

Gaps and opportunities in sustainable medicines use in resource limited settings: a situational analysis of Uganda

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Abstract

Resource constraints and widespread poverty among populations undermine disease prevention in low- and middle-income countries (LMICs) and ensure that these countries carry a disproportionate share of the global disease burden. Lack of access to efficacious medicines in LMICs further exacerbates this inequity. Addressing inequitable access to medicines and assuring their sustainable use is critical to the well-being of these populations. Whilst inadequate access to medicines in LMICs has drawn much attention, less is known about the sustainable use of available medicines, particularly to ensure their efficacy and mitigate harm to the population and the environment. Uganda has adopted various measures to ensure sustainable medicines use, including a national medicines policy, essential medicines list, medicines regulation framework, and promotion of domestic medicines production. Despite progress, challenges remain to achieving sustainable medicines use in the country, including fragmented access, inappropriate use, poor-quality, and inappropriate disposal. There is need to consolidate the globally embraced One Health approach (fostering collaboration between human, animal and environmental health sectors) to addressing these challenges as espoused in the country's One Health strategic plan. Medicines supply chain management in public sector health facilities needs to be strengthened to minimize inventory shortages (stock-outs). A strategy for universal health insurance can minimize economic barriers to medicines access. Enhanced professional and medicines regulation in the private health market needs to be implemented. There are opportunities to build further capacity in

Uganda, particularly infrastructure for regulation of its healthcare systems, policy and governance, workforce capacity building, and population action and engagement.

Introduction

Sub-Saharan Africa (Eastern, Western, Central and Southern Africa) is home to 18 of the world's poorest countries and at least 40% of its population live below the international poverty line of US\$ 1.90 per day [1]. Consequently, the region suffers a high burden of disease and weak health systems, and lags behind other global regions in life expectancy (average of 64.5 years versus global average of 73.3) [2]. Communicable (infectious) diseases, particularly malaria, HIV/AIDS, tuberculosis, lower respiratory tract infections and diarrhoea dominate morbidity and mortality in the region and cause over 53% of all recorded deaths [2]. The region accounted for 94% of the 229 million malaria cases [3] and 68% of the 37.9 million people living with HIV in 2019 [4]. The region has also recorded a significant increase in non-communicable disease burden in recent decades, including cancers [2, 5].

The development of quality assured efficacious medicines over the last century has reversed the course of many fatal and disabling diseases globally, greatly enhancing human life expectancy and quality of life. For example, the scale up of antiretroviral therapy in the world in early-to-mid 2000s reduced the annual global deaths from AIDS-related illnesses from 1.7 million in 2004 to 770,000 by 2018 [4] and transformed HIV from a fatal disease to a chronic illness [2]. In Uganda, a low income country in East Africa with one of the highest HIV burdens in the world [4], the roll out of antiretroviral therapies (ART) in 2004 dramatically reduced mortality rate per 1000 person-years from 116.4 to 39.9 by 2009 [6]. Globally, a 45%

reduction in fatalities from tuberculosis was realized from enhanced coverage of anti-tuberculosis treatment programmes over the last two decades [2].

The clinical efficacy of antimicrobial drugs depends on continued therapeutic sensitivity of target microbial pathogens as these have evolutionary adaptive mechanisms for evading drug action which can be quickly activated on drug exposure, a phenomenon called antimicrobial resistance (AMR) [7-10]. Ordinarily, infections with AMR cease response to standard (first line) drugs which are often the safest, most affordable, most efficacious and most accessible treatments available [8, 11-13]. Antimicrobial resistance may involve multiple first line drugs, a phenomenon called multi-drug resistance (MDR); or extend to second line drugs, a phenomenon called extensive drug resistance (XDR); or affect drugs with unrelated modes of action, which is termed cross-resistance [9, 11, 13-15]. Antimicrobial resistance has been documented for almost all current antibiotics globally and can spread from one member of a microbial population to another [7-9]. Uganda is among the countries with a high burden of AMR. In *Staphylococcus aureus* isolates from patients and hospital environments, a high prevalence of methicillin resistance (32% to 100%) and MDR (76%) have been reported in the country [16, 17]. Furthermore, there is ceftriaxone resistance in 67% of *Escherichia coli* and 85% of *Klebsiella pneumoniae*; ciprofloxacin resistance in 61% of *E. coli* and 77% of *K. pneumoniae*; chloramphenicol resistance in 44% of *E. coli* and 83% of *K. pneumoniae*; and MDR in 60% of *Salmonella typhi* isolates in Uganda [16]. Among TB patients in Uganda, 1.7% of sputum samples have MDR mycobacteria [18] while 78% of rifampicin-resistant (RR) TB isolates are MDR [19].

