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Research Article

Availability and Use of Long-Acting Insulin Analogues Including Their Biosimilars across Africa: Findings and Implications

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ABSTRACT

Background: Prevalence rates of diabetes mellitus are growing across Africa with an appreciable number likely to be on insulin to manage their condition. This has significant implications on future morbidity and mortality exacerbated by high complication rates. Complication rates in patients requiring insulins are enhanced by hypoglycaemia. Long-acting insulin analogues were developed to reduce hypoglycaemia and improve patient compliance. However, they are typically appreciably more expensive than human and other insulins in Africa, and continuing controversies surrounding their benefits limits their listing on national Essential Medicine Lists (EMLs). Biosimilars can reduce the prices long-acting insulin analogues. This needs assessing.

Methods: Mixed methods approach including documentation of insulin utilisation patterns and prices among a range of African countries. In addition, input from senior level government, academic, and healthcare professionals from across Africa on the current situation with long-acting insulin analogues as well as potential changes needed to enhance future funding of long-acting analogue biosimilars.

Results: There is variable listing of long-acting insulin analogues on national EMLs across Africa due to their high prices and issues of affordability. Even when listed, utilisation of long-acting insulin analogues is limited by similar issues including affordability. Appreciably lowering the prices of long-acting insulin analogues *via* biosimilars should enhance future listing on EMLs and use accompanied by educational and other initiatives. However, this will require increased competition to lower prices.

Conclusion: There are concerns with value and funding of long-acting insulin analogues across Africa including biosimilars. A number of activities have been identified to improve future funding and listing on EMLs.

Keywords: Africa; Long-acting insulin analogue biosimilars; Cross-national study; Diabetes; Drug Utilization; Essential Medicines List; Health Policy; Insulin glargine; Prices

INTRODUCTION

We have seen incident and prevalence rates of diabetes mellitus grow across countries, with this trend continuing [1,2]. Global incident cases rose to 22.94 million in 2017, rising by more than 100% since 1990 [1]. Overall in 2019, there were 463 million people with diabetes mellitus worldwide, with an appreciable number from Low- and Middle-Income Countries (LMICs) [3]. Across Africa, there is an estimated 15.9 to 19 million with diabetes mellitus, with prevalence rates likely to reach 34.2 million in sub-Saharan Africa by 2040, and potentially up to 42 to 47 million across Africa by 2045 [4-6]. We have also seen high prevalence rates for patients with diabetes among individual African countries [4,7]. For instance in Ghana, an estimated 6.46% of the adult population have diabetes mellitus. However, this is likely to be an appreciable under-estimation with a significant number of people with diabetes undiagnosed due to a lack of awareness of their condition [8,9]. In Malawi, the prevalence of NCDs, including diabetes, hypertension, and obesity, is rising similar to other African countries [7,10]. Recent estimates suggest prevalence rates for patients with diabetes in Malawi range from 2.4% to 5.6% of the population, with prevalence rates expected to rise further unless addressed, with similar rates in Zambia at 4.2% of the population and rising [11,12]. Prevalence rates are higher in Uganda with 10.1% of the population estimated to have diabetes and growing [13]. Whilst diabetes is predominantly Type 2 Diabetes (T2DM) across Africa, up to 35% or more of patients with diabetes in LMICs, including those in Africa, require insulin, either alone or in combination with oral therapies, to manage their condition [14-17].

Growing prevalence rates will increase the worldwide economic burden of diabetes mellitus to between US$2.1 to US$2.5 trillion by 2030, which includes both direct and indirect costs, equating to 2.2% of Gross Domestic Product (GDP) [18]. There is also a considerable economic burden due to diabetes mellitus across Africa, which reflects a general increase in Non-Communicable Diseases (NCDs) across the continent [19]. NCDs include Coronary Vascular Diseases (CVD) and diabetes, with morbidity and mortality associated with NCDs likely to exceed those associated with infectious diseases in Africa by 2030 [6,20-24].

In 2015, the cost of diabetes mellitus in sub-Saharan Africa, including both direct and indirect costs, was estimated at US$19·45 billion, equating to 1.2% of GDP, with the majority being direct costs including the costs of medicines [23]. These costs are estimated to increase to between US$35·33 billion and US$59·32 billion (1.1% to 1.8% GDP) by 2030 unless addressed, with the costs associated with diabetes mellitus enhanced by the complications of poor glycaemic control and associated co-morbidities [23]. Complications include renal disease, potentially leading to dialysis and transplantations, diabetic feet ulcerations resulting in lower extremity amputations, complications with the eyes leading to blindness, as well as a greater risk of heart attacks and strokes [3]. These complications appreciably increase hospitalisation costs among patients with diabetes in Africa, which is a growing concern [25].

As a consequence of the growing prevalence rates coupled with increasing complication rates, diabetes mellitus is known to be among one of the top three causes of outpatient morbidity in primary healthcare facilities in Ghana [26]. There are also concerns generally with the management of patients with diabetes mellitus across Africa, including South Africa. These include addressing high rates of hypoglycaemia as well as adherence to treatments to decrease associated morbidity and mortality, with community-based projects potentially helping to address key issues of identification and management [27-29]. Overall, diabetes mellitus is seen as a leading cause for CVD, disability, and death across sub-Saharan Africa, alongside reducing the quality of life of patients; consequently, needs to be carefully managed [7,23,30-

32]. Rising rates of NCDs, including diabetes mellitus, among Southern African countries have also been linked with increased aged standardised mortality rates [33].

