Management of type 1 diabetes in low- and middle-income countries: Comparative health system assessments in Kyrgyzstan, Mali, Peru and Tanzania

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Abstract

Aims: To describe and compare the health system responses for type 1 diabetes in Kyrgyzstan, Mali, Peru and Tanzania.

Methods: The Rapid Assessment Protocol for Insulin Access, a multi-level assessment of the health system, was implemented in Kyrgyzstan, Mali, Peru and Tanzania using document reviews, site visits and interviews to assess the delivery of care and access to insulin.

Results: Despite the existence of noncommunicable or diabetes strategies and Universal Health Coverage policies including diabetes-related supplies, this has not necessarily translated into access to insulin or diabetes care for all. Insulin and related
INTRODUCTION

It is estimated that globally in 2017 there were 9 million people with type 1 diabetes. Since the first use of insulin in 1922, the management of type 1 diabetes has dramatically improved in many settings due to a wide range of factors including access to insulin, delivery devices, self-monitoring equipment and health system responses. In many low- and middle-income countries (LMIC) the true burden of type 1 diabetes is unknown and health systems are poorly equipped to address this complex chronic disease, including poor availability and affordability of insulin. This results in high rates of mortality in LMICs for type 1 diabetes.

Global discourse on health systems and noncommunicable diseases (NCD) has focused on two elements. Firstly, the need to focus on Primary Health Care (PHC) and on the integration of NCD services at this level of the health system. The second component is Universal Health Coverage (UHC) with the aim of protecting individuals from the financial burden of care. Both PHC and UHC are essential in achieving the health-related Sustainable Development Goals. Although diabetes is included as one of the priority NCDs by the World Health Organization (WHO), global focus has been on prevention of type 2 diabetes through lifestyle-related risk factors.

The global response to NCDs and diabetes has neglected the specificities of type 1 diabetes. As prevention of type 1 diabetes is not possible, access to insulin and care, including trained healthcare professionals and diabetes education, are essential to ensure the survival of people living with this condition. Therefore, the aim of this study is to gain an in-depth understanding of the barriers to type 1 diabetes care in Kyrgyzstan, Mali, Peru and Tanzania to understand health system responses to type 1 diabetes in order to improve delivery of care.
2 | METHODS

The Rapid Assessment Protocol for Insulin Access\textsuperscript{17} has been previously used in different contexts\textsuperscript{18–22} and studies the delivery of care and insulin through a multi-level assessment of the health system using site visits, document reviews and interviews applying different targeted questionnaires.\textsuperscript{17} Purposive samples were used with targeted questionnaires at the: Macro level (Ministries of Health, Finance, and Trade; National diabetes associations; educational establishments; central medical stores; private wholesalers of medicines and medical equipment); Meso level (regional and district health offices; health facilities; pharmacies (public and private); laboratories (public and private)); and Micro level (health professionals; traditional healers [where appropriate]; and people with diabetes and their carers).

All tools were translated, ethical clearance was obtained from: the Ministry of Health in Kyrgyzstan; the Comité d’Éthique de la Faculté de Médecine et d’Odonto-Stomatologie, Bamako, Mali; Comité Institucional de Ética en Investigación de la Universidad Peruana Cayetano Heredia, Lima, Peru; and the National Institute of Medical Research in Tanzania. Informed consent was provided by all participants. In Kyrgyzstan and Mali, the Meso and Micro levels were carried out in different locations in the country in order to assess diabetes care in different contexts. In Peru and Tanzania, data were collected only in the capital city. More data on each country can be found in Table 1.\textsuperscript{1,23,24} Currency conversions for all countries except Tanzania used the average exchange rate between the local currency and US$ for 2018, whereas in Tanzania this was the average for 2019. The price of all insulin formulations was standardized to 10 ml 100IU/ml vial equivalent. For affordability the proportion of wages that the lowest-paid unskilled government worker would need to spend to cover the monthly costs of their diabetes management was calculated.\textsuperscript{25} For availability interviewers checked if the item was present or not in each facility visited where this item should be present. Analysis of results used the following themes\textsuperscript{7,18}: Positive policy environment; Organization of the health system; Data collection; Diagnostic tools and infrastructure; Medicine procurement and supply; Availability and affordability of medicines and care; Healthcare workers; Patient education and empowerment; Adherence issues; and Community involvement and diabetes associations.