Uganda is a landlocked country in East Africa, with a population of 42 million [20]. The country's gross domestic product (GDP) per capita stands at a lowly USD 910, and 21% of

the population live below the poverty line [20]. With most of the country's population unable to finance all their socio-economic needs, the availability of affordable health care is essential to maintaining a healthy people. In 2001 Uganda removed the need for user fees at public healthcare facilities, resulting in an 80% increase in visits, primarily from those in lower socioeconomic status [21]. Despite this, both the public and private health sectors contribute equally to health care delivery in Uganda, and both are essential to promotion of sustainable medicines use practices.

Antimicrobial resistance increases treatment failure, length of hospital stays, duration of treatment, cost of treatment, drug toxicity with second line treatments and fatalities [8, 9, 11-13, 15, 22], and threatens the sustainability of microbial chemotherapy. The drivers of AMR selection and spread such as the inappropriate use of antimicrobial drugs in humans and animals, poor medicines quality, indiscriminate waste disposal, poor infection control in clinical settings, inadequate vaccination coverage, and lack of universal health coverage [7, 8, 10, 11, 22, 23] ought to be addressed. These drivers of AMR cut across human, animal and environmental spheres, hence effective mitigation necessitates a holistic approach that integrates human health, animal health and the environment, a framework called One Health [24, 25]. A global concept and an integral component of both international and national health agendas, the One Health approach involves working together of the human health, animal health and environmental health sectors in a multidisciplinary collaboration to preserve a healthy ecosystem [7, 25-27]. Under the One Health approach for AMR, integrating and harmonizing interventions to improve antimicrobial use in humans and animals through collaborative and coordinated participation of the human health, animal health, environmental health and environmental science sectors are essential [7]. The One Health approach has been adopted for disease and AMR control in Uganda, with a One

Health framework and an intersectoral national One Health Platform (NOHP) established in 2016, and a five year national One Health strategic plan launched in 2018 [28].

The high disease burden in sub-Saharan Africa means that fostering sustainable medicines use is essential to health security in the region. To achieve this, understanding the current situation of sustainable medicines use in this region is essential. In this review, the gaps, threats, facilitators and opportunities to sustainable medicines use in Uganda (**Table 1**) are discussed providing insights into the situation of sustainable medicines use in the sub-Saharan Africa context. Given the special importance of communicable diseases in the country and the region, and the threat that the AMR contagion poses to human existence, we use antimicrobial use and resistance as a case study on the state of sustainable medication use in a resource limited setting.

Gaps in sustainable medicines use

An understanding of the gaps in sustainable medicines use in a health system is essential to the design of needs-responsive interventions for mitigation. Among impediments to sustainable medicines use in Uganda, inappropriate medication practices dominate, while poor quality medicines and inappropriate medicines disposal have sporadically been reported. Despite the dangers of antibiotic misuse to the environment, overuse, missed doses, incomplete treatment and empirical prescribing (without appropriate diagnostics including culture and sensitivity and blood tests) of these medicines is pervasive in public and private sector health facilities [29-31]. In Uganda and resource limited settings generally, the rural poor lack access to effective, formal healthcare and fulfill many healthcare needs through informal providers and self-medication [32, 33]. Furthermore, sharing of prescribed

antibiotics amongst household members is common, as is the unauthorized practice of using antibiotics for animal treatment and growth promotion [34, 35].