We have previously documented potential ways to improve the management of patients with both Type 1 Diabetes Mellitus (T1DM) and T2DM across Africa given the increasing burden and the resultant implications [4,7]. Ways forward included enhancing the availability of medicines including insulins as well as equipment and facilities to improve early diagnosis and monitoring of blood glucose levels at home [2,7,17,34-36]. We are aware that the availability and affordability of medicines to treat patients with diabetes mellitus, especially insulin, can be a key issue among African countries, similar to other LMICs, exacerbated in the case of insulin by three principal manufacturers globally accounting for up to 96% of the global market by volume and up to 99% by value [37-44]. This is highlighted in the studies by the ACCISS (Addressing the Challenge and Constraints of Insulin Sources and Supply) group and others documenting the key challenges globally with limited competition generally surrounding the availability and affordability of insulins especially in LMICs [42,43,45]. There are though ongoing initiatives to enhance competition among manufacturers to help lower insulin prices. These include the WHO prequalification initiative, which is expected to increase the flow of quality-assured insulins thereby potentially providing countries, especially LMICs, with a greater choice of insulins and patients with lower prices [41,46]. This builds on a number of initiatives among African countries to enhance access and availability of insulins.

In Cameroon, the Changing Diabetes in Children's (CDiC) initiative was launched in 2010 in conjunction with the International Diabetes Federation and local governments to offer free diabetes care to children and adolescents with T1DM as access and availability of medicines including insulins, as well as monitoring equipment, was a major issue [47-49]. This included a range of free insulins, namely regular insulins (Actrapid®), intermediate-acting insulins (Insulatard®) and pre-mixed insulins (Mixtard 30®) [48].

In Kenya, concerns with high rates of undiagnosed diabetes, which can be as high as 60% of those patients with diabetes, as well as issues of affordability of medicines especially among diabetes patients with co-morbidities, has resulted in a number of initiatives to try and address these issues [7,50-52]. This includes the Base of Pyramid (BoP) project, which aimed to enhance diagnosis as well as establish a ceiling price of KSh 500–600 (US$5) for insulin Mixtard® 1000IU (10mls 100IU/ml) in participating healthcare facilities, surrounding markets and private pharmacies. As a result, enhance the affordability of medicines for patients with diabetes including insulin given current high co-payment levels [51]. This equates up to a two-thirds price reduction [51].

Patient illnesses can have catastrophic consequences for families in Nigeria and other African countries where there are high patient co-payments; consequently, treatments should be carefully considered before being prescribed [53,54]. This is particularly important in Nigeria where published studies have shown that the costs of medicines to treat patients with diabetes can range from 72.3% to 90% of total costs, much of which will be out-of-pocket [55,56]. The situation may ease among children with diabetes in Nigeria with Novo Nordisk seeking to offer insulin free to children during 2021 similar to the CDiC initiative in Cameroon [57].

In Tanzania, studies have found that the different types of insulin were only available in public health facilities on a limited number of occasions, e.g., 8% to 17% of occasions, with other studies showing that stock-out of insulins and other key medicines for patients with diabetes is a frequent occurrence in the country, which is a concern with affordability a key issue in Tanzania [30,37,58]. There are ongoing initiatives to address this including the Christian Social Services Commission (CSSC) and Biocon recently signing a memorandum of understanding to take part in a pan-African project entitled 'Mission 10 cents'. Within this project, insulins, including recombinant human insulin (rh-insulin), will be sold at a cost of less than 10 US cents per day, with Tanzania potentially a pilot for other African countries. This is beneficial given the potential impact of the cost of insulin on African families without universal healthcare [46,59].

There are also concerns with the lack of consumables to monitor blood glucose levels across a number of African countries including Zimbabwe, with the cost of tests a deterrent to their use among patients with diabetes attending public healthcare institutions potentially compromising their care [7]. This needs to be addressed going forward to reduce future morbidity and mortality associated with diabetes across Africa.

As mentioned, there are issues with adherence to prescribed medicines among patients with diabetes across Africa [27,60-63]. These concerns increase the need to improve the management of patients with diabetes mellitus and associated CVD across Africa to further reduce future morbidity and mortality [64]. This includes improving glycaemic control and reducing rates of hypoglycaemia, which is a concern as hypoglycaemia is one of the most feared issues associated with diabetes, enhanced by the lack of consumables to monitor blood glucose levels across Africa [7,28,36,65,66].

Long-acting insulin analogues were developed to reduce the risk of hypoglycaemia, especially nocturnal hypoglycaemia. Alongside this, provide greater convenience to patients given the reduced number of injections, with improved convenience enhancing compliance, resulting in improved outcomes including reduced hypoglycaemia and its consequences [3,67-74]. As a result, we are now seeing the utilisation of long-acting insulin analogues exceeding that of human insulins among upper-middle and high-income countries, reflected in worldwide sales of long-acting insulin glargine at US$3.88 billion in 2018, potentially rising to US$9.26 billion by 2025 [39,75]. Concurrent with this, worldwide sales of long-acting insulin detemir were US$2.7 billion in 2015 and growing at 7.5% per year [76].

