Availability and affordability of essential medicines and diagnostic tests for diabetes mellitus in sub-Saharan Africa: A systematic review.

CURRENT STATUS: UNDER REVIEW

BMC Health Services Research  BMC Series

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DOI:
10.21203/rs.3.rs-16103/v1

SUBJECT AREAS
Health Economics & Outcomes Research  Health Policy

KEYWORDS
Availability, affordability, essential medicines, diagnostic tests, diabetes mellitus, Sub-Saharan Africa
Abstract

Background Currently, sub-Saharan Africa (SSA) is experiencing a steady increase in the prevalence of diabetes mellitus (DM) coupled with a prevailing high burden of communicable diseases. To effectively address this burgeoning burden of DM, optimal access to affordable essential medicines and diagnostic tests for DM in healthcare systems should be prioritised. We conducted a systematic review of the evidence on the availability and affordability of essential medicines and diagnostic tests for DM in SSA as recommended by the World Health Organization Package of Essential Non-communicable Disease Interventions for Primary Health Care in Low-Resource Settings.

Methods PubMed, Science Direct and African Journals Online databases were searched for original research articles conducted in sub-Saharan Africa and published between 2000 and 2018 reporting availability and affordability of essential medicines and diagnostic tests for diabetes mellitus.

Results Twenty one original cross-sectional studies were included in the systematic review, with the majority conducted in Eastern Africa (n=11, 58%). The availability of essential medicines and diagnostic tests was largely sub-optimal. For oral hypoglycaemic agents and insulin, angiotensin-converting-enzyme inhibitors, statins and aspirin, availability ranged from 0-100%, 0-96.5%, 0-84% and 53%-100% respectively. Considering diagnostic tests, availability of blood glucose tests, urine protein and ketone tests, serum creatinine tests, lipid profile tests and electrocardiography ranged from 6-100%, 33.3-100%, 0-86.4%, 0-65.9% and 5.7-54.6% respectively. The lowest priced generic (LPG) glibenclamide, metformin and aspirin cost <1.2 days’ wages. However, the cost of LPG insulin (any type), captopril and simvastatin ranged from 3.85-18.7 days’ wages, 1.2-6.41 days’ wages and 6.5-30 days’ wages respectively. Blood glucose tests, urine protein and ketone tests and serum creatinine tests cost <3.3 days’ wages.
Conclusions Optimal access to affordable essential medicines and diagnostic tests for DM remains a significant challenge in SSA. This represents a significant barrier towards the attainment of sustainable development goals and universal health coverage. Pragmatic region-specific solutions are urgently needed to address this challenge.

Background

Sub-Saharan Africa (SSA) is currently experiencing a rapidly increasing burden of non-communicable diseases (NCD) such as diabetes mellitus (DM) coupled with a high burden of communicable diseases such as HIV and tuberculosis [1, 2]. This high dual burden of NCD and communicable diseases poses a significant economic strain on the poorly structured healthcare systems and meagre health resources.

According to the 2019 International Diabetes Federation (IDF) estimates, Africa has about 19 million adults living with DM. This translates to a regional prevalence of 3.9%. The region has the highest proportion of people with undiagnosed DM (60%) and it is estimated to have the greatest future increase in the burden of diabetes (about 47 million adults with diabetes in 2045 which is a 143% increase) [3].

Despite this projected significant increase in the regional burden of DM, SSA still faces an insurmountable challenge of equitable access to affordable essential medicines and diagnostic tests for DM in healthcare systems [4]. In September 2011, the United Nations General Assembly high-level meeting recognized the magnitude of the NCD epidemic globally and its threat to national economic development. One of its commitments was to improve access to medicines to treat NCD (DM inclusive) [5].

Optimal availability of affordable essential medicines and diagnostic tests for NCD in healthcare systems is fundamental in addressing the growing burden of NCD, DM inclusive. As part of its 2013–2020 Global Action Plan (GAP) for prevention and control of NCD, the WHO included a target of ≥ 80% availability of affordable essential medicines
and basic technologies required to treat major NCD [6].

There is need for contemporary evidence on the extent of availability and affordability of essential medicines and diagnostic tests integral in the management of DM in SSA. These findings will help inform appropriate intervention strategies to address the challenge of inequitable access.

To-date, no systematic review has been published on availability and affordability of essential medicines and diagnostic tests for DM in SSA. This systematic review collated data from original research studies that investigated the availability and affordability of essential medicines and diagnostic tests for DM in SSA, as recommended by the WHO Package of Essential Non-communicable Disease Interventions for Primary Health Care in Low-Resource Settings (WHO-PEN) [7].

Methods

Search strategy and study selection

The systematic review was first registered in PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD42018093455). After registration, a literature search of PubMed, Science Direct (Elsevier) and African Journals Online databases for original research articles published between 2000 and 2018 was performed. The references of the selected research articles and published review articles were also searched for additional original studies to include in the systematic review.

The search terms used were: “Access OR availability OR pricing OR cost OR affordability AND “essential medicines” OR medicines OR drugs OR therapies AND tests OR “laboratory tests” OR diagnostic OR “point of care” AND “diabetes mellitus” OR diabetes OR “type 2 diabetes” OR “type 1 diabetes” AND Africa OR “Sub-Saharan Africa”.

Only original research articles with information about availability and affordability of
essential medicines and diagnostic tests for DM, conducted in any sub-Saharan African
country and published between 2000 and 2018 were included in the systematic review. We
excluded published review articles, original research articles whose full texts were not
accessible and those published research articles published in languages other than
English.