Studies of antimicrobial drug quality in Uganda have largely focused on antimalarials, reporting a high burden of poor quality and non-quality assured antimalarials [36, 37].

Meanwhile inappropriate pharmaceutical waste disposal and environmental contamination are emerging as neglected risks to sustainable medicines use in Uganda. Active pharmaceutical ingredients have been found in both surface waters and waste treatment facilities [38]. Households in Uganda dispose of unused medications into general waste dumpsters and rubbish pits [34] which contribute to environmental pollution.

Threats to sustainable medicines use

A large population and inadequate pharmaceutical budgets have perpetually combined with human resource and technological inadequacies in medicines management to simultaneously exacerbate the frequent stock-out of essential medicines [39, 40]. Stock-outs of medicines and limited health commodities are a primer to AMR because they perpetuate missed, incomplete and inappropriate doses, as well as deprive prescribers of diagnostic tools, leading to an overreliance on empirical diagnoses and management of infections. Additionally, stock-outs drive patients from public sector health services to the private health market where profit-motivated practices compromise adherence to treatment guidelines and appropriate medicines use. Meanwhile, large volumes of medicines and health commodities have often expired in public health facilities and warehouses in Uganda [40], posing a challenge of disposal and predisposing to environment contamination. At the heart of public sector medicines management challenges is also a severe shortage of pharmacists in public health facilities. Until recently, Uganda, a country with a population of over 40 million people

employed only 31 pharmacists [41], which severely compromised the human resource capacity to manage medicines and health products efficiently from medicines selection through quantification (forecasting), inventory management and use.

The regulation of both retail medicines supply and health professional practice in Uganda is weak. Human medicines retail supply is characterized by abundance of unlicensed drug outlets operated by unqualified personnel and indiscriminate over-the-counter (OTC) prescribing and dispensing of prescription-only-medicines by pharmacies and small drug shops [31, 42]. Similarly, private-for-profit health care providers in Uganda are characterized by a highly dominant informal sector with unqualified personnel, lack of equipment, weak laboratory services and professional malpractices due to weak enforcement of professional policies and laws [32].

The veterinary health sector is another hotspot for unsustainable medicines use. In Uganda, the veterinary health sector is fully liberalized, and both veterinary health care and retail drug supply are dominated by the private sector [43, 44]. However, most farming communities have no access to qualified veterinarians, and depend on unqualified personnel and informal suppliers (mobile vendors, cattle markets, and roadside shops) as the primary providers of veterinary health care and retail drug supply, coupled with self-treatment of livestock by farmers [43]. Overall, the veterinary health profession and medicines supply chain are weakly regulated and there is widespread medicines misuse and overuse [43, 45], which for antimicrobials fuels AMR. Uganda's medicine regulatory agency (the NDA) regulates production and trade of both human and veterinary drugs under the stewardship of the Ministry of Health while veterinary professional practice is regulated by the Uganda Veterinary Board (UVB) under the Ministry of Agriculture, Animal Industry and Fisheries

[46-48]. The NDA, the UVB and their mother Ministries need to work together in a One Health Approach to promote equitable access to qualified veterinary professionals and licensed veterinary pharmaceutical suppliers in animal farming communities

Lastly, Uganda relies heavily on imports for its pharmaceutical supplies. At least 90% of the registered pharmaceutical products in Uganda are imported, mostly from India [49].

Overreliance on pharmaceutical imports deprives the country of control over manufacturing, which increases risk of laundering of poor quality products by unscrupulous vendors, regardless of prior good manufacturing practice certification.

Facilitators of sustainable medicines use practices

Uganda has a strong policy, legal and institutional framework for governance of the country's pharmaceutical sector, encompassing a National Medicines Policy (NMP) to guide development of the sector; legislation for medicines regulation; a competent medicines regulatory agency; and a dedicated public pharmaceutical supply management agency [48-51]. The NMP aims to ensure the availability, accessibility, affordability and appropriate use of good quality essential drugs and health supplies to Uganda through strengthening medicines supply chain management, regulation and quality assurance, and domestic pharmaceutical manufacturing [49]. The NMP prescribes that medicines selection for publically funded procurement addresses priority needs of the population by following the Vital, Essential, and Necessary (non-essential) (VEN) criteria upon which medicines and health supplies are classified according to their importance and health impact in the Essential Medicines and Health Supplies List of Uganda (EMHSLU) [51, 52]. This categorization promotes optimal management of finite resources and availability of life-saving medicines. The annual procurement plans from public health facilities are consolidated by National

Medical Stores (NMS) which procures medicines on behalf of the facilities, accruing economic benefits of pooled procurement.

