Costs of hospitalisation for severe illness in HIV-1 exposed infants in Uganda: A prospective incidence-based cost of illness study

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Abstract

Background

Data from the Uganda National Household Survey shows that there is an increase in out of pocket payments which has increased financial risk for households due to health expenditure and based on the 2008 World Bank poverty line threshold of $1.25 per day as well as the more than 10% of their total household expenditure on healthcare, approximately 4% of the population was pushed below the poverty line in 2010 due to these payments. Despite committing itself during the Abuja Declaration, the government of Uganda allocated 7.9% of the national budget to the health sector which is way below the 15% agreed upon. This has contributed to Uganda's OOP payments for health being the highest in the east and south African regions. Most direct costs for laboratory tests and treatment of the most common childhood illnesses have been removed in public health facilities, however, other costs associated with the seeking of healthcare like transport costs and money for food still persist. This study estimates the economic burden of severe illness in HIV-1 exposed children through estimating the extent of the direct and indirect costs of hospitalisations incurred by households as well as the implementation costs for BCG vaccination in three health care units in central Uganda.

Methods

The bottom-up approach was used to estimate all costs at patient level. The quantity of health inputs together with their unit costs were initially estimated. The costs were then determined by multiplying the unit costs by the health input quantities (ingredient approach). The direct costs measured were out of pocket payments incurred during the process of seeking healthcare. The cost information was collected in Uganda shillings (UGX). Indirect costs due to morbidity or mortality were measured in terms of the number of foregone working days of caregiving for an ill child (time spent seeking healthcare both as an outpatient and/or during inpatient hospitalisation).

Results

370 cases of illness were recorded in the first 14 weeks. Upper respiratory tract infection with 81 cases (32%) and malaria with 39 cases (15%) were the most common illnesses diagnosed. 40% of prescriptions given out were for antibiotics, followed by analgesics and antimalarials at 22% and 11% respectively. Costs incurred by outpatients ranged from US$ 0 to US$ 368. The direct outpatient medical costs incurred by households are more than four times the costs incurred by inpatients. The total outpatient direct costs were US$ 15 while the inpatient direct costs were US$

3.4. For the outpatient costs, the medical costs higher than the non-medical US$ 9.4 and US$ 5.6 respectively, while among the inpatients the medical and non-medical costs were US$ 2.4 and US$ 0.97 respectively. Overall, the outpatient costs, direct medical costs accounted for over 55% (US $9.4) of the costs incurred while indirect costs contributed just 12% (US $2) to the total outpatient costs. For those children that were admitted, indirect costs were the main costs incurred accounting for 83% (US $16) per episode of illness. The cost per child immunised with the BCG vaccine per year ranged from US$ 1 at Kawaala HC III, followed by US$ 1.4 at Kitebi HC III and US$ 3 at Mukono General Hospital.

Conclusion

In conclusion, this study provides an estimate of direct and indirect costs associated with severe illness in HIV-1 exposed infants in central Uganda. Despite the abolition of user fees in public health facilities, households still incur significant costs for hospitals visits. This has contributed to economic burden of illness on households which has the potential to be catastrophic. Outpatient costs incurred by households were mainly in the form of OOP payments while for households with inpatients, the expenses were majorly costs due to work time missed while seeking or providing care for the sick child. More research is needed on the determinants household costs as well as comparison of costs incurred between HIV-1 exposed and unexposed children.

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Acronyms and abbreviations

AEFI	Adverse Events Following Immunisation
ART	Anti-Retroviral Treatment
BCG	Bacille Calmette-Guerin
CI	Confidence Interval
DPT	Diptheria-Pertusis-Tetanus
EID	Early Infant Diagnosis
GVAP	Global Vaccination Action Plan
HC	Health Centre
Hib	Haemophilus influenza b
HIV	Human Immunodeficiency Virus
HSC	Health Services Commission
IHME	Institute of Health Metrics and Evaluation
KCCA	Kampala Capital City Authority
LMIC	Low- and Middle-Income Country
MDG	Millennium Development Goal
NSE	Non-Specific Effects
OOP	Out Of pocket
PMTCT	Prevention of Mother To Child Transmission
SDG	sustainable Development Goal
TB	Tuberculosis
UDHS	Uganda Demographic Health Survey
UHC	Universal Health Care
UNHS	Uganda National Household Survey
VHT	Village Health team
WHO	World Health Organisation

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"I can do all this through him who strengthens me."

Philippians 4:13

Introduction

Background

Data from the Uganda National Household Survey (UNHS 2016) shows that there is an increase in out of pocket (OOP) payments which has increased financial risk for households due to health expenditure [1]. Based on the 2008 World Bank poverty line threshold of $1.25 per day as well as the more than 10% of their total household expenditure on healthcare, approximately 4% of the population was pushed below the poverty line in 2010 due to these OOP payments [2]. Increases in OOP payments which in low income countries are mainly down to the limited public funding of the healthcare system modify health seeking behaviour and healthcare utilisation [3, 4], which in turn may negatively impact health outcomes like child mortality [5]. The burden of disease in children in low income countries is high [4] which makes understanding the economic burden on the public healthcare system and households as well as the financial risk faced by households important. Morbidity and mortality in children can be lowered with an increase in public spending which would also reduce the financial burden of illness on households. Higher levels expenditure coupled with moderate levels of OOP spending may result in lower mortality rates in both mothers and their children [6].

A lot of progress has been made to improve new-born child health such as the reduction in the global under-five mortality rate from 93 deaths per 1,000 live births in 1990 to 39 deaths per 1,000 live births in 2018 [7]. However, many children still suffer and die from serious health issues. In 2017, approximately 5.4 million children under the age 5 died, represented 85% of all child deaths globally. Of these, 2.5 million deaths occurred within the 1st month of life, 1.6 million at the age 1-11 months and 1.3 million at the age 1-4 years [4].

Most of these children died from preventable causes. In 2016, the leading causes of death among children under age 5 globally included preterm birth complications (18%), pneumonia (16%), intrapartum complications (12%), congenital anomalies (9%), diarrhoea (8%), neonatal sepsis (7%) and malaria (5%). These deaths indicate a limited access of children and communities to basic health services such as vaccination, treatment of infectious diseases, appropriate nutrition and access to clean water and proper sanitation [7, 8].

Over 50% of the deaths of children under the age of 5 occurred in sub-Saharan Africa where the under-five mortality rate was 76 deaths per 1,000 live births in 2017, including a neonatal mortality rate at 27 deaths per 1,000 live births [7]. Most of these deaths were due to preventable illnesses including pneumonia, diarrhoea and malaria [9, 10]. Under 5 mortality rates in Uganda are going down, and the country performs generally better than other countries in sub-Saharan Africa. In 2017, the under 5 mortality was 49 deaths per 1,000 live births, while the neonatal mortality rate was 20 deaths per 1,000 live births [1, 4]. In 2016, 5,992 children under the age of 5 died of malaria in Uganda while 6,997 and 14,578 children died from diarrhoea and acute respiratory infections respectively [11].

Several interventions have been introduced across sub-Saharan Africa to curb and prevent deaths that arise from the various illnesses that plague children under 5. Immunisation plays a crucial role in preventive medicine, and research shows that it is more cost-effective to vaccinate children against vaccine-preventable diseases due to various health benefits of protection against these illnesses, which results in reduced morbidity and mortality attributable to the illnesses [12-14]. However, access to these interventions by those who need them the most has been limited. In some developing countries, the coverage of basic vaccinations is way below the targets set in the Global Vaccine Action Plan (GVAP) [15, 16]. In Uganda, children are universally immunised against six common vaccine preventable diseases; tuberculosis, diphtheria, whooping cough (pertussis), tetanus, polio and measles. This aims to achieve the third sustainable development goal (SDG 3): ensuring healthy lives and promoting the wellbeing for all and at all ages. More specifically target 3.2 of the SDGs is to end preventable deaths of new-borns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births and under-5 mortality to at least as low as 25 per 1,000 live births by 2030 [17].

It is a huge challenge for Uganda to achieve the set targets as the vaccine coverage is still relatively low. For instance, in 2013 coverage of the required immunisations among 1-year olds of the measles vaccine, DTP3, HepB3 and Hib3, were 26%, 25%, 24% and 28% respectively [18]. In Uganda, routine vaccine coverage at the appropriate age of 12 months was 49% in 2016, while only 55% of children aged 12 – 23 months were vaccinated that same year [1, 19, 20]. Only 36% of those who needed antibiotics for pneumonia received them, while 49% of children with

diarrhoea received oral rehydration salts. Of those at risk of contracting malaria, access to insect treated nets was at lowly 49% (range 44 – 54%) [16, 21].

Bacillus Calmette-Guerin (BCG) is a vaccine for tuberculosis (TB). The vaccine is widely used in countries with a high prevalence of TB as a way of combating the most severe forms of childhood TB like meningitis and miliary diseases [22]. The World Health Organisation (WHO) recommends that a single dose of the BCG vaccine should be given to all healthy infants after birth, unless the child shows symptomatic HIV-1 infection [23] as a way of preventing the severe forms of TB as well as deaths associated with TB . Although Uganda has managed to progress in the fight against TB, it did not achieve the set MDG target of a prevalence rate of 103 per 100,000 population [24]. With an increase in the prevalence rate from 159 to 253 per 100,000 population [25], more is needed in the fight against tuberculosis. With an estimated 1 million children under the age of 15 suffering from TB (52% <5 year olds) and another 233,000 dying each year [26], programmes like the vaccination of the BCG vaccine have been spread even further. Uganda has an estimated BCG coverage of around 89% [20].

The increase in the incidence of severe illnesses in children under the age of 5 has been exacerbated by the HIV/AIDS scourge, especially in sub-Saharan Africa. An estimated 800,000 (CI 620,000 – 1,000,000) people acquired HIV in eastern and southern Africa in 2018, of which 26% of the new infections were among young women (aged 15 – 24 years) [27]. An estimated 1.8 million (CI 1.3 – 2.4 million) children under the age 15 years were living with HIV in that same year. In 2017, there was a decline in the number of new infections among children, however, there were still 160,000 (CI 110,000 – 260,000) new infections and 110,000 (CI 63,000 – 160,000) deaths among children in 2018 [27, 28].

Many infants that receive the BCG vaccine at birth are HIV-1 exposed as they are born to HIV positive mothers. For the past 30 years, Uganda has been at the forefront in the fight against HIV/AIDS. It has managed to reduce the number of new HIV-1 infections in all ages from 97,000 (CI 87,000 – 110,000) in 2005 to 50,000 (CI 42,000 – 59,000) in 2017 [29], thus the HIV incidence per 1,000 population has decreased from 3.54 (CI 3.13 – 4.09) in 2010 to 1.37 (CI 1.15 – 1.64). Uganda has 1,300,000 people living with HIV with 72% (68 – 77%) on ART treatment. With a prevalence of 6%, the number of HIV/AIDS related deaths have also decreased from 47,000 (CI 40,000 – 57,000) in 2010 to 26,000 (CI 20,000 – 34,000) in 2017 [29, 30].

There are around 750,000 (710,00 – 810,000) women aged 15 years and above living with HIV in Uganda. Of these, 92% (CI 87 – >95%) know their status and 79% (CI 75 – 85%) are on antiretroviral treatment [29]. The prevalence in women of child bearing age (15 – 49 years) is 7.5% (CI 6.9 – 8.1%) [30]. Through the prevention of mother to child transmission (PMTCT) programme, more than 95% (CI 68 - >95%) of pregnant women living with HIV have access to antiretroviral medication [29]. This has lowered the number new HIV-1 infections through vertical transmission to 1% after 6 weeks and 5.3% after breastfeeding [31].

With improved access to ART, more women living with HIV are getting pregnant because of improved health. The introduction of PMTCT which reduces the risk of transmission from mother to child has also contributed to more pregnancies as there is a possibility of having an HIV negative baby [32, 33]. However, poor Early Infant Diagnosis (EID) with a rate of only 48% (CI 42 – 59%) [29] affects the provisions of services such as BCG vaccination which may have to review the timing of the vaccine. Giving the BCG vaccine to HIV-1 infected infants is potentially harmful [34], but the low mother to child transmission rates reduce the risk of giving the BCG vaccine to potentially HIV-1 infected infants.