Essential medicines and diagnostic tests of interest were those recommended in the
management of DM by the WHO Package of Essential Non-communicable Disease
Interventions for Primary Health Care in Low-Resource Settings (WHO-PEN) [7]
(summarised in Table 1). Despite the exclusion of glycated haemoglobin (HbA1c) and
serum ketone tests in the WHO-PEN, we also obtained information from the studies about
their availability and affordability because of their relevance in optimal diabetes care in
clinical practice.

Table 1
Package of Essential Non-communicable disease (PEN) disease interventions for primary healthcare in low resource
settings: Essential medicines and diagnostic tools for diabetes.

| Essential medicines | Type 1 diabetes mellitus | Type 2 diabetes mellitus |
|---------------------|--------------------------|--------------------------|
| All types of insulin | Oral hypoglycaemic agents. | Medicines with a role of reducing cardiovascular risk in patients with diabetes and 10 year cardiovascular risk > 20%. |
| -Aspirin | -Angiotensin converting enzyme inhibitors (ACEI). | -Statins. |

| Essential diagnostic tools | -Glucometers. | -Glucose strips. |
|-----------------------------|---------------|------------------|
| -Urine protein test strips. | -Urine ketone strips. When resources permit. |
| -Lipid profile. | -Serum creatinine. |
| -Serum troponin. | -Urine microalbuminuria. |
| -Electrocardiography (ECG). | |

We obtained the information on study country, study period, type and number of health
facilities surveyed, type of essential medicine and diagnostic test studied and estimates of
availability and affordability as reported in the original studies involving primary data
collection. In all these studies, availability was defined as the proportion of health
facilities where the essential medicine(s) and diagnostic test(s) of interest was found present at the time of primary data collection in the study. Affordability was defined as the estimated total number of days’ wages the lowest-paid government worker would be required to pay to purchase a full monthly standard dose of the medicine or to pay for the diagnostic test as recommended by the WHO and Health Action International (HAI). We considered the availability of any essential medicine or diagnostic test of ≥ 80% as optimal, as recommended by the WHO GAP for prevention and control of NCD [6]. We did not define optimal affordability because no internationally recognised definition exists.

The titles and abstracts of all identified studies were initially assessed for eligibility. Two independent reviewers (DK and RES) screened full texts of all initially selected research articles for information of interest. In cases of disagreements in the selection of the eligible studies, a third reviewer (DA) offered an independent additional opinion. The studies that met the inclusion criteria following mutual agreement of all the reviewers were then exported to Endnote citation software.

Using a pre-tested data extraction form, six extra co-authors (IS, DA, DK2, JM, JIS and MJN) independently reviewed these selected eligible original research articles for key information about author and year of publication of the study, period when study was conducted, study setting, essential medicine and diagnostic test studied and study findings about availability and affordability.

Assessment of methodological quality, bias and data extraction process

The methodological quality of the identified studies was assessed by three independent reviewers (DK, RES and DA) using the adapted Newcastle-Ottawa Scale (NOS). A maximum score of 8 was considered for the selected cross-sectional studies (Table 3) [8]. The quality assessment tool for observational cohort and cross-sectional studies published by the National Heart, Lung and Blood Institute was used to evaluate the risk of bias of
cohort and cross-sectional studies (Table 4) [9]. The PRISMA guidelines for the reporting of systematic reviews and meta-analysis were followed (Table 5) [10]. The studies were rated as either having a low, moderate or high risk of bias. Rating of studies was independently performed by two reviewers (DK and RES) and inconsistencies were resolved by consulting a third reviewer (DA).

Table 3
Criteria for the adapted Newcastle-Ottawa Scale regarding star allocation to assess quality of studies

| Study details | Selection | Comparability | Outcome |
|---------------|-----------|---------------|---------|
|               | Representativeness of sample (••) | Non-respondents (•) | Ascertainment of exposure (•) | Assessment of outcome (•) | Statistical test (•) | Total (8*) |
| 1. Kibirige D et al, 2017 | • | - | • | - | • | 5 |
| 2. Musinguzi G et al, 2015 | • | - | • | - | • | 5 |
| 3. Bekele A et al, 2017 | • | - | • | - | • | 4 |
| 4. Carlson S et al, 2017 | • | - | • | - | • | 4 |
| 5. Armstrong-Hough M et al, 2018 | • | - | • | - | • | 5 |
| 6. Bintabara D et al, 2018 | • | - | • | - | • | 5 |
| 7. Katende D et al, 2015 | • | - | • | - | • | 4 |
| 8. Peck R et al, 2014 | • | - | • | - | • | 4 |
| 9. Getachew T et al, 2017 | • | - | • | - | • | 4 |
| 10. Rogers HE et al, 2018 | • | - | • | - | • | 4 |
| 11. Whyte SR et al, 2015 | • | - | • | - | • | 3 |
| 12. Beran D et al, 2005 | • | - | • | - | • | 3 |
| 13. Mendis S et al, 2007 | • | - | • | - | • | 3 |
| 14. Kalungia CA et al, 2017 | • | - | • | - | • | 3 |
| 15. Mhlanga B et al, 2014 | • | - | • | - | • | 3 |
| 16. Chikowe I et al | • | - | • | - | • | 3 |
|                  | Kibirige D et al. 2017 | Musinguzi G et al. 2015 | Bekele A et al. 2017 | Carlson S et al. 2017 | Armstrong-Hough M et al. 2018 | Bintabara D et al. 2018 | Katende D et al. 2015 | Peck R et al. 2014 | Getache T et al. 2017 | Rogers HE et al. 2018 | Whyte SR et al. 2015 |
|------------------|------------------------|-------------------------|---------------------|----------------------|-----------------------------|------------------------|---------------------|---------------------|----------------------|----------------------|----------------------|
| 1. Was the research question or objective in this paper clearly stated? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 2. Was the study population clearly specified and defined? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 3. Was the participation rate of eligible persons at least 50%? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