Domestic manufacturing of essential medicines and health products is crucial to sustainable medicines use as it cushions a country's health care system from risks associated with importation such as vulnerability to supply chain disruptions and inadequate regulatory control of drug quality at point of manufacture. Uganda's NMP prescribes several strategies to promote domestic manufacture of pharmaceuticals, including; offering tax holidays to domestic manufacturers, selective national procurements for the domestically manufactured products, levying higher taxes on imported medicines with domestic manufactured equivalents, regular inspection of local manufacturers to enhance compliance to Good Manufacturing Practices (GMP), and support for local manufacturers to achieve regional or international certification [51]. Uganda's differential tax approach that levies higher taxes on imported products, called Buy Uganda Build Uganda (BUBU) policy, was recently extended to the local pharmaceutical industry by raising import verification fees on selected locally manufactured pharmaceuticals from 2% to 12% [53]. The number of domestic pharmaceutical manufacturers in Uganda has steadily increased from 11 in 2009 [54] to 29 in 2021 [55].

In 1993, Uganda established a national medicines regulatory agency, the National Drug Authority (NDA) with mandate of ensuring that drugs available to the country's population are safe, efficacious, and appropriately used [48]. The NDA achieves this by performing several regulatory functions, namely; medicines registration (marketing authorization), licensing of pharmaceutical outlets, GMP inspections for medicine manufacturers, post-market surveillance, import and export control, control of advertisement and promotion of

medicines, and quality control testing of medicines. The NDA licenses four types of pharmaceutical supply outlets with varying scope of services in Uganda, namely; retail pharmacies, drug shops, wholesale pharmacies, and dual wholesale/retail pharmacies [48, 56]. Retail pharmacies dispense both prescription only medicines (POMs) and over-the-counter (OTC) medicines to patients; drug shops dispense only OTC medicines; wholesale pharmacies do bulk distribution of both POM and OTC medicines to retail pharmacies, drug shops and health facilities; and wholesale/retail pharmacies do both retail and wholesale supply. Most pharmacies in Uganda are located in the capital Kampala and surrounding districts in Central Uganda [57, 58] which deprives the rural countryside where over 75% of Ugandans live of access to medicines [59]. By providing both wholesale supply and retail dispensing of medicines under one roof, the vertical integration in dual wholesale/retail pharmacies enhances access to medicines in the event of sparse pharmacy density in an area, and was intended to promote equitable access to medicines in the country [58, 60]. It is also reported that wholesale/retail pharmacies are more viable financially than either form alone as they bring in both wholesale and retail revenues which encourages entrepreneurs to open pharmacies in the underprivileged rural countryside [58].

Opportunities for sustainable medicines use

The opportunities to optimise sustainable use of medicines in Uganda exist at four levels: policy and governance, workforce capacity building, systems strengthening, and population action and engagement. These are aligned with a recent research roadmap for AMR [61]. The NDA of Uganda is responsive and proactive to the pharmaceutical regulatory and quality assurance needs of the country, working closely with international regulatory authorities and

partners [49]. Policy gains made by the NDA and the NMS provide a solid platform for developing strategies to address the gaps identified in sustainable medicines use in human health. In the case of antimicrobials, Uganda developed an Antimicrobial Resistance National Action Plan (NAP) in 2018 with cross sector participation embracing a One Health agenda [62]. The NAP recognises the need for the four above principles in sustainable medicines use, demonstrating engagement across all four domains.