Based on studies showing nearly a 1000-fold increased risk of disseminated BCG infection among HIV-1 infected infants, recent WHO guidelines consider HIV-1 infection a contraindication to BCG vaccination [35-37]. In low and middle-income countries (LMICs), diagnosis of HIV-1 at birth (when the vaccine is to be given) is poor [29, 34, 36] making the implementation of this guideline difficult. As a result, all HIV-1 exposed infants, including those yet to be diagnosed as HIV-1 infected continue to receive BCG at birth [34, 36]. In Hoima district Uganda, Malande and colleagues found out that the existing program or system in place for identification, reporting and management of Adverse Events Following Immunization (AEFIs) is not well known by the health workers and community. They also determined that the ministry of health does have a system in plan, but there has been a delay in national roll out and implementation of this system [38].

Thus, an alternative approach has been proposed in which the vaccine is delayed until the exposed infants are diagnosed as not having HIV-1 infection [34, 36]. On the other hand, if vaccinating HIV-1 exposed babies with BCG at birth protects them against serious infections other than TB, i.e., through nonspecific effects (NSEs) [39-41], delaying vaccination could result in increased morbidity and even mortality. In addition, delaying BCG vaccination to a later time when a

definitive diagnosis is made could reduce its coverage due to loss to follow-up [34]. The appropriate timing for BCG vaccination that maximises both specific and possible NSEs, particularly in HIV-1 exposed children, is presently unknown.

There are several initiatives that have been instituted by the government of Uganda in collaboration with international partners with the aim of lowering the morbidity and mortality of under 5 children from these diseases. Together with the World Bank, through the Global Water Security and Sanitation Partnership the government of Uganda found that US$ 117 million is lost annually by Uganda due to poor sanitation, where US$ 1.1 million is lost through productivity losses whilst sick or accessing healthcare for diarrhoeal diseases and US$ 21 million is spent each year on healthcare of diarrhoeal diseases either directly or indirectly [42].

Health financing in Uganda

The healthcare system in Uganda is arranged in a hierarchical order structured into national, regional referral hospitals and general hospitals. At the district level, health facilities are classified into four categories; from Health Centre I (HC I) to HC IV. HC I is the lowest level in the health system and it comprises of Village Health Teams (VHTs). They mostly provide community-based preventive and promotive health services. HC IIs are parish level facilities that serve approximately 5,000 people. They are led by an enrolled nurse and they offer preventive, promotive and outpatient curative health services as well as outreach care. HC IIIs serve approximately 20,000 people. They supervise VHTs and HC IIs in their sub-county. HC IIIs provide maternity, inpatient healthcare services as well as laboratory services. HC IV (District Hospitals) provide all services offered at HC IIIs as well as carry out emergency surgery and blood transfusion services. For General Hospitals, in addition to the services offered at HC IVs, they also provide in service training, consultation and community-based research. They provide services to over 500,000 people [43-45].

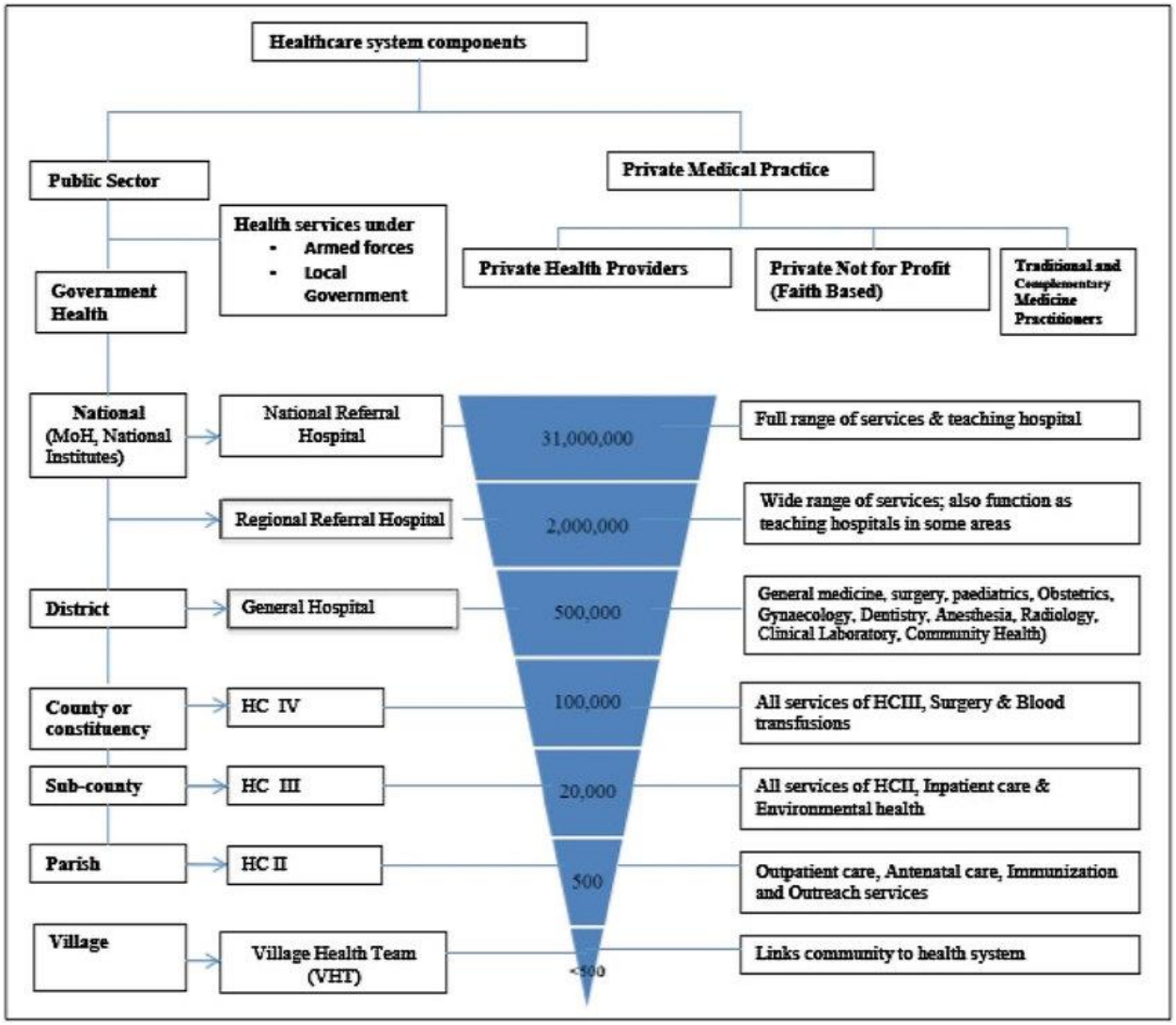


Figure 1: Structure of the health system in Uganda

Source: Acup C., et al. (2016)

The sources of health financing are public (ministry of health and local governments), user fees (mainly household OOP expenditure), development partners (donor funds and Non-Governmental Organisations), community programs as well as voluntary health insurance [45].

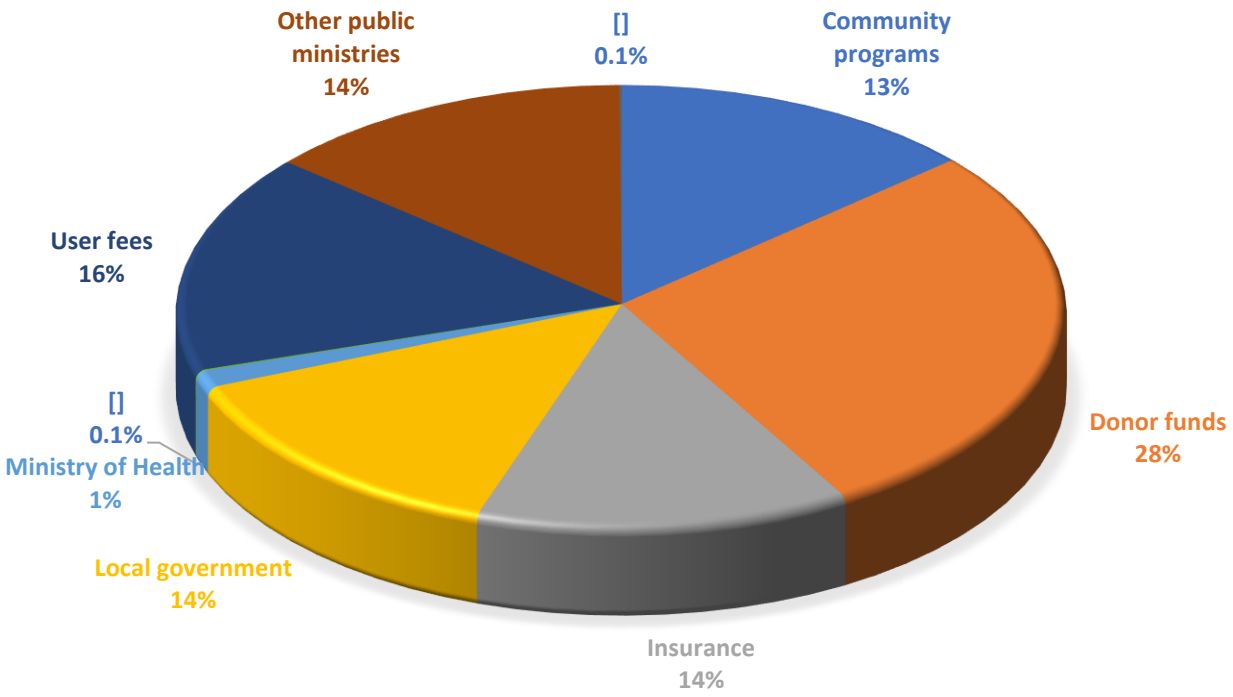


Figure 2: Sources of funding for hospitals and level IV primary care facilities7

Source: Uganda Hospital and Health Centre IV Census Survey 2014

Economic burden on public healthcare system

To achieve universal health coverage (UHC), a societal perspective of the costs incurred by both healthcare service providers and households should be determined and well understood. It is important to determine and keep track of people that need health services get them and whether they have financial protection for healthcare expenses. Target 1(a) of the sustainable development goals (SDGs) focuses on resource mobilisation especially in the least developed countries as a necessity for implementation of programmes and policies, while target 3(b) emphasises the provision of essential medicines and vaccines at an affordable and sustainable basis as well as development of medical research. Target 3(c), which is about the medical workforce, focus on a substantial increase in health financing, the recruitment, development, training and retention of the health workforce in developing countries [4, 46], and highlights what needs to be covered when estimating the economic burden on the healthcare system as services are delivered to the population.

Following the Abuja Declaration in 2001, Heads of States of the African Union committed to allocate at least 15% of annual budgets to the health sector [47]. However, Uganda has failed to achieve the set target and the allocation has stagnated below 10% of the overall budget [48]. A large portion of the healthcare financing therefore remains dependent on donor funding. A World Bank institute of development studies analysis in 2000 showed that the health services in Uganda depended more on donor funding than in other selected countries [49, 50]. This has led to challenges such as procurement delays, stock out of medicines and supplies as well as recruitment and deployment of health workers by the health service commission (HSC) and ministry of health respectively [51]. This makes facility costing crucial in health financing and planning.

The low government allocation has contributed to OOP payments being one of the main forms of healthcare financing in Uganda. Households constitute a major source of funding of the national health expenditure at 42.4%, donor funding at 38% and the rest by the central government [52] as shown by Figure 3 below.