Table 4
The National Heart, Lung and Blood Institute Quality Assessment Tool to evaluate the risk of bias of cohort and cross-sectional studies
| Inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants? | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | No |
| For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? | No | No | No | No | No | No | No | No | No | No | No |
| Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? | No | No | No | No | No | No | No | No | No | No | No |
| For exposures that can | No | No | No | No | No | No | No | No | No | No | No |
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?  
   | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

10. Was the exposure(s) assessed more than once over time?  
    | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |

11. Were the outcome measures (dependent variables) clearly defined, valid, reliable?  
    | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Question                                                                 | Study 1 | Study 2 | Study 3 | Study 4 | Study 5 | Study 6 | Study 7 | Study 8 | Study 9 | Study 10 |
|--------------------------------------------------------------------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|----------|
| 1. Was the research question or objective in this paper clearly stated?  | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes      |
| 2. Was the study population reliable, and implemented consistently across all study participants? | No      | No      | No      | No      | No      | No      | No      | No      | No      | No       |
| 12. Were the outcome assessors blinded to the exposure status of participants? | No      | No      | No      | No      | No      | No      | No      | No      | No      | No       |
| 13. Was loss to follow-up after baseline 20% or less?                    | NA      | NA      | NA      | NA      | NA      | NA      | NA      | NA      | NA      | NA       |
| 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? | NA      | NA      | NA      | NA      | NA      | NA      | NA      | NA      | NA      | NA       |
| Authors                                                                  | Beran D et al, 2005 | Mendis S et al, 2007 | Kalungia CA et al, 2017 | Mhlanga B et al, 2014 | Chikowe I et al, 2018 | Jingi A et al, 2014 | Nyarko KM et al, 2016 | Okpetu EI et al, 2018 | Cameron A et al, 2009 | Mendis S et al, 2012 |

Beran D et al, 2005
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Kalungia CA et al, 2017
Mhlanga B et al, 2014
Chikowe I et al, 2018
Jingi A et al, 2014
Nyarko KM et al, 2016
Okpetu EI et al, 2018
Cameron A et al, 2009
Mendis S et al, 2012
| Question                                                                 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
|------------------------------------------------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 1. Is the outcome clearly specified and defined?                       |     |     |     |     |     |     |     |     |     |     |
| 2. Were the participation rate of eligible persons at least 50%?       | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 3. Was the participation rate of eligible persons at least 50%?       | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 5. Was a sample size justification, power description, or variance and effect estimates provided? | No  | No  | No  | No  | No  | Yes | No  | No  | No  | No  |
| 6. For the analyses in this paper, were the exposure(s) of interest measured? | No  | No  | No  | No  | No  | No  | No  | No  | No  | No  |
| Question                                                                 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
|------------------------------------------------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? | No  | No  | No  | No  | No  | No  | No  | No  | No  | No  | No  |
| 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? | No  | No  | No  | No  | No  | No  | No  | No  | No  | No  | No  |
| 9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Question | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|----------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|
| 1. Was the exposure(s) assessed more than once over time? | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| 2. Were the outcome measures (dependent variable(s)) clearly defined, valid, reliable, and implemented consistently across all study participants? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 3. Were the outcome assessors blinded to the exposure status of participants? | No | No | No | No | No | No | No | No | No | No | No | No | No |
| 4. Was loss to follow-up after baseline 20% or less? | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| 5. Were key potential confounding variables measured and implemented consistently across all study participants? | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
and statistically for their impact on the relationship between exposure(s) and outcome(s)?

Table 5
PRISMA CHECKLIST FOR THE SYSTEMATIC REVIEW.

| #  | Checklist item                                                                 | Reported on page # |
|----|---------------------------------------------------------------------------------|--------------------|
| TITLE |                                                                                |                    |
| Title | Identify the report as a systematic review, meta-analysis, or both. | 1                  |
| ABSTRACT |                                                                                      |                    |
| Structured summary | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 3–4               |
| INTRODUCTION |                                                                                |                    |
| Rationale | Describe the rationale for the review in the context of what is already known.                   | 5                  |
| Objectives | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 6                  |
| METHODS |                                                                                |                    |
| Protocol and registration | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 6                  |
| Eligibility criteria | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 6–7               |
| Information sources | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify | 6                  |
| Section/topic | Checklist item | Reported on page |
|---------------|----------------|------------------|
| Search        | 8              | 6               |
| Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. |
| Study selection | 9              | 6-7             |
| State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). |
| Data collection process | 10             | 7-8             |
| Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. |
| Data items    | 11             | 7               |
| List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. |
| Risk of bias in individual studies | 12             | 8               |
| Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. |
| Summary measures | 13            | NA              |
| State the principal summary measures (e.g., risk ratio, difference in means). |
| Synthesis of results | 14            | NA              |
| Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis. |
| Risk of bias across studies | 15            | 35 (Attached as a separate file) |
| Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). |
| Additional analyses | 16            | NA              |
| Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. |
| RESULTS       |                |                 |
| Study selection | 17            | 8-9             |
| Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. |
| Study characteristics | 18          | 9               |
| For each study, present characteristics for which data were extracted. |
### Results

The search yielded a total of 5,487 published articles. Eighty-five duplicates were identified and removed. Of the remaining 5,402 articles, a total of 12 articles that were
editorials, review articles, systematic reviews, study protocols and a study published in French were excluded leaving 5,390 articles whose titles and abstracts were screened. Of these, 5,329 articles were excluded leaving 61 articles whose full texts were extracted and assessed for eligibility. Only 21 original research articles met the inclusion criteria described above and were included in the final systematic review [11–31] (Fig. 1).