3 | RESULTS

A total of 773 interviews were carried out in the four countries with 5% at the Macro level; 28% at the Meso level; and 67% at the micro level (Table 1).

3.1 Positive policy environment

In Kyrgyzstan the Mandatory Health Insurance Fund included free medical services for people with diabetes, as well as insulin.\textsuperscript{26} Mali had three different insurance mechanisms: Obligatory Medical Assistance (health insurance scheme financed by employee and employer contributions in both the public and private sectors); the Medical Assistance Regimen (offers free services for the most vulnerable in Mali); and a system of Voluntary Medical Insurance for people working in the informal sector. All these schemes cover diabetes medicines, consultations and laboratory tests.\textsuperscript{27} Peru also had different insurance plans: Comprehensive Health Insurance (Seguro Integral de Salud in Spanish) for vulnerable populations; a social security system (ESSALUD) for workers in the formal sector; an insurance system for the armed forces; and private insurance.\textsuperscript{28} All of these included different elements of diabetes care. In Tanzania, the National Health Insurance Fund covered insulin, syringes and test strips plus the management of acute and chronic complications.\textsuperscript{29} In addition, in Tanzania for those who did not have insurance, within the public sector there is a component of cost sharing and exemption.

In Kyrgyzstan, NCDs have been included in the national health reform programs since 2006 with a comprehensive program for the prevention and control of NCDs for 2013–2020. Diabetes is also prioritized through the adoption of a specific diabetes program (2018–2022), as well as a specific law on diabetes adopted in 2006. Mali adopted its national NCD plan, which included diabetes, in 2015 and diabetes is part of the current Health System Development plan. Peru’s national NCD plan 2005–2012 (which is still valid) included diabetes. In Peru most diabetes-related activities focused on type 2 diabetes although legislation protecting people living with diabetes approved in 2005 was modified in 2018 to include type 1 diabetes. Tanzania’s second National NCD Strategic Plan 2016–2020 comprised diabetes. Work is ongoing on the third National NCD Strategic Plan 2021–2025 incorporating both type 1 and type 2 diabetes.

3.2 Organization of the health system

Many health professionals and people with diabetes stated the initial presentation of type 1 diabetes was Diabetic Ketoacidosis (DKA) thus requiring the health system to be able to address an acute presentation of type 1 diabetes. Follow-up care in the four countries was centralized at major paediatric hospitals, in many cases regardless of age, with some care devolved to regional centres. Tanzania has decentralized care for type 1 diabetes to 33 public sector clinics across the country. Guidelines in Kyrgyzstan and Peru exist only for type 2 diabetes. In Mali and Tanzania, the delivery of care for type 1 diabetes is reliant on external
support for insulin, supplies and consultations, but this is only for children and young adults. Most individuals with type 1 diabetes in these four countries had a consultation once a month, with people facing long waiting times and finding it hard to navigate the system for laboratory tests, accessing medicines, and specialists.

### 3.3 Data collection

National health data systems in the four countries exist, as well as facility and national diabetes registers. However, these did not provide how many people truly have type 1 diabetes, with people with type 2 diabetes using insulin sometimes being defined as having type 1 diabetes. In addition, there is a lack of human and material resources, and time to manage these registers. In Mali a specific database for people with type 1 diabetes has been established with support from a donation program and an international collaboration. The Tanzanian Diabetes Association has established a registry for the centres providing care for children across the country. In both cases, these registers are not integrated into the overall Ministry of Health data collection system with only Kyrgyzstan

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**Table 1 Data on each surveyed country [1; 23; 24]**