However, Hemmingsen et al. (2021) in a recent systematic review of long-acting insulin analogues in T1DM found that long-acting insulin analogues did not show any patient benefits, or harms, for severe nocturnal hypoglycaemia versus Neutral Protamine Hagedorn (NPH) insulin [77]. These authors also found no true beneficial or harmful effect for long-acting insulin analogues in other measures [77]. More recently though in a systematic review combined with a network analysis, Tricco et al. (2021) found that long-acting insulin analogues led to fewer major or serious hypoglycaemic (OR 0.63) or nocturnal hypoglycaemic episodes (OR 0.74) as well as a reduced HbA1c levels (mean difference -0.14

percentage points) [78]. This is a key issue given ongoing concerns with the value of long-acting insulin analogues versus NPH and other insulins among LMICs in view of their appreciably higher costs, which has resulted in calls for disinvestment in some LMICs [79-82]. We are also aware that most studies involving long-acting insulin analogues have been conducted in higher- versus lower-income countries where the dynamics of the populations can be very different especially surrounding access and availability of medicines [39,83].

Alongside this, Ewen et al. (2019) showed there was a considerable price difference between human insulins (US$5 per 1000 IU) and long-acting insulin analogues (US$33/1000IU) affecting their funding and use among a range of LMICs [39]. However, a number of studies have now shown that the higher acquisition costs of long-acting insulin analogues can potentially be offset by savings from averted costs of hypoglycaemia and other diabetes-associated complications, although this is not always the case [72,73,84-88]. Consequently, further research is needed among patients with diabetes mellitus across Africa to determine the extent to which long-acting insulin analogues reduce the risk of long-term diabetic complications in practice to enhance their potential for funding alongside possible price reductions with the advent of biosimilars given current considerable differences in prices [39]. We are aware following the availability of biosimilars such as biosimilar infliximab and biosimilar adalimumab that they can appreciably lower the cost of biologic medicines and enhance their use as seen with adalimumab in Denmark where expenditure was reduced by 82.8% following the availability of biosimilars, with the cost of insulin glargine also appreciably reduced in Bangladesh following biosimilars [89-92].

In view of the ongoing controversies and issues surrounding long-acting insulin analogues, including higher costs, these are currently not included in the World Health Organization Essential Medicines List (WHO EML) [93]. This is despite their growing use in a number of upper-middle and higher-income countries including European countries [39,94,95]. However, there is variable use among lower-income countries [39]. In Bangladesh, only NPH and other similar insulins are funded in public hospitals whilst there is 100% co-payment for long-acting insulin analogues, similar to parts of India [39,92]. However, there is growing use of long-acting insulin analogues in ambulatory care in Bangladesh in view of their perceived benefits, which is increasingly biosimilar insulin glargine under the guidance of physicians [92]. Long-acting insulin analogues are also currently not funded within the public healthcare systems in South Africa and Zambia due again to concerns with higher costs than NPH insulins and other similar insulins with no perceived clinical advantage [96,97]. Long-acting insulin analogues are though listed in the EMLs of Kenya, Namibia and Zimbabwe along with other African countries [7,98-100]. However, there can be issues of affordability limiting their prescribing [100].

We are aware, as mentioned, that the availability of biosimilars can appreciably lower the cost of biologic medicines and enhance their use [89,90]. There have though been concerns regarding limited price reductions to date for biosimilars of long-acting insulin glargine including among some LMICs, along with price reductions by the originator company, impacting on their funding and use in practice [39,95,101,102].

As a result, we believe there is a need to re-assess current utilisation and expenditure patterns for insulins, including long-acting insulin analogues and their rationale, across Africa. This includes potential ways to reimburse and fund long-acting insulin analogues such as insulin glargine and insulin detemir within public healthcare systems across Africa including their incorporation into national EMLs and Standard Treatment Guidelines (STGs) given increasing recognition of their value and use among higher-income countries [3,39,94]. However, this needs to be balanced against the recent findings of Hemmingsen et al. (2021) [77]. In addition, investigate potential prices for the different insulins among the different African public healthcare systems where available. Alongside this, investigate possible price reductions for long-acting insulin analogues *via* biosimilars to enhance their funding within public healthcare systems. These are the objectives of this paper, which build on our recently published studies regarding the management of diabetes mellitus across Africa as well as those conducted by Ewen et al. (2019) [4,7,39].

METHODOLOGY

We adopted a mixed methods approach. This included information from the co-authors, who are a mixture of senior-level personnel from governments and their advisers, clinicians, academia, and rational medicine use advisers, from across Africa to provide information on the current situation regarding long-acting insulin analogues within the public healthcare system in their country, i.e., whether listed in the EML or STGs in their country. In addition, potential solutions to encourage funding and use of long-acting insulin analogues if currently not listed or funded within their country. This includes the extent of potential prices and price reductions for long-acting insulin analogues to enhance their listing within national EMLs through 'biosimilars' - 'e.g.,' for insulin glargine as the first biosimilar for long-acting insulin analogues available across countries [95]. This builds on our two recent papers regarding the management of patients with diabetes across Africa as well as the use of long-acting insulin analogues within a limited number of African countries [4,7,100,103].