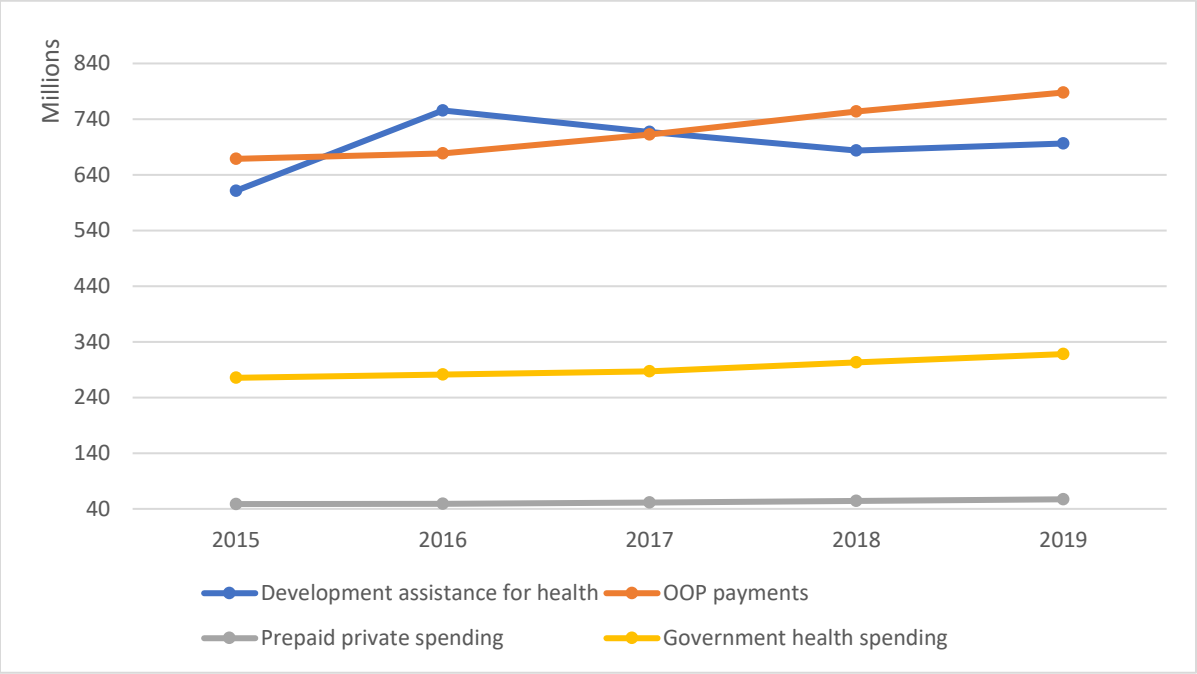


Figure 3: Trends in health financing in Uganda

Source: Adapted from the Institute of Health Metrics and Evaluation (IHME)

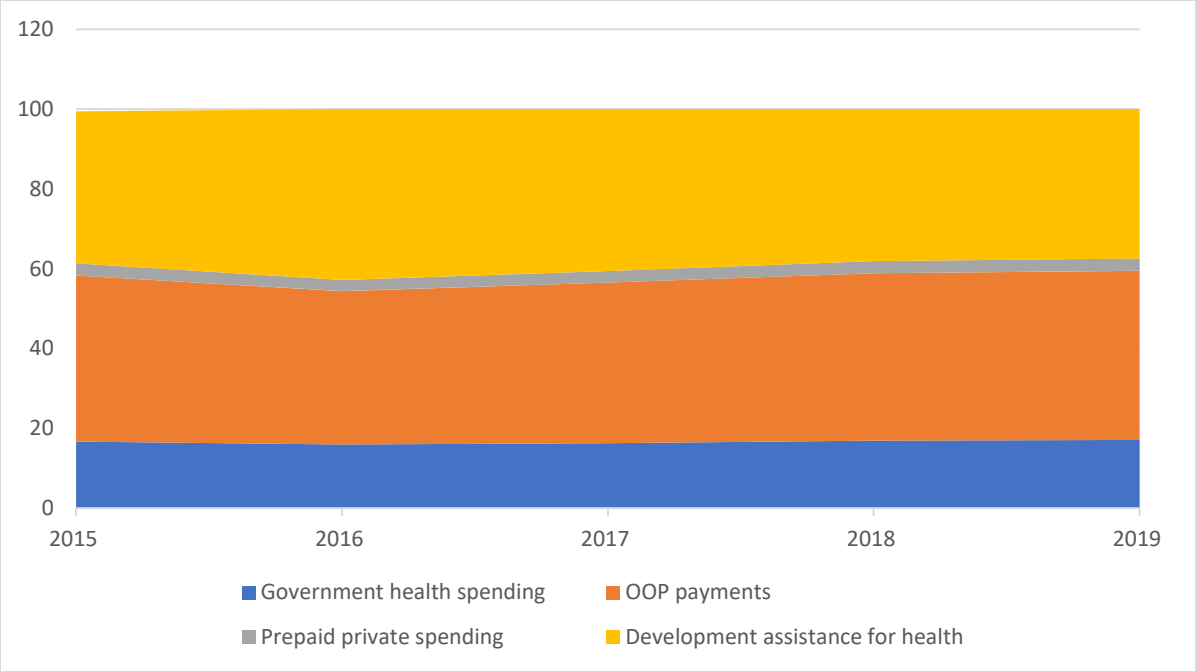


Figure 4: Trend in percentage contribution to total health expenditure (THE)

Source: Adapted from the Institute of Health Metrics and Evaluation (IHME)

Household economic burden and financial risk of healthcare

Uganda's OOP payments for health are the highest in the east and south African regions [53]. With a large proportion of the population relying on low paying jobs in the agricultural sector, 73% of male workers and 63% of female workers, the risk of catastrophic spending on health is enormous especially as only 1% of the population has health insurance [52, 54, 55]. The median monthly earnings of people in paid employment is 190,000sh, or about US$ 52 [55]. This means that most households may struggle with costs, especially those with hospitalised children. Costs that are challenging include non-medical costs, like transport and food, and costs of medicines, that often must be procured privately. High costs in turn may lead to modification of their health seeking behaviour.

Target 3.8 of SDG 3 is to "achieve universal health coverage, including financial risk protection, access to quality essential healthcare services and access to safe, effective, quality and affordable essential medicines and vaccines for all" [17]. In order to achieve this, the evidence of the economic burden of these diseases on the healthcare system as well as on individual households is useful in resource allocation and to design prevention and treatment programs in a country's

healthcare system. Several studies have been carried out to determine the economic burden and predictors of healthcare seeking behaviour for the different illnesses.

A study in Bangladesh found an association between concurrent diarrhoea and pneumonia in children under the age 5 with low maternal education, younger age, low family income and severe acute malnutrition [56]. This finding emphasises that these diseases disproportionally affect children from low income families which are compounded by the high economic burden of the treatment. Another study in the same country found that most of the spending for clinical care of childhood diarrhoea and ARI was on outpatient care provided by unqualified providers. Also, the costs were higher for poorer households compared to richer households maybe because they mostly visited unqualified providers [57].

Another study from Ethiopia found that the economic burden is especially high among poor households with direct costs accounting for nearly 40% of the treatment costs per malaria episode [58]. In Uganda, a study on out of pocket payments shows that parents especially in urban centres, prefer private healthcare to the public health system. 71% of healthcare costs were out of pocket for items such as consultation, medicines, transport or hospitalisation, with medication taking 54% of these payments [3]. In eastern Uganda Matovu and colleagues found that rural households spend significantly larger amounts of time and money seeking care from community medicine distributors instead of formal health facilities. This shows that home and community based treatment may be more cost saving for rural poor communities that are also affected the most by the burden of treating these diseases [59].

Study Justification

Although most direct costs for laboratory tests and treatment of the most common childhood illnesses have been removed in public health facilities [42, 60], other costs associated with the seeking of healthcare like transport costs and money for food still persist. Furthermore, patients commonly need to purchase medication privately when drugs that were supposed to be provided for free are out of stock. In the financial year 2019/2020, the government of Uganda has lowered the amount of money allocated to the health sector from 9.2% of the national budget in the previous year to 7.9% of the national budget this year [61]. This is likely to increase the economic pressure on the services rendered in public health facilities. In turn this is likely to increase the cost of illness for healthcare services to the general population. However, the ministry of health has been tasked to develop a National Health Insurance Scheme and parliament has been asked to fast-track the National Health Insurance Bill so as to immediately implement the scheme when it is ready [61, 62].

The indicators 3.8.1 and 3.8.2 of target 3 of the SDGs are about coverage of essential health services and lowering the proportion of households with large expenditures on health as a share of their total household expenditure respectively. This study estimates the economic burden of severe illness in HIV-1 exposed children through estimating the extent of the direct and indirect costs of hospitalisations incurred by households as well as the implementation costs for BCG vaccination among these children in primary health care units in central Uganda.

Objective

To determine and compare the potential direct and indirect treatment costs of outpatient and inpatient care for HIV exposed infants vaccinated with BCG in Uganda.

Specific objectives

Determine

a) The unit cost for families per affected child of severe illness related to conditions targeted by BCG vaccination

b) The implementation cost per child for the vaccination with BCG

Methodology

Study setting

This study took place in two districts in central Uganda; Kampala and Mukono districts both of which are found on the shores of L. Victoria.

KEY:

Kampala district Mukono district

Fig. 5: Map of Uganda showing districts with study sites

Kampala district is the capital city of Uganda and in 2014 had an estimated population of 1,507,080 [63]. Kampala is administered by the Kampala Capital City Authority (KCCA) on behalf of the central government and is comprised of 5 administrative divisions which are semi-autonomous with their own budgets. Under its Directorate of Public Health Services and Environment, KCCA oversees 10 health centres [64]. Kampala district being an urban centre has just 10% of its households engaged in either crop growing or livestock farming with the majority of households (91%) having at least one member engaged in a non-agricultural enterprise [65]. Vaccinations are routinely provided by all government/KCCA health centres and some privately-owned health facilities. Over 99% (95% CI 98.4–99.7) of infants receive the BCG vaccine soon after birth [66]. Two of the study sites are KCCA health centre IIIs. The study was conducted in Kawaala Health Center III, Kitebi Health Center III in Kampala district. Kawaala Health Centre III is found in Kawempe division while Kitebi Health Centre III is found in Rubaga division.

The third study site was in Mukono district at Mukono General Hospital. Mukono district is a peri-urban area located 21kms to the east of Kampala. In 2014, Mukono district had an estimated population of 596,804 [63]. Mukono district is divided into 4 constituencies with Mukono municipality being semi-autonomous from the rest of the district. Agriculture is the main source of income in the district with over 67% of households engaged in either crop growing or livestock farming [65]. The 2018 Uganda AIDS country report showed that, the central 2 region in which Mukono district is located had an HIV prevalence of 7.6% [67]. The study was carried out at Mukono General Hospital which was upgraded from Health Centre IV in January 2020.

These centers were chosen based on their proximity to Kampala and to laboratories, which are essential for the main trial that this study is part of, that require specimen processing of the high number of HIV-1-infected women attending their antenatal and birth clinics [30, 31]. These three government facilities together support at least 1200 deliveries per month.

Selection of participants, inclusion and exclusion criteria

This study was nested within a larger randomised controlled trial in Uganda about "Early versus late BCG vaccination in HIV-1 exposed in Uganda" [68], where the infants are randomised to be vaccinated with BCG either within 24 hours after birth or after 14 weeks. The following exclusion and inclusion criteria were used to determine recruitment of infants in the main study:

Inclusion criteria

A baby born at a participating study clinic is included if they:

1. Have a mother with a positive HIV-1 test (ELISA or rapid test)
2. Are receiving peri-exposure prophylaxis as part of the standard/national Option B+ guidelines in Uganda
3. Have a mother who is of legal age for participation in clinical research studies in Uganda or is an emancipated minor
4. Have a mother/caregiver who resides within the study area, is not intending to move out of the area in the next 4 months and is likely to be traceable for up to 12 months
5. Have a mother/caregiver who gives informed consent to trial participation
6. Have a mother who has received ART for at least 4 weeks

Exclusion criteria

A new-born child is excluded if they have:

1. Serious congenital malformation(s)
2. Severe illness requiring hospitalization
3. A birth weight <2.0 kg
4. A mother participating in another research study on the day of enrolment or a mother who will participate in another research study within the next 3 months
5. A mother or other household member with symptoms and signs of TB on the day of enrolment
6. A severely ill mother with a condition or conditions requiring hospitalization

Follow up collection of data

In the main RCT, follow-up visits at the study clinic were scheduled on day 7 and at weeks 2, 6, 10, 14, 15, 26, 28, 48 and 52 after birth. At each of these visits, mothers were interviewed about illness, hospital visits and hospitalization while supplementary information was obtained from the hospital records. Illness and hospitalization data were based on both the previous and current visits. Upon enrolment and on subsequent visits, mothers or other caregivers were informed about symptoms and signs of severe illness and were encouraged to contact the study clinic in case the baby developed any of these symptoms. Each mother was provided with a durable notebook, in which she was instructed and trained to note down all relevant events experienced by her child. The front page of the book had clear reminders that she needs to contact the study team in case the child visits a health clinic, a physician or is admitted to a hospital.

Hospital costs for immunisation programmes were recorded separately, through interviews with the hospital in-charge, and the head of the immunisation department.