|                      | Kyrgyzstan | Mali          | Peru                | Tanzania          |
|----------------------|------------|---------------|---------------------|-------------------|
| **Geographical location** | Central Asia | West Africa | South America | East Africa |
| **World Bank income group [23]** | Lower-middle-income | Low-income | Upper-middle-income | Lower-middle-income |
| **Gross National Income per capita Purchasing Power Parity (current US$) [23]** | 5110 | 2280 | 12,450 | 3140 |
| **Monthly salary of lowest paid government worker (US$)** | 75.9 | 71.9 | 282.9 | 129.0 |
| **Population [23]** | 6,322,800 | 19,077,690 | 31,989,256 | 56,318,348 |
| **Life-expectancy at birth (total years) [23]** | 71.4 | 58.9 | 76.5 | 65.0 |
| **Health expenditure (% of Gross Domestic Product) [23]** | 6.2 | 3.8 | 5.0 | 3.7 |
| **UHC service coverage index** | 70 | 38 | 77 | 43 |
| **Number of people with type 1 diabetes [1] (Number of people with type 1 diabetes estimated from data collected during this study)** | 2910 (2324) | 1550 (628) | 3860 (737) | 10,970 (4000) |
| **Period of data collection** | January to March 2018 | April to July 2018 | February to June 2018 | May to July 2019 |
| **Number of Regions included in the assessment** | 3 (Bishkek, Issy Kul and Osh) | 8 (Bamako, Gao, Kayes, Koulikoro, Mopti, Segou, Sikasso, and Timbuktu) | 1 (Lima) | 1 (Dar es Salaam) |
| **Total number of interviews** | 333 | 362 | 35 | 43 |
| **Macro** | 4 | 10 | 8 | 15 |
| **Meso** | 121 | 83 | 5 | 10 |
| **Micro** | 208 | 269 | 22 | 18 |
having an integrated data system for type 1 diabetes. No such register exists in Peru.

Patient records remained paper based with the challenge of the information not always following the individual throughout the system. Beyond the actual availability of data, there is also an issue of how data were used for monitoring as well as its linkage with quantification of needs for insulin and other supplies.

3.4 | Diagnostic tools and infrastructure

In all countries, issues were raised with fluctuating supplies of consumables for all laboratory tests for measuring blood glucose and HbA1c. This impacted the availability and affordability of reagents and diagnostic tools for the health system as well as for the individual. For example, in Kyrgyzstan glycosylated haemoglobin (HbA1c) tests were only available in the private sector. In Mali and Peru, HbA1c tests were unaffordable to many, even in the public sector where costs were US$12.7 and US$13.5–21.0 respectively, although these were free for people in Peru with insurance.

3.5 | Medicine procurement and supply

Insulin was included in the national essential medicines lists in the four countries, with Kyrgyzstan being the only country with analogue insulin on this list. Kyrgyzstan, Mali and Tanzania had centralized procurement of insulin. In Peru, at the time of data collection, insulin was purchased directly by regions. This changed to centralized procurement in 2020. All countries reported problems with quantification of needs at facilities, and of distribution of insulin within the country. For Mali and Tanzania, donation programs for children and youth complemented the national supply.\(^3\)\(^1\),\(^3\)\(^2\) In all countries except Kyrgyzstan, insulin was available in private pharmacies. Insulin was available at both hospitals and PHC in Kyrgyzstan, Mali and Tanzania, but only in hospitals in Peru.

3.6 | Availability and affordability of insulin and blood glucose meters

Figure 1 describes the availability of insulin, insulin syringes, blood glucose meters (BGM) and test strips. Insulin was available in 100% of facilities only in Kyrgyzstan. Syringes were only available in Mali in the private sector and Peru in the public sector where they are widely available.

There was no availability of BGMs and strips in the public sectors in Kyrgyzstan and Peru. In Mali, public sector availability was lower than in the private sector for BGMs, whereas in Tanzania it was the opposite. For BGMs, the Kyrgyz health system does not supply these, but as of 2012 the cost of 200 strips per year was covered by health insurance. However, uptake of this scheme was low as prescriptions needed to be provided by family

![Figure 1](image-url)
doctors whereas most people with type 1 diabetes are cared for by specialists and many people are not able to afford the meter or were unaware of this scheme. Access in Peru to BGMs and strips was limited to minors receiving medical attention at the National Institute of Children’s Health in the capital city. Both Mali and Tanzania benefit from donations of insulin, syringes, BGMs and strips.

Table 2 presents the minimum and maximum costs for different elements of diabetes care. The average lowest-paid unskilled government worker would need to spend from 4 days’ wages in Peru to a full month’s salary in Mali to pay for a month’s diabetes care (Table 2).

### 3.7 Healthcare workers

Management of type 1 diabetes is entrusted to specialists mainly at hospitals in main urban areas. Because of a lack of training, family doctors did not manage this condition. In some specialist diabetes clinics, nurses and other staff were involved in aspects of management and care including counselling and patient education. However, in all four countries, there was a lack of truly interdisciplinary teams for the management of type 1 diabetes. Although additional trainings may exist through a variety of projects and programs these mainly focused on type 2 diabetes.