With respect to biosimilars, we will only be interested in biosimilars of long-acting insulin analogues given the current controversies surrounding their use including appreciably higher prices than NPH and other insulins [39]. Patterns of current insulin use within the country will though be documented where such data sets are available to provide a background for the current situation across Africa. This will typically be data from hospitals as currently there is generally no national comprehensive data available for the public healthcare system among a number of African countries, which is unlike the situation across Europe [104-106]. This is similar though to the approach among a number of Asian countries [92,107]. We will though be using national data sets in South Africa. Utilisation data will be converted into Defined Daily Doses (DDDs) for comparative purposes where pertinent similar to other studies alternatively, kept as pack data. The DDDs have been based on a DDD of 40 for insulin, e.g. the DDD for soluble human insulin 100IU/3ml cartridge is 7.5 DDDs (300/40) [104,105,108,109].

We will also collect data on the utilisation and prices of long-acting insulin analogues from community pharmacies and drug stores in Nigeria since patients typically purchase their medicines from such stores [103]. This is similar to the methodology employed when

assessing the impact of COVID-19 on utilisation and prices of pertinent medicines and equipment in Nigeria and other African countries in the months following the pandemic and similar to the recent studies across Asia including Bangladesh [92,107,110,111]. Prices where pertinent will be converted to US$ using current conversion rates for comparative purposes.

We did not collect data on mark-ups in pharmacies as our main objective in Nigeria and other pertinent African countries was to collect actual pricing and expenditure data. We are aware though that Ball et al. (2019) had collected data on pricing components of insulins in a number of LMICs including African countries, where cumulative mark-ups can range from 8.7% to 565.8% [112]. This is an important area, which we will comment on when discussing possible future activities across Africa to enhance usage and funding of long-acting insulin analogues.

We also did not collect experiences regarding the registration of insulins across Africa. We are aware though of the circulation of falsified and substandard antidiabetic medicines including insulin, with these manufacturers taking advantage of rising prevalence rates of diabetes across Africa, further compounded by the proliferation of internet run pharmacies that are not well regulated In LMICs [113]. However, steps are being taken to address such activities including the Lomé initiative placing falsified and substandard medicines on the highest political agenda in Africa with ongoing measures to strengthen the legal response to these medicines [114,115]. Alongside this, initiatives to accelerate mutual recognition for new medicines among African regions such as the West Africa Region [116]. These progammes are in addition to the current WHO prequalification initiative to enhance the availability of quality-assured and lower priced insulins to address issues of affordability among patients and governments [41,46].

Similar to our previous studies regarding the management of patients with diabetes across Africa, we will not split the African countries down into low- or middle-income African countries as a number of the issues surrounding the management of patients with diabetes mellitus appear similar across Africa [4,7]. This includes issues of affordability along with issues of diagnosis and regular monitoring of blood glucose levels [4,7]. However, we will break the participating African countries down into those that currently list and/or fund long-acting insulin analogues within their public healthcare systems and those that do not. This is because we believe the different African countries can learn from each other when it comes to suggesting potential ways forward to enhance listing and/or funding of long-acting insulin analogues within their public healthcare systems. This will principally be originator long-acting insulin analogues unless stated as we and others have previously shown limited funding and utilisation of long-acting insulin analogues across Africa and with it likely limited availability and use of biosimilars of long-acting insulin analogues [7,39,103].

We will also investigate whether those African countries that do not list or fund long-acting insulin analogues routinely have lower GDP levels per head of population versus those African countries that list these insulins since issues of affordability and access could play a greater role in countries with low GDP/capita. We will use the latest data from the World Bank to document current rates [117].

We did not seek ethical approval as we were not dealing with patients, in line with national legislation and institutional guidelines [107,110,118]. Besides, the pharmacists taking part in the study freely provided the requested information having been allowed to refuse to participate if wished. This is in line with previous studies undertaken by the co-authors in related areas including analysis of policies to enhance the rational use of medicines and biosimilars, pricing policies and issues surrounding generics, which all involved direct contact with health authority personnel, healthcare professionals and other key stakeholders [4,7,90,104,105,119,120].

RESULTS

Typically among the African countries, there is currently limited utilisation of long-acting insulin analogues in the public healthcare system, similar to our previous findings [7]. This is exacerbated by currently considerable cost differences between long-acting insulin analogues and the different human insulins, with a number of African countries currently struggling with resources and capacity, including personnel, to fund early diagnosis of diabetes as well as standard insulins such as NPH insulins and self-monitoring of blood glucose levels [7,37,121]. Furthermore, there is currently variable listing of long-acting insulin analogues within the EMLs of African countries [96,121].

Table 1-summarises typical insulins available across counqtries and those contained within the current; WHO EML, Table 2-summarising the current situation regarding African countries that currently list long-acting insulin analogues within their EMLs and/or STGs and those that do not alongside current

Table 1: Different insulin preparations and their classification excluding ultra short acting [122,123].

Classification	Examples and associated brand names (where pertinent)
Short-acting/rapid-acting insulins	Insulin Aspart
	Insulin Lispro
	Neutral insulin (Actrapid®)
Intermediate (NPH) insulin/longer-acting insulins	Human insulin isophane
Premixed human insulins	Insulin isophane and insulin regular (Humulin® 70/30®)
	30% insulin soluble and 70% isophane insulin (Mixtard 30®)
Long-acting insulin analogues	Degludec
	Detemir
	Glargine
WHO EML (21st)	Insulin injection (soluble)
	intermediate-acting insulin (as compound insulin zinc suspension or isophane insulin)

Table 2: Current GDP/capita and listing of long-acting insulin analogues in country EMLs across Africa.