**Study Characteristics, Methodological Quality And Risk Of Bias**

All selected studies were cross-sectional in design. There was an observed heterogeneity of the study findings. Among the 19 studies conducted in one region of SSA, the majority were from the Eastern region \( n = 11, 58\% \) [11–21]. About 26\% \( n = 5 \) [22–26]and 16\% \( n = 3 \) [27–29] of the remaining studies were conducted in the Southern and Western region respectively. Two studies were conducted in more than one region of SSA [30, 31].

According to the quality assessment tool for observational cohort and cross sectional studies, all the original cross-sectional studies included in the systematic review were considered as having a low risk of bias (Tables 4). The majority of the studies had low methodological quality (Table 3).

**Availability Of Essential Medicines For Dm**

The availability of the different essential medicines for DM as recommended by the WHO PEN are shown in Table 2.

| Study, year and reference | Country (ies) where study was done and study period | No. of health facilities surveyed | Number of essential medicines and diagnostic tests studied | Key study findings |
|--------------------------|--------------------------------------------------|---------------------------------|----------------------------------------------------------|-------------------|
| A: Eastern region        |                                                  |                                 |                                                          |                   |
| 1. Kibirige D et al, 2017 | Uganda, 15th January 2017 to 28th February 2017 | 22 public hospitals, 23 private hospitals and 100 privately owned pharmacies. | Insulin (Short-acting, Intermediate-acting and Pre-mixed). OHA (Glibenclamide, Glimepiride and Metformin) ACEI (Captopril) | Availability of medicines - Intermediate-acting insulin-34.7%
- Pre-mixed insulin-60.1%
- Short-acting insulin-68.8%
- Statins-84% |

Table 2

Availability and affordability of essential medicines and diagnostic tests for diabetes in Sub-Saharan Africa.
- ACEI (Captopril)
- Aspirin
- Statins (Simvastatin, Atorvastatin and Rosuvastatin)

Diagnostic tests
- Glucometers
- Serum creatinine
- Lipid profile
- Microalbuminuria tests.
- Serum troponin
- Urine protein and ketone testing strips
- ECG
- HbA1c
- Serum ketone tests

- Aspirin-95.1%
- ACEI-96.5%
- Any OHA present-100%.

Availability of diagnostic tests
- Microalbuminuria tests-6.8%
- Serum ketones-11.4%
- Serum troponin-43.2%
- HbA1c tests-43.2%
- ECG-54.6%
- Lipid profile-65.9%
- Serum creatinine-86.4%
- Glucometers-97.7%
- Urine protein and ketone testing strips-100%

Affordability of essential medicines
- Short-acting insulin-4.7 days’ wages
- Intermediate-acting insulin-4.9 days’ wages
- Pré-mixed insulin-4.9 days’ wages.
- Metformin 500 mg-2.8 days’ wages.
- Glibenclamide 5 mg-0.7 days’ wages.
- Glimepiride 2 mg-3.2 days’ wages.
- Aspirin-0.9 days’ wages.
- Captopril-2.8 days’ wages.
- Simvastatin-6.5 days’ wages.
- Atorvastatin 20 mg-7.6 days’ wages.
- Rosuvastatin 10 mg-7.6 days’ wages.

Affordability of diagnostic tests
- Blood glucose testing-1.1 days’ wages.
- Urine protein and ketone testing — 1.3 days’ wages.
- Serum ketones testing-2.1 days’ wages.
- Serum creatinine-2.4 days’ wages.
- Lipid profile-7.5 days’ wages.
- HbA1c-8.6 days’ wages.
- Microalbuminuria-9.6 days’ wages.
- ECG-10.7 days’ wages.
- Serum troponin-11.3 days’ wages.

2. Musinguzi G et al, 2015[11].

-Uganda.
-June to October 2012.
-126 health facilities (74 public and 52 private)

ACEI.