### 3.8 Patient education and empowerment

Diabetes education in Kyrgyzstan, Mali, Peru and Tanzania is delivered by both doctors and specialized nurses, and in Peru by nutritionists as well, but due to workloads the time spent on this is often insufficient. Both Kyrgyzstan and Peru have specific education and support for type 1 diabetes that is delivered only at tertiary-level facilities. Interviewees in both countries considered this insufficient, and ill-adapted to the needs of people with type 1 diabetes. In contrast, in Mali and Tanzania specific tools and approaches have been developed through support from insulin donation programs as well as the work of the NGO Santé Diabète in Mali and the Tanzanian Diabetes Association. From the individual’s perspective much of the education and support received seemed more adapted to type 2 diabetes, focused on nutrition and physical activity, and not covering the specificities of type 1 diabetes.

### 3.9 Adherence issues

Other barriers to care included socio-economic and geographical (urban vs. rural) factors, as well as other issues

| Country | Minimum | Maximum |
|---------|---------|---------|
| Kyrgyzstan | $0.0 | $189.6 |
| Mali | $0.0 | $120.0 |
| Peru | $0.0 | $41.6 |
| Tanzania | $0.0 | $172.6 |

**Table 2** Annual costs of different components of diabetes care in Kyrgyzstan, Mali, Peru and Tanzania

- **Insulin**
  - Kyrgyzstan: $0.0 - $189.6
  - Mali: $0.0 - $120.0
  - Peru: $0.0 - $41.6
  - Tanzania: $0.0 - $172.6
- **Syringes**
  - Kyrgyzstan: $0.0 - $36.5
  - Mali: $0.0 - $73.0
  - Peru: $0.0 - $43.8
  - Tanzania: $0.0 - $82.2
- **BGM**
  - Kyrgyzstan: $0.0 - $16.0
  - Mali: $0.0 - $26.6
  - Peru: $0.0 - $25.1
  - Tanzania: $0.0 - $10.7
- **Strips**
  - Kyrgyzstan: $0.0 - $233.6
  - Mali: $0.0 - $341.6
  - Peru: $0.0 - $666.2
  - Tanzania: $0.0 - $666.2
- **Consultation fee**
  - Kyrgyzstan: $0.0 - $21.5
  - Mali: $0.0 - $84.0
  - Peru: $0.0 - $44.1
  - Tanzania: $0.0 - $25.1
- **HbA1c**
  - Kyrgyzstan: $0.0 - $37.6
  - Mali: $0.0 - $50.8
  - Peru: $0.0 - $54.0
  - Tanzania: $0.0 - $52.7
- **Transportation costs**
  - Kyrgyzstan: $0.0 - $1.0
  - Mali: $0.0 - $14.4
  - Peru: $0.0 - $5.6
  - Tanzania: $0.0 - $11.3
- **Total**
  - Kyrgyzstan: $324.7 - $774.3
  - Mali: $706.8 - $1277.1
  - Peru: $424.2 - $891.5
  - Tanzania: $821.2 - $1981.0

**Note:** Assuming 2 vials of insulin per month; 1 syringe per day; cost of BGM amortized over 2 years; 2 blood glucose tests per day; 1 consultation every 3 months; 1 HbA1c test every 3 months; Travel for 1 consultation every 3 months.
related to inequity between certain populations. In Peru, interviews brought to light the complexities of managing care by an individual and their family, especially for individuals with “low” education levels and low economic resources. Diet was also reported in Kyrgyzstan as a barrier to adherence with lower educated and lower socioeconomic families having challenges affording what was seen as an “appropriate diabetes diet.” The use of traditional medicine and “supplements” in Kyrgyzstan was also a possible barrier to adherence with contrasting and contradicting recommendations compared to what allopathic providers advise. In Mali, access to appropriate education materials and the cost of treatment were mentioned by individuals with diabetes as the main barriers to adherence. In Tanzania, the main barrier mentioned for adherence was access to strips for BGMs. As presented in Table 2, the overall cost of care was also an important barrier to adherence.