Country	GDP/ capita (US$)*	Current listing of long-acting insulin analogues in EMLs	
		Listed in EML	Not listed in EML
Malawi	625.3		√
Uganda	817		√
Zambia	1,050.90		√
Tanzania	1,076.50		√
Zimbabwe	1,128.20	√	
Cameroon	1,499.40	√	
Kenya	1,838.20	√	
Nigeria	2,097.10	√	
Ghana	2,328.50	√	
Eswatini	3,415.50		√
Namibia	4,211.10	√	
South Africa	5,090.70		√
Botswana	6,711.00		√

*GDP/capita based on the latest World Bank data [117].

GDP/capita levels. The rationale for these findings is expanded within the synopsis for each country.

Whilst the surveyed African countries with lower GDPs/capita tended not to list long-acting insulin analogues in their EMLs, this was by no means universal with the analogues not listed among three out of the four included African countries with the highest GDP/capita (Table 2).

African countries where long-acting analogues are funded/listed in the public healthcare system

Cameroon: Long-acting insulin analogues are available within the healthcare system of Cameroon, with patients with diabetes principally managed in ambulatory care [7]. However, access and availability of insulins, as well as monitoring equipment, is a major issue with high co-payment levels outside of sponsored programmers' such as the 'Changing Diabetes in Children' (CDiC) initiative in conjunction with the International Diabetes Federation and local governments [17,47]. This is reflected by only Mixtard® and Actrapid® (Table 1) being dispensed within a leading ambulatory care facility in Cameroon, with overall expenditure within this facility rising over 2-fold between 2015 and 2019, with this trend likely to continue. Prices of long-acting insulin analogues will need to appreciably reduce with for instance biosimilar long-acting insulin analogues to address issues of affordability in Cameroon given current high co-payment levels, similar to other African countries [39].

Ghana: Two long-acting insulin analogues, insulin glargine and detemir, were approved by the Ghanaian Food and Drugs Authority since 2018, with long-acting insulin analogues currently listed in the Ghanaian EML [39,124]. However, long-acting insulin analogues are currently not included in the Ghanaian STGs for treating patients with diabetes nor currently reimbursed within the National Health Insurance Scheme (NHIS) due to their higher costs, severely limiting their prescribing within the public healthcare system [125,126]. Payment of service delivery among patients with diabetes in Ghana is both by insurance (national or private) and out-of-pocket; however over 90% of patients with diabetes are reported to be NHIS subscribers. The NHIS reimbursement list typically contains all medicines reimbursed by the government, and is based on the Ghanaian EML and the STGs. However, inclusion in the EML may not necessarily lead to inclusion in the NHIS as seen with the long-acting insulin analogues, similar to the current situation with the STGs.

As a result, there has been a sustained increased use of standard insulins including NPH or premixed insulins by physicians in the public hospitals in recent years in Ghana with very limited use of long-acting insulin analogues (Table 3). This is exacerbated by concerns with the catastrophic impact of illnesses such as diabetes outside of the NHIS and other schemes [127]. Such concerns may be reduced among children with diabetes in Ghana with Novo Nordisk seeking to offer insulin free to children during 2021 under is CDiC initiative, similar to the historic initiative in Cameroon [57].

There has been a similar increase in the use of premixed 30/70 insulin within Keta Hospital in Ghana rising from 580 packs in 2015 to 802 in 2019 (38.3% increase), with this increase expected to continue (Table 4). Currently, there is no prescribing of long-acting insulin analogues within Keta Hospital due to price differences and affordability between the various insulins. This is likely to remain until there are appreciable price reductions for long-acting insulin analogues through for instance biosimilars.

Ghana's National Medicines Policy document outlines data requirements for selecting essential medicines for national reimbursement. Medicines must be shown to be efficacious and cost-effective versus current standards reflecting the current demographic and economic situation within the country (Table 2). This enhances the need for more local research to be conducted to strengthen the case for potential funding of long-acting insulin analogues including their biosimilars and stronger communication of their benefits to policymakers [128]. This confirms the identified gap in knowledge regarding the overall cost-effectiveness of long-acting insulin analogue biosimilars within Africa, which needs to be addressed going forward.

The availability of long-acting insulin analogues could potentially address issues of adherence to prescribed medicines, which remains a major challenge for patients with diabetes in Ghana [129]. However, similar to other African countries, there needs to be an appreciable lowering of the price of long-acting insulin glargine *via* lower-cost biosimilars to enhance their availability and usage within the public health system in Ghana [130]. Local production

Table 3: Insulin dispensing patterns in recent years in the Cape Coast teaching hospital, Ghana, in DDDs.

Insulin type	2018	2019	2020 (Mid-Year)
Premixed insulins (30% insulin soluble/ 70% isophane) – 1000IU	197075	211700	163700
Other insulins, e.g. isophane – 10000IU	25000	35100	23000
Insulin glargine 3mls/ 100IU/ml (originator)	0	0	30
Total	222075	246800	186730
% insulin glargine	0%	0%	0.02%

of biosimilars of long-acting insulin analogues, including pens and cartridges, may be one way forward to lower prices and enhance their future use [131].