Availability of any of the essential medicines
- ACEIs-93.2%
| Study                                    | Location & Time                | Facilities | Medications                           | Availability of Essential Medicines | Availability of Diagnostic Tests |
|-----------------------------------------|--------------------------------|------------|---------------------------------------|-------------------------------------|----------------------------------|
| 3. Bekele A et al, 2017¹²               | Ethiopia. March to July 2014   | 873        | Insulin (type not specified), Glibenclamide, Glucometers, Urine protein and ketone testing strips. | Insulin: 9%. Glibenclamide: 28%. |                                  |
| 4. Carlson S et al, 2017¹³             | Uganda and Kenya. 2011 and 2012 | 340        | ACEI (Captopril or lisinopril), ECG. | ACEI (captopril or lisinopril): 45.6%. | ECG: 9.1%.                       |
| 5. Armstrong-Hough M et al, 2018¹⁴     | Uganda. 2013                   | 196        | Short-acting insulin, Metformin, Glibenclamide, Statins (simvastatin), Any ACEI |                                  |                                  |
| 6. Bintabara D et al, 2018              | Tanzania. 2014-2015            | 725        | Any ACEI.                            | ACEI: 21%.                          |                                  |
| 7. Katende D et al, 2015                | Uganda. November 2012-April 2013 | 28         | Metformin. Glucometers               | Metformin: 17.9%. Glucometers: 32%. |                                  |
| 8. Peck R et al, 2014                   | Tanzania. November 2012-May 2013 | 24         | Metformin. Glucometers.              |                                  |                                  |
| 9. Getachew T et al, 2017               | Ethiopia. 2016                 | 547        | Glicazide or Glipizide, Insulin (any type), Glibenclamide, Metformin, ACEI, Aspirin, Glucometers, Urine protein and ketone testing strips. | Glicazide or Glipizide: 4%. Metformin: 31%. |                                  |
| 10. Rogers HE et al, 2018               | Uganda. 2013                   | 53         | Metformin, Any sulphonylurea, Insulin (Ultra short-acting, short-acting, intermediate-acting and long-acting). Any ACEI, Glucometers, ECG, Serum creatinine. | Metformin: 52.8%. |                                  |
| 11. Whyte SR et al, 2015. | Uganda. November 2011 and February 2012 |
|--------------------------|----------------------------------------|
| 6 health facilities (83.3% were public) | |  |
| 
| 12. Beran D et al, 2005 | Mozambique and Zambia. April and May 2003 in Mozambique and Sept and October 2003 in Zambia. |
| 5 hospitals and 6 lower tier health centres in Mozambique. 13 hospitals and unspecified number of referral health centres in Zambia. | Insulin (pre-mixed, short-acting and intermediate-acting insulin). Glucometers. |
| | | |
| 13. Mendis S et al, 2007 | Malawi — 2005 |
| 20 public and 16 private health sector facilities. | Insulin (3 types) Glibenclamide Metformin ACEI (captopril and enalapril). Lovastatin (statin) | |
| Study (Year) | Country | Period | Setting | Medicines | Availability | Affordability |
|-------------|---------|--------|---------|-----------|--------------|---------------|
| 14. Kaluniga CA et al, 2017 | Zambia | January to June 2016 | 15 public health facilities | Insulin (short-acting and long-acting), Glibenclamide, Metformin | Availability of the essential medicines: Short-acting insulin: 22.2%, Long-acting or intermediate-acting insulin: 37.8%, Metformin: 51.1%, Glibenclamide: 51.1% | 19.6 days’ wages. Monotherapy with LPG oral captopril and enalapril (ACEI or ARB) cost < 1 day’s wages. |
| 15. Mhlanga B et al, 2014 | Swaziland | December 2012-January 2013 | 10 public facilities and 10 private retail pharmacies | Glibenclamide, Metformin, ACEI (Captopril and Enalapril) | Availability of the essential medicines: Glibenclamide: 90%, Metformin: 100%, Captopril: 90%. Affordability of the essential medicines: The lowest priced generic Metformin, Glibenclamide and Captopril: 1.2 days’ wages. | |
| 16. Chikowe I et al, 2018 | Malawi | November to December 2016 | 55 health facilities (76.4%-public facilities) | Insulin (type not specified), Glibenclamide, Metformin, Glucometers. | Availability of the essential medicines: Insulin: 1.8%, Glibenclamide: 9.1%, Metformin: 14.5%. Availability of the diagnostic tests: Glucometers: 38.2%. | |
| C: Western region | | | | | | |
| 17. Jingi A et al, 2014 | Western Cameroon | 2012 | 2 private and 9 public health facilities | Insulin (Short-acting, Intermediate-acting and Pre-mixed), OHA (Glibenclamide and Metformin), ACEI (Captopril and Ramipril), Statins (Simvastatin), Aspirin, Diagnostic tests, Glucometers, HbA1c, Serum creatinine, Lipid profile, Urine protein and ketone testing strips, ECG | Availability of medicines: Intermediate-acting insulin (Insulatard): 10%, Glibenclamide, Metformin, Short-acting insulin (Actrapid) and Premixed insulin (Mixtard): all at 80%, Simvastatin-10%, Ramipril-20%, Captopril-30%, Aspirin: 70%. Availability of diagnostic tests: ECG: 10%, HbA1c: 20%, Lipid profile: 40%, Serum creatinine: 80%, Urine protein and ketone testing strips: 90%. Glucometers: 100%. | Availability of essential medicines: Glibenclamide 5 mg; 0.34 days’ wages. |
| Study | Country/Region | Number of Facilities | Availability of Medicines | Availability of Diagnostic Tests |
|-------|----------------|----------------------|---------------------------|---------------------------------|
| 18. Nyarko KM et al, 2016 | Ghana. (9th June to 28th June 2013) | 24 health facilities (21 public and 3 private hospitals) | Long-acting insulin | Glucometers. | - Long-acting insulin: 16.7%. - Short-acting insulin: 20.8%. - Glibenclamide: 20.8%. - Metformin: 25%. - ACEI (Enalapril or lisinopril): 25%. - Statins: 12.5%. - Aspirin: 79.2%. - Lipid profile: 16.7%. - Serum creatinine: 16.7%. - Urine protein and ketone testing strips: 25%. |
| 19. Okpetu EI et al, 2018 | Nigeria. (June to July 2013) | 6 public primary health facilities. | Glucometers. | - Glucometers: 33.3%. - Urine protein and ketone testing strips: 100%. |
| 20. Cameron A et al, 2009 | - 36 LMIC (11 African countries included) - Western region (Cameroon, Chad, Ghana, Mali and Nigeria) - Eastern region (Ethiopia, Kenya, Sudan, Tanzania and Uganda) - Southern region (South Africa) | 45 national and subnational surveys | Glibenclamide. | - Mean availability of glibenclamide in 8 African countries reported: 37.3% and 60.6% in the public and private sector respectively. - Affordability of LPG glibenclamide in 7 African countries was 1.1 and 1.8 mean days' wages. |
| 21. Mendis S et al, 2012<sup>32</sup> | -May 2008 -8 LMIC (3 African countries) - Western region (Benin) & Eastern region (Eritrea and Sudan). -January 2009 to January 2011. | –30 health facilities in the 3 African countries. -Long-acting insulin. -Short-acting insulin. -Metformin. -Glibenclamide. -Enalapril. -Simvastatin or Lovastatin. -Aspirin. -Urine protein and ketone testing strips. -Glucometers. -Lipid profile. -Serum creatinine. | Availability of essential medicines in Benin, Eritrea and Sudan respectively: -Long-acting insulin: 0%, 0% and 21.4%. -Short-acting insulin: 0%, 0% and 28.6%. -Metformin: 25%, 0% and 42.9%. -Glibenclamide: 41.7%, 0% and 71.4%. -Enalapril: 33.3%, 0% and 28.6%. -Simvastatin or Lovastatin: 8.3%, 0% and 35.7%. -Aspirin: 100% in all 3 countries. Availability of diagnostic tests in Benin, Eritrea and Sudan respectively: -Urine protein and ketone testing strips: 100%, 67% and 92%. -Glucometers: 67%, 17% and 75%. -Lipid profile: 25%, 0% and 33%. -Serum creatinine: 33%, 0% and 58%. -Serum troponin: 8%, 0% and 8%. |