Data management

All trial procedures were standardized. Training exercises were undertaken, and scheduled refresher sessions were conducted during the trial. Using Open Data Kit (ODK, https://opendatakit.org), pre-coded electronic Case Report Forms (eCRFs)/questionnaires with range and consistency checks were applied. Entered data was checked for consistency and any errors corrected on site.

Source documents and files will not be destroyed without specific written permission from the PI and will be kept for at least five years after the end of the study. Only the PI, Co-PI, study coordinator and authorized study personnel had access to the CRFs and supporting documents that were kept on password-secured computers to ensure participant confidentiality. To ensure correct operation according to standard operating procedures (SOPs) all system users were trained in their use and evaluated on a regular basis.

Plan of analysis

Cost of illness estimation and valuation

Costs were collected from the perspective of the national health care system as well as the perspective of the households of the affected children. Household costs were collected as part of the main trial, and questions about direct costs of medical care during the observation period were asked. The health care providers costs included intervention costs related to providing the BCG vaccine as well as costs related to management of illnesses related to the vaccine (disease costs). Intervention costs were collected at the three health centres of the main trial; Kawaala Health Center III, Kitebi Health Center III and in Mukono General Hospital. Disease cost information was collected at 3 facilities randomised from a list of 21 health centers and hospitals in the study area.

The epidemiological approach used to estimate the economic costs of severe illness in children was an incidence-based prospective method with a bottom-up approach. The cost of illness was estimated by identifying and quantifying the cost generating components of seeking healthcare and determining the monetary value of the various components, where the monetary value was opportunity cost, the value of the foregone opportunity to use in a different way those resources that were used to seek healthcare during or lost due to an illness [69, 70]. Because the costing was incidence-based, all costs for the recorded cases, both direct (direct medical costs and direct non-medical costs) and indirect costs were assigned to the year in which the disease first appeared and converted to a common base year. In case of preventive measures, this method provided an estimate of the savings that accrued when the preventive measure was implemented [70-72].

The bottom-up approach was used to estimate all costs at patient level. The quantity of health inputs together with their unit costs were initially estimated. The costs were then determined by multiplying the unit costs by the health input quantities (ingredient approach). The direct costs measured were out of pocket payments incurred during the process of seeking healthcare. The cost information was collected in Uganda shillings (UGX). Indirect costs due to morbidity or mortality were measured in terms of the number of foregone working days of caregiving for an ill child (time spent seeking healthcare both as an outpatient and/or during inpatient hospitalisation). All direct costs were estimated in monetary terms, while indirect costs were valued using a human capital approach. We calculated the indirect costs (production losses) by multiplying the time lost due to

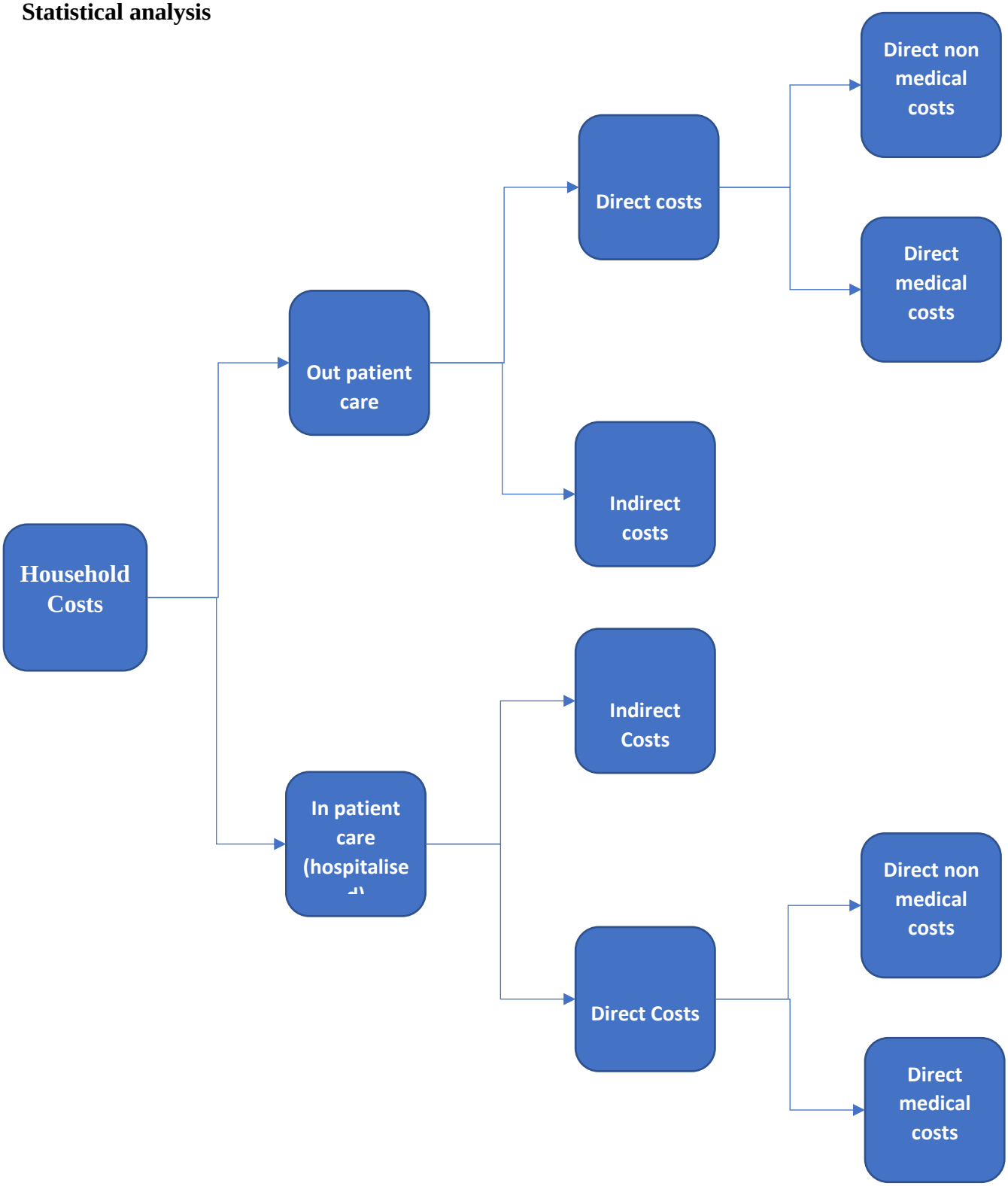
a child's illness with the average daily wage rate of the caregiver [73-76]. Using the 2018 National Labour Force Survey (NLFS) report, the average daily wage rates of caregivers from different employment sectors were calculated by dividing the average monthly wage rate by the 20 working days in a month [55].

Facility cost data was collected and analysed using an Excel based tool. We used a three-step process including (i) identification, (ii) estimation and (iii) valuation. This was done using a micro costing approach where costs were identified and estimated independently at all wards/departments involved in the treatment, before each item was valued and the cost estimates were aggregated for the intervention. Number of patients/children treated were used to calculate unit prices, while we used allocation keys such as area occupied by the treatment, staff time spent on a particular ward etc. to allocate shared resources to the intervention.

The accounts and records departments provided data used to estimate and perform the facility cost analysis. The records departments provided consumption data like the number of vaccine doses administered, the number of hospital births per year and the number and specifications of the equipment available at the different health centres. Information about cost estimates like the cost of vaccines, medication, equipment as well as utilities (water and electricity), staff salaries and work-load times was obtained from the accounts departments at the health facilities and from the district health officers.

All costs were then be converted to US dollars using the official Bank of Uganda average exchange rate for 31st December 2019 (1 USD = 3660.21 UGX) [77].

Statistical analysis



STATA statistical software, version 14 [78] and SPSS statistics 25 were used to analyse all patient level data. The cost information collected was stratified and presented by study site. For all patient level costing data, we report the mean with standard deviation (SD) and 95% confidence intervals, and the median. Principal components analysis (PCA) was used to construct a wealth index based on household characteristics, such as availability of various household assets, housing conditions, water source, and ownership of land. The first principal component with an Eigen value of 2.08 was used to construct a wealth index by which households were ranked. The Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy was 0.65.

Ethical consideration

Ethics permission to conduct the study was obtained from the School of Medicine, Research and Ethics Committee at Makerere University (SOMREC) as well as from the Regional Committees for Medical and Health Research Ethics in Norway (REK). The trial was also approved by the National Council of Science and Technology and the National Drug Authority in Uganda. The study was performed in accordance with International Conference on Harmonization (ICH) guidelines for Good Clinical Practice. Written individual informed consent in local language was obtained from each of the participating mothers by trained study staff. The consent process explained the nature of the study, the risks and benefits of participating in the study, the intervention and that intervention allocation is by a random process. In situations requiring translation or in cases where the mother was unable to read and write, the consent process took place in the presence of an independent third person, who acted as a witness and also co-signed the consent form. Confidentiality of information and the right of the participant to withdraw from the study at any time during the study was explained to the mothers. All study staff were trained on participant confidentiality and autonomy.

Results

Participant characteristics

Table 1: Socio-demographic characteristics

	Kawaala HC III	Kitebi HC III	Mukono General Hospital
	391	375	567
Mother's age (years)	n (%)	n (%)	n (%)
16 - 20	16 (4.09)	39 (10.40)	42 (7.41)
21 - 30	275 (70.33)	262 (69.87)	354 (62.43)
31 - 40	98 (25.06)	73 (19.47)	166 (29.28)
≥41	2 (0.51)	1 (0.27)	5 (0.88)
Household head			
Husband	304 (77.75)	326 (86.93)	444 (78.31)
Respondent	51 (13.04)	24 (6.40)	71 (12.52)
Mother/mother in law	9 (2.30)	14 (3.73)	20 (3.53)
Father/father in law	1 (0.26)	0 (0.00)	8 (1.41)
Others	26 (6.65)	11 (2.93)	24 (4.23)
Education status			
None	17 (4.35)	23 (6.13)	25 (4.41)
Primary	155 (39.63)	156 (41.61)	230 (40.56)
Secondary	204 (52.17)	183 (48.80)	274 (48.33)
Certificate	8 (2.04)	8 (2.13)	19 (3.35)
Degree	6 (1.54)	2 (0.53)	13 (2.29)
Other	1 (0.26)	3 (0.80)	6 (1.06)
Marital status			
Single	44 (11.25)	109 (29.07)	28 (4.94)
Married	67 (17.14)	50 (13.33)	53 (9.35)
Co-habiting	269 (68.80)	210 (56.00)	468 (82.54)
Widowed	3 (0.77)	3 (0.80)	5 (0.88)
Divorced/separated	8 (2.05)	3 (0.80)	13 (2.29)
Employment status of household head			
Yes	322 (82.35)	359 (95.73)	538 (94.89)
No	69 (17.65)	16 (4.27)	29 (5.11)
Total monthly income of household (US$)			
0 - 99	242 (61.89)	334 (89.07)	468 (82.54)
100 - 199	127 (32.48)	26 (6.93)	66 (11.64)
200 - 299	13 (3.32)	13 (3.47)	25 (4.41)
300 - 399	1 (0.26)	1 (0.27)	0 (0.00)
400 - 499	5 (1.28)	0 (0.00)	4 (0.71)
≥500	3 (0.77)	1 (0.27)	4 (0.71)

The analysis is based on 1,333 mothers fulfilled the inclusion criteria and consented to participate. The mothers who took part in the study had ages ranging from 16 – 44 years, with the mean age of 27.5 years (SD 5). Most participants were Baganda (59%), while 77% were Christians. 71% of the respondent mothers had at least completed the primary level of education, with 90% of participants being able to read and 91% being able to write.

The mean household size was 4, (with a range of 1 – 30). In 81% of households, the main income provider was the husband/partner, of whom 53% were self-employed. The mean household monthly income was US$ 55.

Diagnoses and treatments received

Out of the 1333 children in the study, 370 (28%) cases of illness were recorded in the first 14 weeks after birth (Table 2). The number of ill children whose caregivers first sought healthcare treatment from private health service providers was 172 (47%) compared to 126 (34%) who first visited a public health facility. 44 (12%) of caregivers self-medicated when the children fell ill, 26 (7%) did nothing and 3 (0.81%) used traditional herbal medicine to manage the child illnesses.