There is an opportunity to build the technical and clinical competence of healthcare workers, working within the identified competencies of WHO and professional societies. The Pharmaceutical Society of Uganda (PSU) and the Infectious Diseases Institute at Makerere University are both active in promoting antimicrobial stewardship and championing the role that pharmacists play. Research partnerships between hospitals in the UK and Uganda as part of the Fleming Fund and THET (Tropical Health and Education Trust) partnership have demonstrated the opportunities for sustainable knowledge transfer in antimicrobial stewardship [63, 64]. However, the majority of pharmacists continue to work in the community. This is an opportunity for developing community engagement in sustainable medicines use. There are also opportunities for building stronger collaborative relationships and mentoring between community, academic and hospital pharmacy settings, co-ordinated through the PSU as part of accredited continuous professional development programmes to incentivize uptake.

Systems strengthening can occur across all parts of the medicines supply and use processes including assuring the sustained availability of the products on the EMHSLU, developing partnerships in health to leverage economically viable procurement contracts for medicines and support effective forecasting through surveillance of medicines use and shortages [65]. In

Uganda, the supervision, performance assessment and recognition strategy (SPARS) implemented by the Ministry of Health aims to build staff capacity and has demonstrated success in supply, stock and storage management of medicines in lower level healthcare facilities [66].

At population level there needs to be better engagement with civil society on effective use of medicines, including antibiotics, particularly in addressing the health inequalities which push people to seek over-the-counter antibiotics or take antibiotics not prescribed to them.

Universal health insurance would facilitate universal health coverage and improve medicines use and address some of these inequalities. Furthermore, taking a One Health approach and addressing the gaps in medicines supply and use chains across animal, environmental and human health requires an understanding of the consequences of medicines use across sectors.

Conclusion

Many gaps remain in securing sustainable medicines use. The threats of weak and fractured medicines supply and use are manifested across the One Health environment. The unintended consequences include emergence of AMR, increase in communicable and non-communicable diseases, and damage to the environment. These threats are exacerbated in countries with health systems that are under pressure from limited resources and high demand for healthcare. In Uganda, the key existing threats to sustainable medicines use are lack of robust regulation in the private health sector, an overreliance on medicines imports, lack of adequate surveillance, forecasting and weak medicines management systems. There are opportunities to build on the progress Uganda has made in developing infrastructure for regulation of its healthcare systems and policy and governance, workforce capacity building, systems strengthening, and population action and engagement.

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Table 1. Snapshot of gaps, threats, facilitators and opportunities for sustainable medicine use in Uganda

Gaps in sustainable medicine use	Threats to sustainable medicine use
• High burden of poor quality and non-quality assured medicines • Inappropriate disposal of medicines and other pharmaceutical wastes • Inappropriate medicine use practices such as inappropriate use of antibiotics for animal treatment and growth, sharing of medicines among household members • Presence of informal illegal providers • Rampant self-medication with antibiotics and other POMs	• Inadequate pharmaceutical budget for the public sector • Frequent stock-outs and expiry of medicines in the public sector • Inadequate pharmaceutical personnel in the country • Heavy reliance on importation of pharmaceuticals • Limited access to veterinarians and veterinary pharmaceutical outlets • Weak regulation of veterinary pharmaceutical outlets and personnel • Indiscriminate over-the-counter prescribing and dispensing of POMs by pharmacies and drug outlets
Facilitators of sustainable medicine use	Opportunities for sustainable medicine use
• Rational medicine selection based on EMHSL, National Formulary and National medicine register • Pooled procurement in the public sector • Harmonized distribution systems and last mile delivery of medicines to public and PNFP facilities • Increased local production of pharmaceuticals facilitated by BUBU policy • Improved regulation and equitable distribution of pharmaceutical outlets throughout the country	• Suitable regulatory infrastructure and capacity for assuring access to quality medicines • Antimicrobial Resistance National Action Plan (NAP) with cross sector participation embracing a One Health agenda • Building stronger collaborative relationships and mentoring between community, academic and hospital pharmacy settings • Building on multipronged SPARS approach for building capacity • Provision of universal health coverage • Strengthening One Health Approach • Strengthening pharmaceutical supply chain systems