3.10 | Community involvement and diabetes associations

The activities of the diabetes associations in the four countries included: education (all); advocacy (all); distribution of medicines and supplies to those in need (Kyrgyzstan and Peru); and awareness raising (Mali and Tanzania). In Kyrgyzstan and Peru, the associations are dedicated specifically to type 1 diabetes. In Mali and Tanzania, the associations had more of a focus on type 2 diabetes, although a specific youth group for type 1 diabetes existed in Tanzania. The activities of the associations in Kyrgyzstan and Peru were more concentrated in the capital cities, versus more national representation and activities by the associations in Mali and Tanzania. In Peru, different hospitals had their own associations with very little collaboration between them, whereas in Mali and Tanzania, national associations were present with different branches throughout the country.

Table 3 presents a summary of the findings of these 11 themes and links them to the WHO health system building blocks. Table 3 shows a wide range of challenges, with some of these cross-cutting, e.g. financing and leadership and governance, whereas others are more context specific, e.g. service delivery and access to medicines and diagnostic tools.

4 | DISCUSSION

Very few studies have compared health system responses for type 1 diabetes in LMICs. From a policy perspective, the inclusion of diabetes-related supplies in the UHC package as well as NCD and diabetes policies was positive, but this has not necessarily translated into improved availability and affordability of insulin and supplies and improved care for type 1 diabetes. For example, Peru included insulin in its benefit package, but this is not readily available in the public sector. The same is true in Tanzania for syringes. Kyrgyzstan was the only country to have 100% availability of insulin in the public sector. However, no syringes were available in the public sector and only 30% of private pharmacies highlighting the challenge of the overall availability and affordability of the full package of tools needed for the management of type 1 diabetes. Test strips and insulin respectively represent 48–82% and 25–36% of total costs, with such costs consuming a substantial proportion of the income for individuals in these countries. Beyond access to these supplies, type 1 diabetes is a complex chronic condition and management requires access to specialist care. In the four countries care remains centralized at tertiary facilities, except in Tanzania where some decentralization has occurred. To date national responses are focused primarily on children and youth and not all people with type 1 diabetes both for delivery of care and donations. Only Kyrgyzstan had a data collection system for type 1 diabetes integrated into the Ministry of Health. All these factors in combination with issues of lack of healthcare worker training and inadequate education and empowerment, result in poor adherence. Although diabetes associations were present in all four countries, their focus is more on type 2 diabetes with their leadership being healthcare professionals versus people with diabetes. Furthermore, these associations are often only located in the capital city and played more of a role in delivery of care and education than in advocating for access to insulin and care.