Table 2: First health service providers sought in case of infant illness in the first 14 weeks after birth

Healthcare service provider	Number (%)
Nothing	26 (7.03)
Herbs	3 (0.81)
Traditional healer	1 (0.27)
Self-medication	44 (11.89)
Pharmacy	38 (10.27)
Health centre	60 (16.22)
Hospital	66 (17.84)
Private clinic	132 (35.68)

In the first two weeks after birth, neonatal sepsis was the most common illness diagnosed 46% and 50% of cases in week 1 and 2, respectively. Malaria ranked second, with 14 cases recorded in the first four weeks. After the fourth week, the cases of both malaria and pneumonia generally increase with 8 (20%) cases of malaria recorded in week four rising to 18 (38%) cases in week fourteen. Pneumonia cases rose from 2 (12.5%) in week 2 to 9 (26.5%) in week 12 and overall it had the third highest number of cases registered 30 (12%). There were no upper respiratory tract infection cases in the second week, the number rose to 12 (25%) in week 14.

Overall malaria and upper respiratory tract infections with 81 (32%) cases and 39 cases (15%) respectively were the most common illnesses diagnosed. Severe anaemia 4 cases (1.6%), diarrhoea 7 cases (2.7%), cough and flu 19 cases (7.4%) and measles 5 cases (1.9%). Other diagnoses that were recorded include; jejunal atresia, severe acute malnutrition, conjunctivitis, broncholitis, chicken pox, coronary artery defect, opthalamia neonatarum, neutrophilia and acute gastro enteritis.

Table 3: Medical diagnoses treatments received by ill infants during the first 14 weeks of follow-up

	Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Pediatric Diagnosis cases									
Neonatal sepsis	15 (46)	8 (50)	4 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	27 (10.5)
Septicemia	1 (3)	1 (6)	1 (2.5)	0 (0)	6 (12)	0 (0)	0 (0)	0 (0)	9 (3.5)
Malaria	3 (9)	3 (19)	8 (20)	9 (39)	23 (47)	4 (29)	13 (38.2)	18 (37.5)	81 (31.5)
Pneumonia	0 (0)	2 (12.5)	4 (10)	4 (17.4)	5 (10)	2 (14)	9 (26.5)	4 (8.3)	30 (11.7)
Upper respiratory tract infection	1 (3)	0 (0)	9 (22.5)	5 (21.8)	4 (8)	3 (21.4)	5 (14.7)	12 (25)	39 (15.2)
Severe anaemia	2 (6)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7.1)	0 (0)	1 (2.1)	4 (1.6)
Measles	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	2 (5.9)	2 (4.2)	5 (1.9)
Diarrhoea	0 (0)	0 (0)	3 (7.5)	1 (4.4)	2 (4)	1 (7.1)	0 (0)	0 (0)	7 (2.7)
Flu and cough	0 (0)	0 (0)	4 (10)	2 (8.7)	4 (8)	0 (0)	3 (8.8)	6 (12.5)	19 (7.4)
Others diagnoses[ŧ]	11 (33)	2 (12.5)	7 (17.5)	2 (8.7)	4 (8)	3 (21.4)	2 (5.9)	5 (10.4)	36 (14)
Treatment given in doses									
Antibiotics	73 (62)	34 (70.8)	54 (46.1)	30 (40.5)	38 (32.2)	15 (36.6)	27 (26)	37 (24.7)	308 (40)
Antimalarials	2 (1.7)	2 (4.1)	11 (9.4)	9 (12.1)	24 (20.3)	2 (4.9)	11 (10.6)	25 (16.7)	86 (11.2)
Analgesic	21 (17.8)	10 (21)	25 (21.4)	19 (25.7)	27 (22.9)	8 (19.5)	22 (21.1)	40 26.7)	172 (22.3)
Cough and flu syrup	2 (1.7)	1 (2.1)	8 (6.8)	2 (2.7)	10 (8.5)	5 (12.2)	10 (9.6)	24 (16)	62 (8.1)
Oral rehydration salts	0 (0)	0 (0)	2 (1.7)	1 (1.4)	4 (3.4)	3 (7.3)	3 (2.9)	9 (6)	22 (2.9)
Multivitamins	5 (4.2)	1 (2.1)	5 (4.3)	2 (2.7)	3 (2.5)	1 (2.4)	6 (5.8)	1 (0.7)	24 (3.1)
Zinckid	0 (0)	0 (0)	3 (2.6)	3 (4.1)	4 (3.4)	3 (7.3)	4 (3.8)	8 (5.3)	25 (3.2)
Dextrose 10% solution	4 (3.4)	0 (0)	0 (0)	1 (1.4)	2 (1.7)	0 (0)	0 (0)	0 (0)	7 (0.9)
Blood transfusion	2 (1.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.3)
Surgery	1 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)
Other prescriptions*	8 (6.8)	0 (0)	9 (7.7)	7 (9.4)	6 (5.1)	4 (9.8)	21 (20.2)	6 (4)	61 (7.9)

ŧ Other diagnoses made in than 1% of children: Bacterimia 8 cases; conjunctivitis 3 cases; colic 2 cases; meningitis 1 case; severe acute malnutrition 1 case; chickenpox 1 case.

* Other treatments given to less than 1% of children: 10 cases oxygen therapy, 8 cases cetirizine syrup, 6 cases I.V hydrocortisone, 4 cases prednisolone tablets, 3 cases tetracycline eye ointment, 3 cases haemoforte, 1 case nevirapine syrup, 2 cases nystatin oral suspension, 2 cases gripe water, 3 cases nasal saline drops, 1 case chloramphenicol syrup.

Because neonatal sepsis and malaria were the most common illnesses in the first 14 weeks, antibiotics and analgesics were the most common treatments administered. Antibiotics accounted

for 40% (308 doses) of all prescribed medication with the most common antibiotics prescribed or administered being intravenous gentamycin and ampicillin syrup. 172 doses (22%) of analgesics were given, with the most common varieties prescribed being rectal paracetamol and paracetamol syrups. For malaria treatment, lonart syrup, and intravenous quinine were most used. For child diagnosed with jejunal atresia (imperforate anus), surgery was done to correct the condition.

Direct household costs

Outpatient household costs

In all 3 health facilities, the major payments were for medicine, with Kitebi health centre III having the lowest cost US$ 5.6 (95% CI 4.46 – 6.77), while Kawaala health centre III had the highest payments US$ 9.8 (95% CI 7.69 – 11.95) (Table 4). The other costs under direct non-medical costs were spent on items such as airtime, pampers for the babies and local treatment for false teeth. For the remaining participants with these costs, the health centres where they sought treatment did not give them a breakdown of costs incurred. They simply had the total bill.

The total direct costs included both direct medical and non-medical costs incurred in seeking healthcare. The direct outpatient costs incurred by the participants varied widely ranging from US$ 0 to US$ 368. The mean facility direct cost per episode illness was US$ 15 (Table 5). The medical OOP payments were 1.68 times the non-medical costs. Payments for medicines (US$ 8.42 95% CI 7.71 - 9.42) accounted for 89% of the direct medical costs and close to 56% of the total OOP payments.

Table 4: Outpatient direct costs to households per episode of illness at the three study sites

Health Centre	Mean	Median	SD	95% CI
Kawaala Health Centre III				
Direct medical costs				
Drug costs	9.82	5.46	21.36	7.69 - 11.95
Laboratory costs	0.71	0.00	1.97	0.51 - 0.91
Consultation costs	0.15	0.00	0.82	0.07 - 0.24
Direct non-medical costs				
Transport costs	1.19	0.27	2.07	0.99 - 1.40
Food	1.55	0.00	3.63	1.19 - 1.91
Additional expenses for caregiver	1.30	0.00	3.27	0.97 - 1.62
Others	1.56	0.00	5.15	1.04 - 2.07
Kitebi Health Centre III				
Direct medical costs				
Drug costs	5.62	1.37	11.38	4.46 - 6.77
Laboratory costs	0.82	0.00	3.07	0.50 - 1.13
Consultation costs	0.22	0.00	1.17	0.10 - 0.34
Direct non-medical costs				
Transport costs	0.82	0.00	1.80	0.63 - 0.99
Food	0.86	0.00	3.26	0.52 - 1.19
Additional expenses for caregiver	0.29	0.00	1.91	0.09 - 0.49
Others	5.19	0.00	14.34	3.73 - 6.64
Mukono General Hospital				
Direct medical costs				
Drug costs	9.30	0.00	20.53	7.60 - 10.99
Laboratory costs	0.95	0.00	2.78	0.72 - 1.18
Consultation costs	0.15	0.00	1.02	0.06 - 0.23
Direct non-medical costs				
Transport costs	1.35	0.00	2.68	1.13 - 1.57
Food	1.00	0.00	4.48	0.63 - 1.36
Additional expenses for caregiver	0.67	0.00	8.72	-0.05 – 1.39
Others	1.64	0.00	5.25	1.21 - 2.07

All costs reported are in 2019 US$

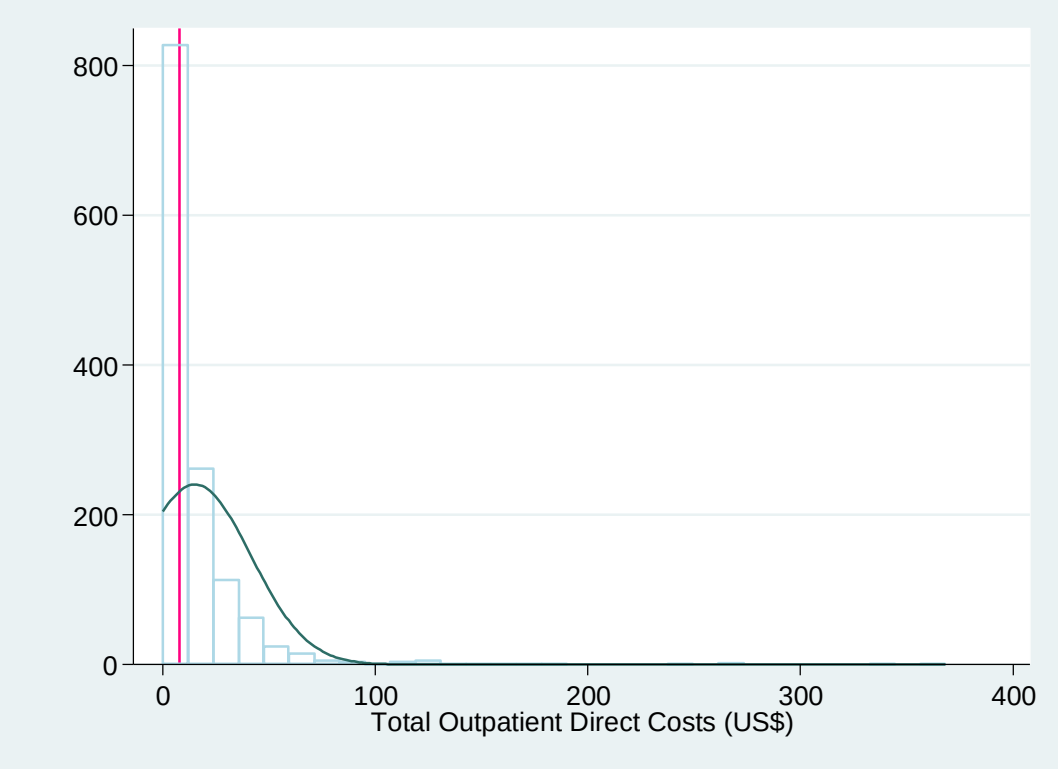


Fig. 6: Distribution of outpatient direct costs showing mean and median costs

Table 5: Total mean outpatient direct costs incurred by households at all facilities combined

	Mean	Median	SD	95% CI
Direct medical costs				
Drug costs	8.42	3.55	18.77	7.71 - 9.42
Laboratory costs	0.84	0.00	2.66	0.70 - 0.99
Consultation costs	0.17	0.00	1.01	0.11 - 0.22
Direct non-medical costs				
Transport costs	1.15	0.27	2.29	1.03 - 1.28
Food	1.12	0.00	3.93	0.91 - 1.33
Additional expenses for caregiver	0.75	0.00	6.05	0.42 - 1.07
Others	2.61	0.00	8.93	2.13 - 3.09
Total direct medical costs	9.43	4.10	20.63	8.32 – 10.54
Total direct non-medical costs	5.63	1.09	12.74	4.95 – 6.32
Total costs	15.06	7.65	26.27	13.65 – 16.48

All costs reported are in 2019 US$

Inpatient household costs

Despite services being free of charge in government health centres and hospitals, caregivers incurred medical costs when their children were hospitalised. Patients from Kawaala HC III incurred the highest costs for both medical and non-medical services, US$ 3.18 and US$ 2.69 respectively, while those at Kitebi HC III had the least medical and non-medical costs, US$ 1.37 and US$ 1.69 respectively. The medical costs incurred by caregivers from Mukono General Hospital were US$ 2.54, while the non-medical costs were US$ 1.69. Overall, the costs paid by caregivers from Kawaala HC III were twice those paid by caregivers from Kitebi HC III.