Kenya: Ongoing concerns with affordability of medicines for diabetic patients, including co-morbidities, has resulted in very variable availability and use of long-acting insulin analogues in Kenya in recent years [7,50,52]. This includes the leading tertiary hospital in Kenya-Kenyatta National Hospital (KNH), a level six hospital, where there has been increasing use of long-acting insulin analogues in recent years despite falling availability of insulins within the hospital [52] (Table 5). Overall, total insulin use within KNH decreased from a total of 591747.5 DDDs in 2015 to 306717.5 in 2019 and 244137.5 between January and October 2020, with this falling use compensated by greater purchasing in local community pharmacies. However, whilst there has been growing use of long-acting insulin analogues in recent years in KNH, this only rose to between 3.2% to 3.6% of total insulin use from 0.51% in 2015 (Table 5).

This usage patterns for insulins in KNH Table 5, reflects current insulins listed within the 2019 Kenyan EML coupled with issues of affordability [99].

However, it is likely there will be limited or no use of long-acting insulin analogues, including potential biosimilars, outside of KNH with patients in Kenya struggling to fund even insulin Mixtard® (Table 1) without access schemes [51]. This was seen in Embu County Referral hospital, which is a level 5 hospital located in Central Kenya, a region with high prevalence of diabetes mellitus in Kenya. Mixtard® was the principal insulin dispensed with usage rising from 2061 packs in 2015 (511,360 Ksh; US$4660) to 5627 packs in 2018 (1,800,640 Ksh; US$16410) before falling to 4742 packs in 2019 with similar utilisation patterns in 2020. There was no dispensing of any long-acting insulin analogue in this referral hospital in recent years.

Consequently, similar to Cameroon and Ghana, prices of long-acting insulin analogues such as insulin glargine or detemir, including their biosimilars, will need to appreciably fall before there is any considerable use. This especially since when any prescribed medicine is not available or stocked in hospitals, patients necessarily need to purchase them directly from community pharmacies. This is a growing occurrence, with patients often needing to pay for these medicines out of pocket thereby making affordability a key consideration in Kenya [100].

Namibia: There is universal access to care for patients in the public sector within Namibia, including free medicines, which can be accessed from primary health care to tertiary institutions [132]. Whilst a wide range of insulins, including soluble and long-acting insulin analogues, are currently available to the public *via* PHCs financed by the Government of the Republic of Namibia, there is currently limited use of long-acting insulin analogues in public sector hospitals in Namibia due to issues of affordability [7].

Long-acting insulin analogues (originator insulin glargine) is currently available in the two main State public hospitals in Windhoek (Capital city of Namibia). These include Katutura Intermediate Hospital (KIH) and Windhoek Central Hospital (WCH). However in KIH, typically only 1-2 pens of insulin glargine (originator) are dispensed per month compared to NPH and other similar insulins being dispensed to over 30 patients a day. In WCH, isophane is the most dispensed insulin (in approximately 70% of patients to improve control of HbA1c levels), with 50% of patients also being dispensed short-acting insulins. Biphasic insulins are also dispensed in WCH – greater when there are shortages of isophane, with little or no dispensing of insulin glargine. However, long-acting insulin analogues are available and used in private hospitals in Namibia as the principal long-acting insulin. This is typically originator insulin glargine with currently no use of biosimilar insulin glargine.

Overall, prices of long-acting insulin analogues such as insulin glargine or detemir will need to fall considerably through biosimilars to enhance their use in the public sector in Namibia, similar to other African countries.

Nigeria: Short-acting or mealtime insulins as well as insulins including premixed and NPH insulin and long-acting insulin analogues, insulin glargine, are currently contained in the Nigerian

Table 4: Changes in utilisation and expenditure on different insulins in keta hospital, Ghana, in recent years.

		2015		2016		2017		2018		2019	
Insulin	Dosage	Util	Exp	Util	Exp	Util	Exp	Util	Exp	Util	Exp
Soluble (human) insulin	1000IU	100	100	110	100	120	150	135	255	145	50
Insulin premixed 30/70	1000IU	580	500	540	660	610	560	793	635	802	800

NB: Utilisation (Util) in Packs and Expenditure (Exp) in local currency at GH¢24.94/1000IU (US$4.31).

Table 5: Total utilisation of insulins in KNH 2015 to 2019 (DDDs) [100].

Insulin type	2015	2016	2017	2018	2019
Rapid acting	950	725	1200	2775	1257.5
Intermediate acting	16250	19025	19425	28062.5	33875
Premixed	571532.5	321050	221210	231690	260510
Glargine	3015	1260	3202.5	8680	11075
Total (DDDs)	591747.5	342060	245037.5	271207,5	306718
% long-acting insulin analogues	0.51%	0.37%	1.31%	3.20%	3.61%

NB: DDDs=defined daily doses.

EML. However, there are concerns with the affordability and availability of insulins including insulin glargine in Nigeria [7].

Among three hospitals in the Northern part of Nigeria, the total annual utilisation of insulin glargine originator was limited versus short and intermediate-acting insulins (Table 1). In 2019, utilisation of insulin glargine (originator) among these three hospitals ranged from 50 to 100 packs of 5x3ml 100IU/ml, with prices per pack ranging from N3600 (US$9.47) to N4300 ($11.42). There were similar utilisation patterns in the first half of 2020; however, prices rose from N4000 (US$10.53) to N4500 (US$11.84).

