml*BSA+500*BSA	500ml+100ml+125ml*BSA+500*BSA	250ml+100ml+125ml*BSA+500*BSA
Allopurinol	100mg*5*3							

Stages IV

	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Cycle 9	Cycle 10
Cyclophosphamide	1400mg*BSA	1000mg*BSA	1000mg*BSA	1000mg*BSA	1000mg*BSA	1000mg*BSA	1000mg*BSA	1000mg*BSA	1000mg*BSA	1000mg*BSA
Prednisolone	60mg*BSA*5	60mg*BSA*5	X	60mg*BSA*5	X	60mg*BSA*5	X	60mg*BSA*5	X	300mg*BSA
Methotrexate	12.5mg	12.5 mg*2	12.5 mg*2	12.5 mg*2	12.5 mg*2	12.5 mg*2	12.5mg	12.5mg	12.5mg	12.5mg
High-dose Methotrexate	X	1000mg*BSA	1000mg*BSA	1000mg*BSA	A	1000mg*BSA	X	X	X	X
Vincristine	X	1.5mg*BSA	1.5mg*BSA	1.5mg*BSA	1.5mg*BSA	1.5mg*BSA	1.5mg*BSA	1.5mg*BSA	1.5mg*BSA	1.5mg*BSA
Doxorubicin	X	30mg*BSA	X	30mg*BSA	X	30mg*BSA	X	30mg*BSA	X	30mg*BSA
			400mg*BSA*2		400mg*BSA*		400mg*BSA*2+		400mg*BSA*2+	400mg*BSA*
Cytarabine	30mg	30mg*2	+30mg*2	30mg*2	2+30mg*2	30mg*2	30mg	30mg	30mg	2 +30mg
Granisetron Oral	1mg*10	1mg*10	1mg*10	1mg*10	1mg*10	1mg*10	1mg*10	1mg*10	1mg*10	1mg*10
Granisetron IV	1mg*4	1mg*4	1mg*4	1mg*4	1mg*4	1mg*4	1mg*4	1mg*4	1mg*4	1mg*4
			500ml+100ml		500ml+100ml+125ml*	250ml+100ml				
Saline 500ml	2500ml*BSA+5000ml+100ml	250ml+100ml+125ml*BSA+125*4	+125ml*BSA+500*BSA*2+125*4	250ml+100ml+125ml*BSA+125*4	BSA+500*BSA+125*4	BSA	500ml+100ml+125ml*BSA+500*BSA	250ml+100ml+125ml*BSA	500ml+100ml+125ml*BSA+500*BSA	250ml+100ml+125ml*BSA
Allopurinol	100mg*5*3	X	X	X	X	X	X	X	X	X
IT Hydrocortisone	15mg	15mg*2	15mg*2	15mg*2	15mg*2	15mg*2	15mg	15mg	15mg	15mg
IV Folinic Acid	X	25mg*BSA*6	25mg*BSA*6	25mg*BSA*6	25mg*BSA*6	25mg*BSA*6	X	X	X	X
IV 5% Dextrose infusion	X	125*BSA*2+3000*BSA*2	125*BSA*2+3000*BSA*2	125*BSA*2+3000*BSA*2	125*BSA*2+3000*BSA*2	125*BSA*2+3000*BSA*2	X	X	X	X
Potassium Chloride	X	10mMol in 500mL	10mMol in 500mL	10mMol in 500mL	10mMol in 500mL	10mMol in 500mL	X	X	X	X

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