Table 6: Direct inpatient household costs per episode of illness incurred by caregivers from each of three study sites

Health Centre	Mean	Median	SD	95% CI
Kawaala Health Centre III				
Direct medical costs				
Drug costs	2.83	0.00	9.87	1.85 - 3.82
Laboratory costs	0.35	0.00	1.98	0.15 - 0.55
Consultation costs				
Direct non-medical costs				
Transport costs	0.63	0.00	1.89	0.44 - 0.82
Food	0.18	0.00	1.23	0.06 – 0.30
Additional expenses for caregiver	0.51	0.00	1.81	0.33 - 0.69
Others				
Kitebi Health Centre III				
Direct medical costs				
Drug costs	1.00	0.00	4.32	0.56 - 1.44
Laboratory costs	0.37	0.00	2.79	0.09 - 0.65
Consultation costs				
Direct non-medical costs				
Transport costs	0.55	0.00	2.56	0.29 - 0.81
Food	0.19	0.00	1.66	0.02 – 0.36
Additional expenses for caregiver	0.20	0.00	1.70	0.03 - 0.38
Others				
Mukono General Hospital				
Direct medical costs				
Drug costs	2.32	0.00	13.05	1.24 - 3.39
Laboratory costs	0.22	0.00	1.35	0.11 - 0.33
Consultation costs				

Direct non-medical costs				
Transport costs	0.45	0.00	1.82	0.30 - 0.60
Food	0.07	0.00	0.96	-0.01 – 0.15
Additional expenses for caregiver	0.25	0.00	1.46	0.13 - 0.37
Others				

All costs reported are in 2019 US$

Medical costs contributed most to total costs in all facilities except for Kitebi HC III were the non-medical costs were higher. More specifically, the costs of medicines were the highest costs incurred across all three study sites. The mean costs of medicines at Kawaala HC III were US$ 2.83 (95% CI 1.85 – 3.82) followed by Mukono General Hospital US$ 2.32 (95% CI 1.24 – 3.39) with Kitebi HC III having the lowest mean costs for medicines at US$ 1.00 (95% CI 0.56 – 1.44) (Table 6). The transport costs spent to and from the hospital ranged from US$ 0.45 – 0.63. Caregivers from Mukono General Hospital had the lowest transport costs US$ 0.45 (95% CI 0.30 – 0.60), while Kitebi HC III had caregivers with the highest transport costs were the mean costs spent were US$ 0.63 (95% CI 0.44 – 0.82). Participants from the two urban health centres spent more on transport as it is common to use “boda bodas” (motorcycle taxis) that charge more than regular vans.

During the hospitalisation period, caregivers for the admitted children have to buy their own food. Caregivers from Kitebi HC III spent the most on food US$ 0.19 (CI 0.02 – 0.36), while those at Kawaala HC III on average spent US$ 0.18 (CI 0.06 – 0.30). Mukono General Hospital had the least expenditure on food US$ 0.07 (CI -0.01 – 0.15). Most participants from Mukono grow their own food which could have contributed to the low food expenses. Other expenses incurred were fees for laboratory investigations. The laboratory fees incurred at Kitebi HC III were the highest, with an average of US$ 0.37 (CI 0.09 – 0.65) as shown in Table 6. At Mukono General Hospital, caregivers had the lowest laboratory costs with an average of US$ 0.22 (CI 0.11 – 0.33) followed by Kawaala HC III were caregivers spent US$ 0.35 (CI 0.15 – 0.55) on average. Across all three health facilities, the inpatient direct costs incurred ranged from US$ 0 – US$257.

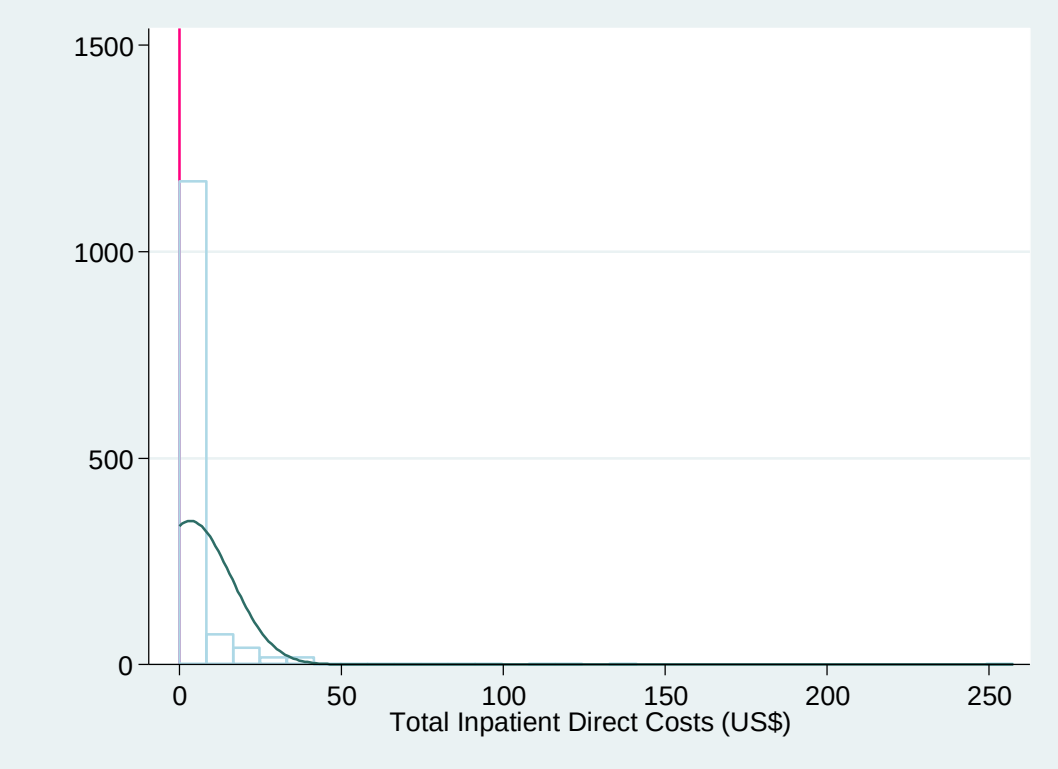


Fig. 7: Distribution of inpatient direct costs showing mean and median costs

Table 7: Total mean inpatient direct costs incurred by households at all facilities combined

	Mean	Median	SD	95% CI
Direct medical costs				
Drug costs	2.10	0.00	10.33	1.55 - 2.65
Laboratory costs	0.30	0.00	2.03	0.19 - 0.41
Consultation costs				
Direct non-medical costs				
Transport costs	0.53	0.00	2.07	0.42 - 0.64
Food	0.13	0.00	3.93	0.91 - 1.33
Additional expenses for caregiver	0.31	0.00	1.64	0.22 - 0.40
Others				
Total direct medical costs	2.40	0	10.93	1.81 – 2.99
Total direct non-medical costs	0.98	0	3.55	0.79 – 1.17
Total costs	3.38	0	12.69	2.69 – 4.06

All costs reported are in 2019 US$

The direct outpatient costs incurred by households are more than four times the direct costs incurred by inpatients. The mean outpatient costs were US$ 15 while the inpatient costs were US$ 3.4. From Table 8, medical costs were the major contributors to direct costs. Outpatient direct medical costs are higher than those incurred by inpatients because, outpatients have to buy medication from private pharmacies outside the health centres, while inpatient services for children under 5 are generally free of charge. For the outpatient costs, the medical costs higher than the non-medical US$ 9.4 and US$ 5.6 respectively, while among the inpatients the medical and non-medical costs were US$ 2.4 and US$ 0.97 respectively.

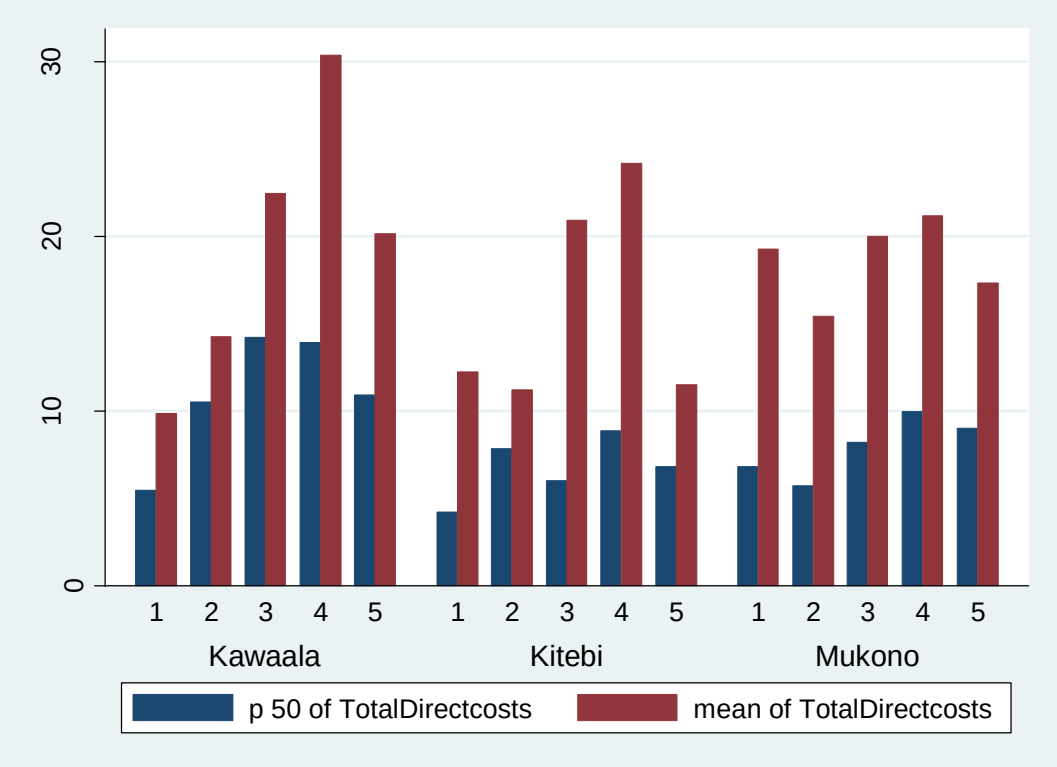


Fig 8: Distribution of total household direct costs by wealth quintiles in US$ per episode of childhood illness

In Kawaala and Kitebi the OOP expenses generally increase across wealth quintiles from the poor to the richest. There were no marked differences in expenditure between the different wealth quintiles at Mukono general hospital.

Indirect household costs

Healthcare for sick children was normally sought for by mothers both in terms of outpatient hospital visits and hospital stay for situations where the children were admitted to hospital. Therefore, the indirect costs were calculated based on the mother's wage rates as they were the ones most likely to costs in terms of lost income due to time spent providing care to the sick child.

Outpatient indirect costs

For the outpatient indirect costs, the mothers spent an average of 2 hours at the health centres or hospital per outpatient visit. During these visits, approximately 70 minutes were spent waiting at different stations in the health centres for the provision of services, while 45 minutes was the actual time spent being attended to (Fig. 9). For these outpatient visits, most of the time spent waiting was at the reception, the doctor's room and during the drawing of blood, while the least amount waiting time was at the x-ray and treatment rooms. In terms of procedure time, doctors spent more time with patients an average of 9 minutes compared to nurses who spent on average 6 minutes attending to patients.