**Insulin**

Generally, availability of insulin as reported by the majority of the studies was sub-optimal basing on the recommended WHO GAP goal of ≥ 80%. Availability of insulin of any type ranged from 0% in Mozambique [22], Benin and Eritrea [31] to 100% in Zambia [22].

In the surveyed health facilities, availability of short-acting insulin was 0% in Benin and Eritrea [31], 6% in Malawi (public health facilities) [23], 11.2% in one study in Uganda [15], 20.8% in Ghana [28], 22.2% in Zambia [24], 25% in Malawi (private health facilities) [23], 28.6% in Sudan [31], 52.8% and 60.1% in two other studies in Uganda [11, 20] and 80% in Cameroon [27].

Availability of intermediate-acting insulin was 0% in Malawi [23], 10% in Cameroon [27] and 16.7%, 34.7% and 47.2% in three studies conducted in Uganda [11, 20, 21].
Availability of pre-mixed insulin was reported by only two studies conducted in Uganda (16.7% and 60.1%) [11, 21] and in Cameroon (80%) [27].

Oral hypoglycaemic agents (OHA)

Availability of oral hypoglycaemic agents (OHA) in the surveyed health facilities ranged from 0% in Eritrea (metformin and glibenclamide) [31] to 100% in Uganda (metformin and glibenclamide/glimepiride) [11] and Swaziland (metformin) [25]. The most studied OHA were glibenclamide and metformin. In addition to those two drugs, one study from Ethiopia also assessed the availability of gliclazide or glipizide which was reported to be very low (4%) [19].

The documented availability of metformin was 11% and 31% in Ethiopia [13, 19], 14.5% in Malawi [26], 25% in Ghana and Benin [28, 31], 33.3% in Tanzania [18], 42.9% in Sudan [31], 51.1% in Zambia [24] and 80% in Cameroon [27]. The additional four studies conducted in Uganda reported the availability of metformin ranging from 16.7-92.5% [15, 17, 20, 21].

The availability of glibenclamide was reported to be 9.1% in Malawi [26], 20.8% in Ghana [28], 25.5%, 50% and 81.1% in three other studies in Uganda [15, 20, 21], 28% and 31% in two studies in Ethiopia [13, 19], 41.7% in Benin [31], 51.1% in Zambia [24], 71.4% in Sudan [31], 80% in Cameroon [27] and 90% in Swaziland [25].

Angiotensin Converting Enzyme Inhibitors (ACEI)

Availability of angiotensin converting enzyme inhibitors (ACEI) ranged from 0% in Eritrea [31] to 96.5% in Uganda [11]. Except for the studies conducted in Swaziland [25], Malawi [23] and two studies conducted in Uganda [11, 20], the remaining nine studies documented low availability of ACEI of < 50% [12, 14-16, 19, 21, 27, 28, 31].

Aspirin
Availability of aspirin was investigated by five studies and was reported present in 53% in Ethiopia [19], 70% in Cameroon [27], 79.2% in Ghana [28], 95.1% in Uganda [11] and 100% in Benin, Eritrea and Sudan [31].

Statins

Five studies reported about the availability of statins ranging from 0% in public facilities in Malawi [23] and Eritrea [31] to 84% in Uganda [11]. The documented availability in other studies was 3.1% in another study conducted in Uganda (simvastatin) [15], 8.3% in Benin (simvastatin) [31], 10% in Cameroon (simvastatin) [27], 35.7% in Sudan (simvastatin) [31] and 56% in private health facilities in Malawi (lovastatin) [23].

Availability Of Diagnostic Tests For Dm

A total of 14 studies (66.7%) investigated the availability of at least one diagnostic test for DM. Among the recommended diagnostic tests for DM in the WHO PEN, availability of blood glucose tests was the most investigated (13 studies, 92.9%) [11, 13, 14, 17-22, 26-29, 31] while microalbuminuria tests were the least investigated (2 studies, 14.3%) [11, 20].

The availability of the diagnostic tests for DM as recommended by the WHO PEN is as shown in Table 2.

Blood glucose tests

Availability of blood glucose tests ranged from 6% in a study conducted in Mozambique [22] to 100% in a study conducted in Cameroon [27]. Only two studies reported optimal levels of availability of blood glucose tests of ≥ 80% [11, 27] while one study conducted in Sudan documented close to optimal levels of availability of 75% [31]. Availability of blood glucose tests in the remaining studies was < 70% [13, 17-22, 26, 28, 29, 31].

Urine protein and ketone tests
Urine protein and ketone tests were the second most investigated diagnostic test (8 studies, 57%) [11, 13, 19, 20, 27-29, 31]. The availability ranged from 33.3% in Ghana [28] to 100% in Uganda [11], Nigeria [29] and Benin [31]. Other studies conducted in Ethiopia [13, 19], Eritrea [31], Cameroon [27], Sudan [31] and Uganda [20] reported availability of 56% and 89%, 67%, 90%, 92% and 92.5% respectively.