The Rapid Assessment Protocol for Insulin Access has been applied in several countries to provide much-needed data to inform improvements in delivery and availability of diabetes care. In each country the sample of interviewees is not representative, but the mix of perspectives, combined with a document review and site visits, allows for a comprehensive view of the challenges. Such purposive sampling is a method commonly used in health services research, and to some degree limits comparability between countries because of potential biases of sampling and interviewer characteristics. Although in Mali and Kyrgyzstan the studies were carried out nationally versus Peru and Tanzania only in capital cities, due to the centralization of care for type 1 diabetes in all countries the depth of information from the four contexts despite differences in numbers of interviews can be seen as comparable.
| Health system element | Kyrgyzstan | Mali | Peru | Tanzania |
|-----------------------|------------|------|------|----------|
| Positive policy environment | UHC package includes free provision of insulin and other diabetes supplies and overall coverage | National policies include diabetes in all countries, but the focus is primarily on Type 2 diabetes, especially in Peru | Care for Type 1 diabetes mainly centralized; PHC not equipped to manage Type 1 diabetes | Dependent on donations and some decentralization of Type 1 diabetes care |
| Organization of the health system | Care for Type 1 diabetes mainly centralized; PHC not equipped to manage Type 1 diabetes | Guidelines only for Type 2 diabetes | Guidelines only for Type 2 diabetes | Guidelines only for Type 2 diabetes |
| Data collection system | Data collection system for Type 1 diabetes integrated into the Ministry of Health | Specific database for Type 1 diabetes | Specific database for Type 1 diabetes | Specific database for Type 1 diabetes |
| Diagnostic tools and infrastructure | Human insulin included in national Essential Medicine List, but problems with quantification of needs and distribution of insulin within the country | insulin is not included in national Essential Medicine List, but available at PHC for children and youth | insulin is only available at PHC hospitals | insulin is only available at PHC hospitals |
| Medicine procurement and supply | Central procurement; donations of insulin for children and youth | Central procurement; donations of insulin for children and youth | Central procurement; donations of insulin for children and youth | Central procurement; donations of insulin for children and youth |
| Availability and affordability of medicines and care | Relatively poor availability of insulin in the public sector; no availability of BGMs in public sector | insulin available in both public and private sectors; availability of BGMs and high cost of these tools | 94% availability of insulin in the public sector; no availability of BGMs in public sector | 100% availability of insulin in the public sector; no availability of BGMs in public sector |
| Healthcare workers | Specific tools developed; involvement of the Tanzanian Diabetes Youth Alliance | Specific tools developed | Specific tools developed | Specific tools developed |
| Patient education and empowerment | Specific education and support for type 1 diabetes that is delivered only at tertiary-level facilities | Specific education and support for type 1 diabetes that is delivered only at tertiary-level facilities | Specific education and support for type 1 diabetes that is delivered only at tertiary-level facilities | Specific education and support for type 1 diabetes that is delivered only at tertiary-level facilities |
| Adherence issues | Overall socio-economic situation and barriers to care; inappropriate approaches to patient education | Specific diabetes association association mainly focuses on Type 2 diabetes; mainly in capital city | Specific diabetes association association mainly focuses on Type 2 diabetes; mainly in capital city | Specific diabetes association association mainly focuses on Type 2 diabetes; mainly in capital city |
| Community involvement and diabetes associations | Diabetes association mainly focuses on Type 2 diabetes; mainly in capital city | Specific diabetes association for Type 1 diabetes; mainly in capital city | Specific diabetes association for Type 1 diabetes; mainly in capital city | Specific diabetes association for Type 1 diabetes; mainly in capital city |
| Financial sustainability | Diabetes association mainly focuses on Type 2 diabetes; mainly in capital city | Diabetes association mainly focuses on Type 2 diabetes; mainly in capital city | Diabetes association mainly focuses on Type 2 diabetes; mainly in capital city | Diabetes association mainly focuses on Type 2 diabetes; mainly in capital city |
Work in Rwanda and Mali has shown improving survival rates through insulin donation programs. In Tanzania and Cameroon, where donated insulin and supplies are available, poor glucose control and high levels of complications despite the relatively short duration of their type 1 diabetes have been found as well as high rates of mortality, especially in rural areas. Thus, type 1 diabetes presents a unique challenge to health systems in LMICs as it requires constant access to insulin as well as a comprehensive health system response. The challenge is how to address a low burden, but highly complex condition when the global NCD and diabetes agenda is pushing for decentralization of care to PHC and prevention. In the 1920s the introduction of insulin allowed for the development of specialized diabetes care with insulin being the foundational tool for which all other elements were built on. Beyond insulin there are a wide range of needs for people with type 1 diabetes and a hierarchical approach could serve as a framework on which to build diabetes services in LMICs and move towards UHC. However, implementation of social insurance schemes with the target of UHC has failed to reach the poorest and most vulnerable populations in LMICs. Specifically for type 1 diabetes, a study by Klatman et al. found that UHC is far from a reality in LMICs and that different countries are at different levels of progress. Thus, a first step to move towards UHC and improved diabetes management would be to ensure access to insulin, other diabetes-related supplies, improving the training of health professionals and models of delivery of care with the ultimate goal as proposed by Feudtner of addressing the “the hopes and therapeutic aspirations of patients and families” through individualized care.

The renewed attention to diabetes on the global health agenda with the launch of the Global Diabetes Compact and the World Health Assembly Resolution, “Reducing the burden of noncommunicable diseases through strengthening prevention and control of diabetes” came about due to the policy window of the centenary of insulin’s discovery. This policy window should the opportunity to not only address the glaring inequity of global access to insulin, but also develop approaches and solutions to ensure access to all necessary supplies and health system resources for people with diabetes as well as an enabling environment.

**AUTHORS’ CONTRIBUTIONS**

Author contributions DB designed the study with the support of AA, SB, JP, KR, AD, MLP, HN, JTM and JZT. DB, ME, RL and ML were responsible for obtaining funding and overall supervision of the project. HH and ASw provided in-depth technical support for the work in Tanzania, AS in Mali and AZ in Kyrgyzstan. JY was instrumental in the development of the initial methodology. DB together with AA, SB, JP, KR, AD, MLP, HN, JTM and JZT analysed the data. DB drafted the initial manuscript with input from all co-authors. All authors approved the final version of the article.

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**CONFLICT OF INTEREST**

All authors declare having no conflicts of interest with regards to this publication.

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