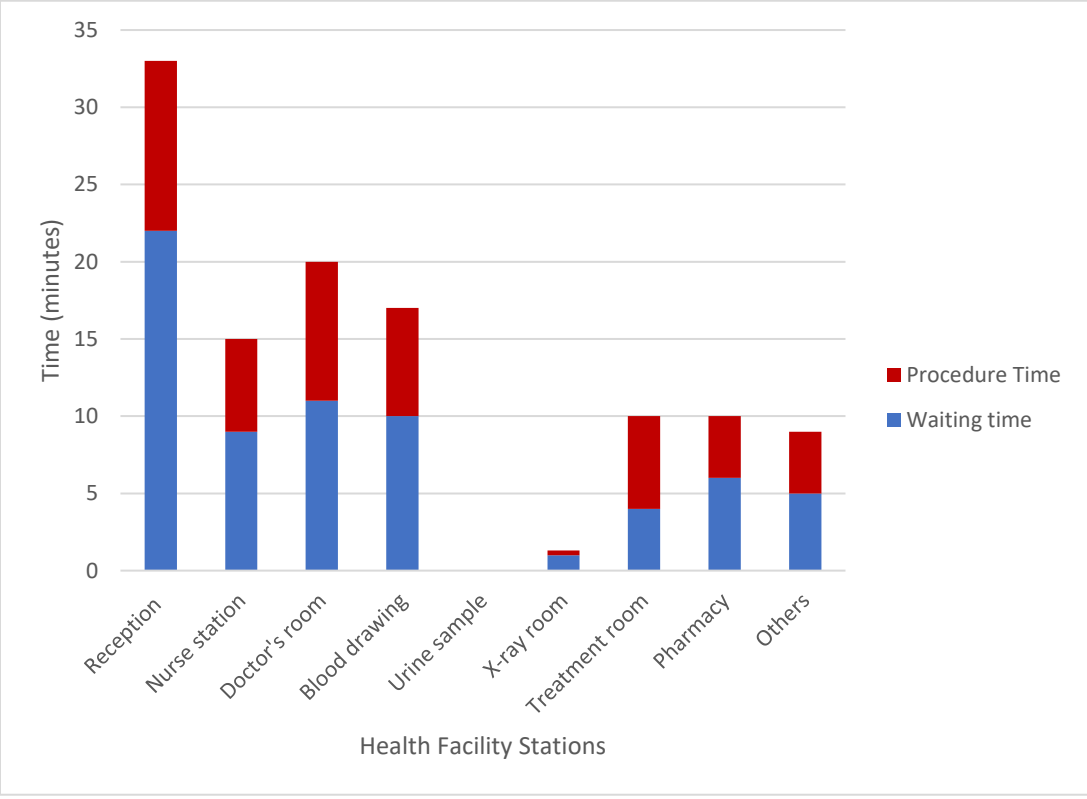


Fig. 9: Average time spent at different stations at the health facilities per outpatient visit

Table 8: Average station time at each of the three health facilities

		KAWAALA HC III	KITEBI HC III	MUKONO GEN. HOSPITAL
		minutes (sd)	minutes (sd)	minutes (sd)
Reception	Waiting	33 (39)	11 (12)	23 (61)
	Procedure	12 (17)	9 (11)	11 (40)
Nurse Station	Waiting	7 (16)	10 (12)	11 (35)
	Procedure	6 (10)	15 (17)	5 (18)
Doctor's Room	Waiting	11 (21)	8 (9)	11 (35)
	Procedure	6 (7)	10 (8)	9 (14)
Blood Drawing	Waiting	8 (12)	5 (8)	12 (29)
	Procedure	8 (10)	5 (8)	7 (13)
Urine Sample	Waiting	0 (0)	0 (0)	0 (0)
	Procedure	0 (0)	0 (0)	0 (0)
X-ray Room	Waiting	6 (16)	0 (0)	0 (0)
	Procedure	3 (7)	0 (0)	0 (0)
Treatment Room	Waiting	10 (35)	6 (10)	2 (7)
	Procedure	13 (26)	8 (12)	4 (11)
Pharmacy	Waiting	0 (0)	4 (8)	8 (20)
	Procedure	0 (0)	4 (6)	5 (10)
Others	Waiting	0 (0)	0 (0)	7 (29)
	Procedure	0 (0)	1 (2)	5 (16)

With a median monthly income of US $52, and an average of 8 hours of work per day [55], this means that each hour of work missed cost US $0.33. Thus, for each outpatient hospital visit, the mothers incurred US $0.66 for the average 2 hours spent at the health centre or hospital as income lost due to seeking of healthcare and caregiving for the sick child.

Inpatient indirect costs

Patients admitted from Kitebi HC III and Kawaala HC III on average were hospitalised for 7 and 6 days respectively, while for those from Mukono General Hospital the average hospitalisation period was 4 days. Overall, the average length of hospital stay was 6 days. With a cost of US $2.6 per day, the income lost due to absence from work by the mothers for each episode of illness that requires hospital admission was US $16.

Table 9: Total household costs per episode of outpatient or inpatient healthcare treatment

	Outpatient costs	% of total	Inpatient costs	% of total
Direct costs				
Medical costs	9.43	60.0	2.40	12.4
Non-medical costs	5.63	35.8	0.97	5.0
Indirect costs	0.66	4.2	16.00	82.6
Total	15.72	100	19.37	100

All costs reported are in 2019 US$

Overall, the among outpatient costs, direct medical costs accounted for over 60% (US$ 9.4) of the costs incurred while indirect costs contributed just 4% (US$ 0.66) to the total outpatient costs. For those children that were admitted, indirect costs were the main costs incurred accounting for 83% (US $16) per episode of illness (Table 9).

Provider costs at facilities

Immunisation clinic costs

At Kawaala HC III, capital costs contributed 7% (US$ 711) of the total immunisation clinic expenditure with the remaining US$ 9021 (93%) falling under recurrent cost expenditure. Of the recurrent costs, US$ 7936 (88%) was spent on drugs and laboratory supplies while staff salaries and allowances US$ 968 accounted for 12% of the recurrent expenditure. Under capital costs most of the expenditure was used to buy equipment US$ 626 (88%). The remaining 12% (US$ 85) was used on buildings.

Recurrent costs accounted for 89% (US$ 11049) of the total costs incurred by the immunisation clinic at Kitebi HC III. Drugs and laboratory supplies cost US$ 9429 (85%) of the total recurrent costs, while US$ 1202 (11%) was spent on clearing staff salaries and allowances. Capital costs were responsible for 11% (US$ 1428) of the total expenditure. The main driver of these costs was equipment that had a value of US$ 1228 (86%) of the total capital costs.

At Mukono General Hospital immunisation clinic, US$ 661 (2%) was spent on capital costs while US$ 32084 (98%) was spent under recurrent costs. US$ 19028 (58%) of the total immunisation clinic expenditure was used to pay staff salaries and allowances, while US$ 12794 (39%) was spent on drugs and laboratory supplies. Of the three health facilities, Mukono General Hospital had the lowest expenditure capital costs. There were no costs incurred for vehicles and vehicle operations as well as capital and recurrent consultancies.

The annual costs for the provision of the BCG vaccine at each of the three health facilities were US$ 9732 at Kawaala HC III, US$ 12477 at Kitebi HC III and US$ 32745 at Mukono General Hospital. On average 32 children are immunised with the BCG vaccine per day at Mukono General Hospital. This totals to 10752 doses per year. At Kitebi HC III and Kawaala HC III on average 9000 and 9720 doses of BCG vaccine are administered every year. Therefore, the cost per child immunised with the BCG vaccine per year ranged from US$ 1 at Kawaala HC III, followed by US$ 1.4 at Kitebi HC III and US$ 3 at Mukono General Hospital.

Table 10: Annual hospital costs of BCG vaccination and delivery of newborns at three health facilities in Uganda

	KAWAALA HC III		KITEBI HC III		MUKONO GEN. HOSPITAL	
	Immunisation Clinic	Maternity Ward	Immunisation Clinic	Maternity Ward	Immunisation Clinic	Maternity Ward
Capital costs						
Buildings	85	1002	199	2035	90	3403
Equipment	626	11899	1228	24393	571	28204
Vehicles	0	0	0	0	0	0
Consultancies	0	0	0	0	0	0
Total capital costs	711	12901	1428	26428	661	31607
Recurrent costs						
Personnel	968	47407	1202	38096	19028	46391
Supplies	7936	12804	9429	11382	12794	26201
Vehicle operations	0	0	0	0	0	0
Building operations	118	4124	418	5295	262	13114
Consultancies	0	0	0	0	0	0
Total recurrent costs	9021	64335	11050	54773	32085	85706
Total costs	9732	77237	12477	81201	32746	117313
%	11.2	88.8	13.3	86.7	21.8	78.2

All costs reported in 2019 US$

Imm clinic: Immunisation clinic; Mat ward: Maternity ward

Maternity ward

At all health facilities, the maternity wards were determined to be the main contributors to the total costs, responsible for more than 80% of the total costs with the exception of Mukono General Hospital. The main cost drivers were staff salaries and allowances. At Kawaala HC III, they contributed 56% (US$ 47407) to the total costs, 42% (US$ 38096) at Kitebi HC III and 44% (US$ 46391) at Mukono General Hospital. These were followed by drugs and laboratory supplies as major contributors with Mukono General Hospital having spent US$ 26200 (26%), Kawaala HC III US$ 12804 (24%) and Kitebi HC III US$ 11382 (22%). With this, the recurrent costs

contributed the largest share to the total costs in the maternity wards. The total recurrent costs at Kawaala HC III were US$ 64336 (84%), while at Kitebi HC III they were US$ 54773 (70%) and US$ 85706 (79%) at Mukono General Hospital. Among the capital costs, equipment costs were responsible for more than 90% of the expenditure except at Mukono General Hospital where they were US$ 28204 (89%). At Kawaala HC III they were US$ 11899 (92%) and US$ 24393 (92%). The cost per immunisation ranged from US$ 1.00 at Kawaala health centre III to US$ 3.00 at Mukono general hospital (Table 11).

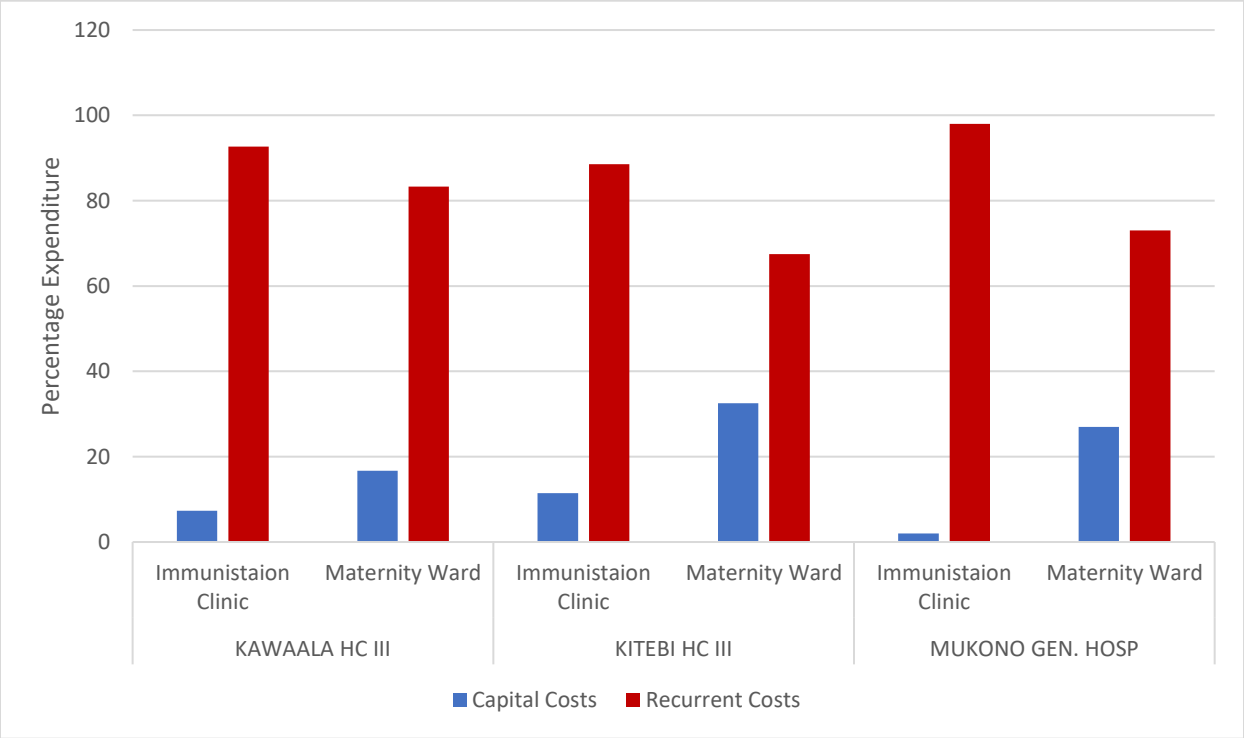


Fig. 10: Annual immunisation clinic and maternity ward expenditures

Table 11: Cost of BCG vaccination per immunized child at three health facilities in Uganda

	Kawaala HC III	Kitebi HC III	Mukono General Hospital
Average number of BCG doses per year	9720	9000	10788
Annualised costs of BCG vaccination (US$)	9732	12477	32746
Cost per immunisaton (US$)	1.0	1.4	3.0

Discussion

Methodological considerations

This study estimates the economic burden of severe illness in HIV-1 exposed children in Uganda. The costs of seeking health, diagnosis and treatment of these complications were viewed from the patients' perspectives.