Among 11 community pharmacies surveyed in 2019 and 2020, the average number of packs of insulin glargine 100IU/ml dispensed ranged from 35 to 110 per year, with an average of 75 packs. Similar patterns were seen in the first half of 2020. Biosimilar Glaritus® accounted for only a small proportion of this at under 10%, with similar low rates of biosimilar dispensing in 2020. This may reflect concerns generally with the quality of non-originator medicines in Nigeria [133]. In addition, limited price differences in reality between the originator and biosimilars, e.g., currently only a 4% difference between the biosimilar and the cheapest originator insulin glargine among the surveyed pharmacies.

Prices of long-acting insulin analogues through biosimilars will need to appreciably fall to enhance their use within public facilities in Nigeria given current high patient co-payment levels and concerns generally with the impact of diabetes on patients' families. This is similar to other African countries.

Zimbabwe: Long-acting insulin analogues have been listed within the EML/STGs of Zimbabwe since 2015 (EDLIZ 7th and 8th editions) [98]. This includes both insulin glargine and insulin detemir. However, in view of their additional costs versus NPH and other insulins, and available resources, their availability within central provincial and district public hospitals in Zimbabwe is currently erratic and inconsistent. Long-acting insulin analogues including degludec were last purchased in 2018 and distributed up to the end of 2019/beginning of 2020.

Usage of long-acting insulin analogues is further limited in Zimbabwe by the economic burden of NCDs generally including diabetes on households [134,135]. Consequently, the most accessible insulins currently in Zimbabwe include short and intermediate acting insulins including premixed insulins (Table 1) Prices of long-acting insulin analogues through biosimilars will have to appreciably fall in Zimbabwe to enhance their use, again similar to other African countries.

African countries where long-acting analogues are currently not funded or listed in the public healthcare system

Botswana: Short and intermediate-acting insulins as well as pre-mixed insulins are currently available in the public healthcare system in Botswana [7]. These insulins are typically available in specialized diabetes clinics, with only a few insulins available in non-specialised clinics using special prescription forms (e.g., *Novo*Mix® and *Novo*Rapid®, i.e. insulin aspart). Long-acting insulin detemir is registered in Botswana but currently unavailable in the public healthcare system. This is likely to be different in the private system. Insulin glargine (originator or biosimilar) is also currently unavailable in the public healthcare system in Botswana.

However, it is envisaged that appreciably lowering the price of long-acting insulin glargine *via* lower-cost biosimilars towards the corresponding prices of NPH and other insulins will increase the availability and use of long-acting insulin analogues within the public health system in Botswana, again similar to other African countries.

Eswatini (formerly Swaziland): Currently, long-acting insulin analogues are not listed in the EML of the Kingdom of Eswatini. The only available insulins within the public healthcare system include insulins such as isophane and premixed insulins (30/70) all at 100units/ml [136]. In addition, whilst insulin protaphane is currently not listed in the Eswatini EML, it is stocked in some government hospitals and Army clinics to help improve patient care in view of its perceived longer action.

Long-acting insulin analogues such as insulin glargine are currently unavailable in the public hospitals in Eswatini; however, they are available in private hospitals. This illustrates issues of affordability with more expensive insulin formulations, including long-acting insulins analogues, as the Kingdom of Eswatini strives towards Universal Healthcare (UHC) in accordance with agreed sustainable development goals for NCDs [137-139].

As a result, there is currently limited prescribing of long-acting insulin analogues in the Kingdom with the current EML/STG being used to guide prescribing practices [140]. This is exacerbated by frequent stock-out of medicines within public facilities especially those for NCDs, with patients guided towards private pharmacies to purchase their medicines subject to high co-payments [140].

The current wholesale prices of insulin protaphane presenting as 5 × 3 ml cartridges is Rand 633.00 (US$42.80), with insulin glargine 100IU/ml 17% higher at Rand 727 (US$49.16) for a 5 × 3 ml cartridge (similar DDDs). This is encouraging with potential reductions in the price of insulin glargine through biosimilars towards isophane insulin, coupled with additional education of key Government personnel in Eswatini. As a result, potentially improving the chances of biosimilar insulin glargine being listed in the EML and funded within the public healthcare system in Eswatini in the future.

Malawi: There are concerns with the identification and management of patients with diabetes in Malawi, especially in rural settings where there is limited availability of standard insulins within health centres [141]. Similarly, standard insulins such as 10ml soluble insulin (100 IU/ml)) was only available among 25.0% of surveyed public hospitals and 36.4% of surveyed Christian Health Association of Malawi (CHAM) facilities in a recent paper [142]. As expected, there was higher availability of these insulins among private pharmacies [142].

Table 6-shows variable dispensing of different insulins in Queen Elizabeth Central Hospital in Malawi between 2015 and 2020, Variations in the availability of different insulins in Malawi *via* the Central Stores include:

- Insulin soluble - no data available for 9-7-15 to 30-6-16 and 1-7-18 to 9-7-19.
- Insulin lente (intermediate acting insulin) - no data available for 1-7-16 to 1-11-16 and 1-7-18 to 1-7-19 and concerns generally with availability.