Lipid profile tests

Availability of lipid profile tests was reported by five studies and this ranged from 0% in Eritrea [31] to 65.9% in one study conducted in Uganda [11]. The remaining studies reported availability of 16.7% in Ghana [28], 25% in Benin [31], 28.3% in Uganda [20], 33% in Sudan [31] and 40% in Cameroon [27].

Serum creatinine tests

Availability of serum creatinine tests was also reported by five studies [11, 20, 27, 28, 31]. Optimal availability of ≥ 80% was only noted in two studies conducted in Uganda [11] and Cameroon [27].

Electrocardiography (ECG)

The documented availability of ECG as reported by four studies was 5.7% and 54.6% in Uganda [11, 20], 9.1% in a study conducted in Uganda and Kenya [14] and 10% in Cameroon [27].

Microalbuminuria tests

Availability of microalbuminuria tests was reported by only two studies conducted in Uganda both documenting low levels of 6.8% and 13.2% respectively [11, 20].

Glycated haemoglobin (HbA1c) tests

Three studies conducted in Cameroon [27] and Uganda (n = 2) [11, 20] investigated the availability of HbA1c tests, noting their presence in 20%, 43.2% and 9.4% of the health
facilities that were surveyed respectively.

Serum troponin tests
Availability of serum troponin tests as reported by three studies was 0% in Ghana [28] and Eritrea [31], 8% in Benin and Sudan [31] and 43.2% in Uganda [11].

Serum ketone tests
Availability of the serum ketone tests was investigated by only one study which reported them available in only 11.4% of the surveyed health facilities, which were all private hospitals [11].

Affordability Of Essential Medicines For DM
Affordability of any of the essential medicines for DM was investigated by five studies [11, 23, 25, 27, 30] (summarised in Table 2).

Oral hypoglycaemic agents
The lowest priced generic (LPG) glibenclamide cost less than 2 days’ wages in all the studies [11, 23, 25, 27, 30]. Except for the study conducted in Uganda [11], LPG metformin cost ≤ 1.2 days’ wages in the rest of the studies [23, 25, 27]. One study assessed the cost of the newer generation sulphonylurea-glimepiride whose monthly dose cost 3.2 days’ wages [11].

Insulin
Affordability of insulin was assessed in three studies [11, 23, 27]. Short-acting and intermediate-acting insulin cost 4.7 and 4.9 days’ wages respectively in Uganda [11]. The cost of short- and intermediate-acting insulin in Cameroon was similar (3.85 days’ wages) [27]. A high cost of the innovator brand of intermediate-acting insulin was reported in Malawi (19.6 days’ wages) [23]. A high cost of pre-mixed insulin was noted in Cameroon (18.7 days’ wages) [27] compared to Uganda (4.9 days’ wages) [11].
Aspirin, ACEI (captopril) and statins
(simvastatin/atorvastatin/rosvastatin)

Affordability of any of the three classes of essential medicines above was investigated by four studies [11, 23, 25, 27]. Only two studies assessed affordability of all the three classes of essential medicines above [11, 27].

Aspirin cost less than a days’ wages in the two studies [11, 27]. The cost of captopril and statins greatly varied among the countries. It cost < 1.3 days’ wages in Malawi [23] and Swaziland [25], 2.8 days’ wages in Uganda [11] and 6.41 days’ wages in Cameroon [27]. Any statin cost > 6 days’ wages in Uganda [11] while simvastatin cost 30 days’ wages in Cameroon [27].

Affordability Of Diagnostic Tests

Affordability of diagnostic tests for DM was assessed by only two studies conducted in Uganda [11] and Cameroon [27]. Blood glucose, urine protein and ketone, serum creatinine tests cost < 3.3 days’ wages in both countries [11, 27]. In comparison, the cost of lipid profile testing in Uganda [11] was twice the cost in Cameroon [27] (7.5 and 3.59 days’ wages respectively).

Both ECG and HbA1c cost > 8 days’ wages in both countries with a higher cost documented in Cameroon. The cost of serum ketone, microalbuminuria and serum troponin tests was investigated by only one study reporting costs of 2.1 days’ wages, 9.6 days’ wages and 11.3 days’ wages respectively [11].

Discussion

This systematic review presents, to our knowledge, the first comprehensive assessment of availability and affordability of essential medicines and diagnostic tests for DM as recommended by the WHO-PEN in SSA.
Universally, the availability of essential medicines and diagnostic tests for DM remains sub-optimal in SSA based on the WHO GAP goal, particularly intermediate-acting insulin, statins, ECG, HbA1c, microalbuminuria and serum troponins tests. All the three types of insulin (short-acting, intermediate-acting and pre-mixed) and statins are largely costly. With the exception of blood glucose, urine protein, urine ketone and serum creatinine tests, the cost of the remaining WHO PEN recommended diagnostic tests was high. Similar findings of sub-optimal availability and high costs of essential medicines and diagnostic tests for DM has been widely reported in most low-and middle-income countries [32–35]. There are several plausible explanations for this. Limited funding of the health sector by the respective governments to procure the appropriate essential medicines and diagnostic tests for DM could explain the low availability observed in the public sector [36].

Substantial attention is given to communicable diseases like malaria, tuberculosis and HIV in SSA with minimal consideration to NCD. Healthcare systems are mainly structured to test, treat and cure communicable diseases, with little emphasis given to longitudinal NCD care. Few global funding initiatives or programs exist in SSA to support equitable access to affordable essential medicines and diagnostic tests for DM as seen with malaria, tuberculosis and HIV.