Costing methodology

In order to capture costs that may not be included in databases or registers, a bottom-up costing method was utilised to collect patient costs. This approach has the challenge of ensuring that the patient sample is unbiased and representative for the entire patient population from which the sample is picked or if it is extrapolated to the national level [79]. The bottom-up approach is also prone to recall bias especially in situations where the patient data is not accurately recorded. In this study, this was minimised by training the study participants about the importance of records keeping, and through providing them with notebooks in which to record all information regarding the child's health and illness. Information like symptoms, clinical diagnoses, treatments received, and the costs incurred was recorded. Micro-costing was used to identify and measure the costs incurred by each patient and the total cost of seeking healthcare and treatment received per patient was estimated. This gives better precision of the different cost estimates.

This study was nested within a randomised clinical trial in which mothers were recruited from the maternity ward after their HIV status at three study sites. The infants were then followed up from birth. This made it suitable to carry out a prospective incidence-based cost of illness study. It was possible to estimate the patient costs from diagnosis to cure. As the intervention is a vaccine, it is

prudent to use an incidence-based cost of illness analysis where an estimate of the savings that may arise when the preventive measure (BCG vaccine) is administered [71, 72].

Discussion of main findings

Burden of childhood illnesses

In this study, the most common cases of illness recorded in the first fourteen weeks were due to malaria which accounted for 32% of all diagnosed cases. This was followed by upper respiratory tract infections with 15% of the reported illnesses with neonatal sepsis and pneumonia at 11%. The effects of malaria, pneumonia, neonatal sepsis and septicaemia on households are important. In the financial year 2018-2019, they were the leading causes of mortality and morbidity in children under the age of 5 in Uganda. They contributed to over 70% of deaths in children under 5 and were responsible for approximately 49% of outpatient department visits [48]. These results are comparable to those from other studies about childhood illnesses in Uganda. A prevalence study of childhood illnesses in central Uganda and another in eight different districts showed that the burden of malaria, acute respiratory infections and pneumonia is high among children under the age of 5 [80, 81]. However, they differ from results from other studies where the burden of URTI and diarrhoea were higher than what we recorded in our study [81-83].

As per W.H.O and UNICEF guidelines in the management of childhood illnesses [84], ampicillin and gentamycin were used to treat bacterial infections while ORS solution was given to infants with diarrhoea. Artemether and quinine by infusion were utilised in the management of malaria. The overlap of symptoms between URTI, malaria and fever could explain the use of antibiotics [85-90]. Recommending the presumptive use treatment of all fevers with antimalarials in malaria endemic areas [91] would explain the numerous doses of antimalarial medication given out.

Health seeking behaviour

Among the 1333 children in the study, 370 cases of illness were diagnosed. We found that 7% of caregivers did not seek healthcare for the ill children, while 12% self-medicated their children. The rate of healthcare seeking for children with symptoms of URTI or fever (>80%) is close to the national average of 80% as reported in in the 2016 Uganda demographic health survey (UDHS) [1].

It has been found by a number of studies that in Uganda, private healthcare providers are the preferred option for many households [1, 80, 92]. In this study, the average waiting time to the OPD per visit was 1 hour which translates into US$ 0.33 in lost income. Research from eastern Uganda showed that the preference of private clinics or drug shops over public health facilities was because these private were more accessible, the treatment was perceived to be cheap and they could also provide services on credit [3]. Also, some government facilities charged unofficial fees [93].

Just like in other studies, the use of traditional healers was very low [94-96]. However, due to stigma associated with their use, the low figures recorded could be as a result of under reporting. The results also show that the majority of caregivers sought healthcare treatment from one source rather than from multiple health facilities.

Household costs

Cost of illness studies provide information that is crucial for economic analyses and evaluations. Through estimating the economic burden of illnesses on households and society in general, they provide a basis for further research and planning. This study estimates the economic burden of severe illnesses in HIV-1 exposed infants. We estimated the out-patient and in-patient costs incurred by households from three different study sites. The costs were in terms of direct (medical and non-medical) and indirect costs. We also determined the implementation costs for health service providers per child vaccinated with BCG at three health facilities.

In this study, the direct costs incurred by outpatients were higher than the indirect costs estimated through time lost taking care of the ill child. This is consistent with observations from another study that investigates the determinants of household costs associated with diarrhoea in three Asian countries [97]. However, for in-patients, indirect costs were approximately responsible for 83% of

the total costs. In both out-patients and in-patients, direct medical costs were driven by costs for medication contributing 89% and 88% respectively. This is consistent with findings from several previous studies [97-100].

The average time caregivers spent while looking after children admitted in hospital was six days. This is comparable to findings from a study about the economic burden of inpatient paediatric care in Kenya where the average was 6.5 days [101]. The indirect costs in the study were estimates of time (days) lost seeking or providing care to the ill child in hospitals. This amount of time is influenced by the caregivers perception of the severity of the illness [80], as this determines when and if to seek healthcare which if the decision is late, the illness may be more severe leading to longer hospital stay. The direct costs incurred during the hospitalisation of the children were lower than those observed in other research studies [101-103]. The abolition of user fees by government in 2001 could explain the low costs. But also, despite the removal of these user fees, these costs prove that households still incur OOP payments to receive treatment at public health facilities where services are supposed to be free of charge.

Households spent US$ 16 and US$ 19 during out-patient visits and in-patient admission respectively as OOP payments highlighting the economic burden on households considering that the median household monthly is just US$ 52. These costs per episode of illness would greatly affect the households purchasing power for other items like rent, food and utilities. This is likely to modify and influence decisions about seeking healthcare for the children. In this study, the OOP health expenditures were 31% and 37% of the monthly income among out-patients and in-patients respectively. W.H.O considers health expenses catastrophic when the OOP payments exceed 40% (in some studies 10%) of the households capacity to cater for other basic needs [104-106].

The cost of BCG vaccination at the three health facilities ranged from US$ 1 – US$3, with an average cost of US$ 1.9. This value is comparable to values from other studies [107-112].

Limitations

The respondents in the study were women most of whom had limited knowledge on household income. This was associated to the fact that majority of households (81%) are headed by male partners who are also the main income earners. Also, some participants had aggregate costs which made it impossible to determine costs for the individual items (e.g. drugs, laboratory investigations, consultations) responsible for the total medical bill.

Approximately 80% of participants sought healthcare and thus had their costing data recorded. Without information on the remaining 20%, we cannot get a true picture of the economic burden of childhood illness on households. Also, costing information for inpatients was collected from participants that visited public health facilities, and we have limited information about the practices and payment terms from these health facilities. Without information on the determinants for seeking healthcare, we do not know how self-selection between private and public health facilities might bias the results.

The indirect costs estimated were time spent at the health facilities. We did not have access to information about travel time, or the time spent before seeking healthcare. The the indirect cost reported in this study is therefore an underestimation of the actual total costs when taking travel time into account. The sources of funding (e.g. loans, savings, sale of household items) used to cater for payment of travel and treatment during the episodes of illness were not determined. They could have given us a clearer picture of the economic burden of illness on households.

For the facility costs, we did not measure costs incurred by the Ministry of Health, KCCA and Mukono Municipal Council in supervising the implementation of the intervention and delivery of services at the respective maternity wards. Thus, the costs for service delivery represent the perspective of local service providers, and not do not incorporate program costs at national and subnational levels.

Conclusion

In conclusion, this study provides an estimate of direct and indirect costs associated with severe illness in HIV-1 exposed infants in central Uganda. Despite the abolition of user fees in public health facilities, households still incur significant costs for hospitals visits. This has contributed to economic burden of illness on households which has the potential to be catastrophic. Outpatient costs incurred by households were mainly in the form of OOP payments while for households with inpatients, the expenses were majorly costs due to work time missed while seeking or providing care for the sick child. More research is needed on the determinants household costs as well as comparison of costs incurred between HIV-1 exposed and unexposed children.

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Appendices

HEALTH CENTER COSTING TOOL

A. What did you do when (name) got ill?

1. [ ] First Episode
0. [ ] Nothing
1. [ ] Herbs
2. [ ] Traditional healer
3. [ ] Self-medication
4. [ ] Pharmacy/drug shop
5. [ ] Health centre ask for medical record).
Note Diagnosis___
Note treatment given
Note name of the health facility_____
Note the body temperature recorded in the book_____
6. [ ] Hospital
(ask for medical record).
Note Diagnosis___
Note treatment given
Note name of the health facility_____
Note the body temperature recorded in the book____
7.[ ] Private clinic
ask for medical record).
Note Diagnosis___
Note treatment given
Note name of the health facility_____
Note the body temperature recorded in the book.

Second Episode got sick.
0. [ ] Nothing
1. [ ] Herbs
2. [ ] Traditional healer
3. [ ] Self-medication
4. [ ] Pharmacy/drug shop
5. [ ] Health centre ask for medical record).
Note Diagnosis___
Note treatment given
Note name of the health facility_____
Note the body temperature recorded in the book_____
6. [ ] Hospital
(ask for medical record).
Note Diagnosis___
Note treatment given
Note name of the health facility_____
Note the body temperature recorded in the book____
7.[ ] Private clinic
ask for medical record).

Note Diagnosis___
Note treatment given
Note name of the health facility_____
Note the body temperature recorded in the book.

B. How much did you spend in total on out-patient care for treatment of the illness for your child?
1.First Episode:
1.[ ] Drugs: _____Ushs
2.[ ] Investigations/ tests:____Ushs
3.[ ] Consultation fee___Ushs
4.[ ] Transportation to and from health facility:___Ushs
5.[ ] Food_____Ushs
6.[ ] Additional expenses for care giver____Ushs
7.[ ] Traditional healer:_____Ushs
8.[ ] Hospital bed days_____Ushs
9.[ ] Others (describe)____Ushs.

2.Second Episode:
1.[ ] Drugs: _____Ushs
2.[ ] Investigations/ tests:____Ushs
3.[ ] Consultation fee___Ushs
4.[ ] Transportation to and from health facility:___Ushs
5.[ ] Food_____Ushs
6.[ ] Additional expenses for care giver____Ushs
7.[ ] Traditional healer:_____Ushs
8.[ ] Hospital bed days_____Ushs
9.[ ] Others (describe)____Ushs.

C. How many times has (name) been admitted in hospital or a clinic? (If no medical records, ask the mother)
_____(#)

D. Baby illnesses - Time spent at different station points

Note name of health facility where the mother sought care
……..

1) How much time did you spend travelling one way from your home to the health center/hospital?
    a) Time of departure
    ……..
    b) Time of arrival
    ……..

2) In total, how much time did you spend at the health center? (time in hours)
    …….
3) Can you please tell me when you arrived and left the hospital?
    a) Time of arrival
    …….

b) Time of departure
…….

4) During this (names) illness, how much time did you spend at the following points?
   a) Reception: waiting time (minutes)
   ……..
   b) Reception: procedure time (minutes)
   …….
   c) Nurse table: waiting time (minutes)
   …….
   d) Nurse table: procedure time (minutes)
   …….
   e) Doctor's room: waiting time (minutes)
   …….
   f) Doctor's room: procedure time (minutes)
   …….
   g) Blood specimen point: waiting time (minutes)
   …….
   h) Blood specimen point: procedure time (minutes)
   …….
   i) Urine specimen point: waiting time (minutes)
   …….
   j) Urine specimen point: procedure time (minutes)
   ……
   k) X-ray: waiting time (minutes)
   ……....
   l) X-ray: procedure time (minutes)
   ……...
   m) Treatment room: waiting time (minutes)
   ……..
   n) Treatment room: procedure time (minutes)
   ……..
   o) Pharmacy: waiting time (minutes)
   ……..
   p) Pharmacy: procedure time (minutes)
   …….
   q) Other: waiting time (minutes)
   …….
   r) Other: procedure time (minutes)
   …….