Glaring knowledge-practice gaps in DM care among healthcare practitioners creating less demand for essential medicines for NCD, absence of some essential medicines on the national essential medicine lists (NEML), lack of incentives to maintain optimal medicine stocks at the health facilities, forecast inaccuracy and inefficient purchasing or distribution systems are other plausible explanations for the sub-optimal availability of essential medicines and diagnostic tests for DM [36–38].

The high costs of all types of insulin (key medicine for all patients with type 1 DM and
some patients with type 2 DM) and statins (an essential medicine for primary and secondary prophylaxis of cardiovascular diseases in patients with type 2 DM) in SSA is of great concern. One plausible explanation for the high costs of insulin in SSA is the market monopoly in insulin production and volume sales by a limited number of multinational companies with minimal generic insulin production. The current shift from the use of human insulin to the newer insulin analogues has further increased insulin costs in SSA [37–39].

The Lancet NCD Action Group in their seminal paper on promoting access to essential medicines for NCD, including DM, acknowledge that improving access to affordable medicines requires a comprehensive health system approach including pharmaceutical sector governance, appropriate pharmaceutical workforce training, pharmaceutical management information systems, procurement planning and sustained financing of medicines [40]. They propose several key strategies to improve access to affordable medicines like legislation to promote generic market entry and submission, appropriate pricing for generic medicines, reduced patient co-payments for generics, rational selection and use of medicines for NCD, good monitoring electronic systems to avert stock-outs and increased financing for NCD medicines from domestic and international sources [40].

To improve access to medicines for NCD, 21 global biopharmaceutical companies have established access to medicine initiatives mainly in LMIC. One systematic review identified 120 of these initiatives with 52% focused on NCD. A worthwhile example is the Novartis Access program which is currently running in 7 countries in SSA (Cameroon, Ethiopia, Kenya, Uganda, Rwanda, Malawi and Tanzania). Its objective is to offer a portfolio of medicines for NCD like metformin to the public sector at a subsided fee of one US dollar and also build health system capacity in preventing, diagnosing and treating NCD, including DM [41]. Novo Nordisk, one of the key multi-national insulin manufacturing
companies also adopted an equity pricing initiative to supply insulin at a much-subsidised fee to a selected number of low-income countries in SSA. The company also supports the Changing Diabetes in Children (CDiC) program in 10 countries in SSA in partnership with Roche Pharmaceuticals, the International Society of Paediatric and Adolescent Diabetes and World Diabetes Federation by offering free insulin and glucometers to children and adolescents living with type 1 DM [42].

In addition to the above recommendations, we propose these broad practical solutions. First, Ministries of Health and other implementing agencies should encourage adherence by healthcare practitioners to evidence-based, locally relevant treatment guidelines of DM. Second, healthcare practitioners should be offered continuous medical education on optimal DM care to improve confidence and knowledge. Third, NEMLS should be updated and modernized through transparent mechanisms to include timely, evidence-based, cost-effective medicines. Finally, there should be public- and private-sector investment in local pharmaceutical production of high-quality generic medicines.

Strengths And Limitations

This is the first systematic review evaluating availability and affordability of essential medicines and diagnostic tests of DM as recommended by the WHO-PEN in SSA. The limitations of this systematic review include heterogeneity of the study results, category of health facilities surveyed and methods of data collection (few studies used the validated WHO-developed Service Availability and Readiness Assessment [SARA] tool). Despite the SARA tool being nationally representative and has been frequently used globally, it doesn’t include price data and hence, cannot be used to obtain information about affordability. The majority of the eligible studies had low methodological quality. All of the reviewed studies were cross-sectional studies that considered a one-time point assessment of availability and affordability. This does not put into consideration time
variations in the availability and cost of essential medicines and diagnostic tests.

Conclusion

This systematic review shows that some essential medicines and diagnostic tests for DM in SSA remain unaffordable and their availability still falls substantially below the WHO defined GAP goal. This underscores the need for concerted national and international efforts to improve equitable access to affordable essential medicines and diagnostic tests for DM in SSA, as part of strategies to achieve the defined sustainable development and universal health coverage goals.

Abbreviations

ACEI- Angiotensin Converting Enzyme Inhibitors, DM-Diabetes Mellitus, ECG- Electrocardiography, GAP- Global Action Plan, HbA1c- Glycated haemoglobin, HAI- Health Action International, LMIC-Low-and middle income countries, LPG- Lowest Priced Generic, NCD-Non-Communicable Diseases, NEML-national essential medicine lists, OHA-Oral Hypoglycaemic Agents, SSA- Sub-Saharan Africa, WHO-World Health Organisation, WHO-PEN- WHO Package of Essential Non-communicable Disease Interventions for Primary Health Care in Low-Resource Settings.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

Not applicable

Competing interests
The authors declare that they have no competing interests.

**Funding**

No funding was received for this review.

**Authors' contributions**

DK1 and RES-conceived the idea and wrote the initial manuscript, DK and RES-performed the search of the online databases and screening of the search results for eligible research articles, IS, DK2, DA, JM, JIS and MJN-independently reviewed the selected articles for eligibility and key information, DK1, RES, IS, DK2, DA, JM, JIS and MJN-reviewed the initial draft of the manuscript, read and approved the final manuscript.

**Acknowledgement**

None.

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Figures
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Records screened (n = 5,390)

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- Editorials = 3
- Review articles = 4
- Systematic reviews = 3
- Study protocol = 1

Full-text articles assessed for eligibility (n = 61)

Full-text articles excluded because they lacked the information of interest for the systematic review (n = 5,329)

Studies included in qualitative synthesis (n = 21)

Figure 1

Flow diagram for the systematic review