Table 6: Packs of insulin dispensed in the queen elizabeth central hospital, Malawi, 2015 to 2020.

Insulin name	2015	2016	2017	2018	2019	2020 (Jan to June)
Soluble insulin injection (INSUGEN-R®, regular)	340	625	1140	830	852	570
Isophane insulin (INSUGEN-R®, NPH))	5719	5090	7640	4360	4560	4850
Premixed (30% insulin soluble and 70% isophane insulin)					110	80

NB: Insugen® is typically supplied by Biocon, India.

Table 7: Current prices among public hospitals in South Africa.

Insulin type	Trade name	Eml status*	Price**
short-acting (Fast-acting) (human)	Actrapid® HM, 100IU/ml, disposable cartridge (5x3ml)	EML	R164.10 (US$11.11)
Intermediate-acting (human)	Protaphane HM, 100IU/ml, disposable cartridge (5x3ml)	EML	R164.10 (US$11.11)
Premixed	Actraphane® HM 30/70, 100 IU/ml, disposable cartridge (5x3ml)	EML	R164.10 (US$11.11)
Insulin glargine (Originator)	Lantus® 100IU/ml, vial (1x10ml)	NON-EML	R534.57 (US$36.25)
Insulin glargine (biosimilar)	Optisulin® 100IU/ml (manufactured by Sanofi), cartridges (5x3ml)	NON-EML	R460.40 (US$31.41)
Insulin detemir	Levemir® 100IU/ml, disposable pen (5x3ml)	NON-EML	R639.20 (US$43.61)

NB: * EML = Essential medicine list; ** Contract price in SA Rand listed on contract circular RT297-2019.

- Insulin biphasic - no data available for 1-1-18 to 1-7-19.
- Usage of premixed insulins properly starting from 2018 onwards with recordings from 2019 onwards (Table 6).

However, electronic medical records are being introduced in hospitals in Malawi to improve the care of patients with diabetes, and we will be monitoring this progress [143].

There are currently no long-acting insulin analogues available in the public healthcare system in Malawi reflecting the lack of listing in the EML [144]. In addition, concerns with appreciably higher costs versus other insulins including NPH and other similar insulins. It may again be that appreciably lower costs of long-acting insulin analogues *via* biosimilars can help enhance their listing and use in Malawi in the future.

South Africa: Increasing prevalence of diabetes in South Africa has resulted in the utilisation of insulin within the public healthcare system in South Africa rising to 3.19billion DDDs in 2019, an increase of 11.1% compared with 2018. Encouragingly, expenditure on insulins went down by 3.6%, suggestive of the additional savings that can be made through economies of scale.

Currently, long-acting insulin analogues are unavailable within the public healthcare system in South Africa due to concerns with their appreciably higher costs versus basal/NPH insulins and no perceived clinical advantage [96]. Having said this, the costs of long-acting insulin analogues are likely to come down in price with greater competition from greater availability of different biosimilars of long-acting insulin analogues (Table 7 for Public Hospitals and Table S1 is shown in Appendix for Private Hospitals).

This will build on the current 28% price difference between 5 by 3ml cartridges of biosimilar insulin glargine versus insulin detemir and a 22.6% price difference between the originator (10 ml 100IU/ml) and biosimilar insulin glargine (5 by 3ml pen sets) on a DDD basis (Table 7). Having said this, the price of the disposable pens for biosimilar insulin glargine are still 2.8 times higher than those of intermediate acting insulins.

The ministerially appointed South African National Essential Medicines List Committee recently reviewed long-acting insulin analogues for use at the tertiary and quaternary level of care [96]. Consideration of therapeutic grouping of intermediate-acting and long-acting insulin analogues, coupled with respective pooled procurement/tendering, may potentially assist with access to long-acting insulin analogues from primary to quaternary levels of care in the future in South Africa with more affordable prices. This builds on current procurement prices for biosimilar insulin glargine within the public healthcare system in South Africa (Table 7).

However, since cost considerations are likely to remain a key issue in South Africa when appraising procurement of medicines within the public system given the desire to maintain universal healthcare whilst faced with growing pressure on resources, prices of long-acting insulin analogue biosimilars will need to fall considerably if they are to be funded within the public healthcare system in South Africa [145].

Tanzania: Currently long-acting insulin analogues are not available with the Tanzanian EML/STGs due to issues of affordability and concerns [146]. The routine availability of appreciably lower costs human insulins such as NPH insulin will make it more challenging for long-acting insulin analogues, including their biosimilars, to become routinely available in the EML. This needs to be addressed before long-acting insulin analogues become routinely available in Tanzania.

Uganda: There are ongoing concerns with the management of patients with diabetes in Uganda, and similar to other African countries an appreciable number of patients are unable to afford prescription medicines especially insulins along with equipment to monitor their blood glucose levels [147,148]. Consequently, there is a continuing need for national strategies to promote improved access to affordable medicines and diagnostic tests for patients with diabetes mellitus and CVD to reduce associated morbidity and mortality in Uganda [148]. There are also ongoing concerns regarding routine screening for complications such as microvascular complications and CVD in Uganda [149].

In Uganda, long-acting insulin analogues, including insulin glargine, are currently not listed in the Ugandan EML, which is a concern given the high rates of hypoglycaemia currently seen.

This reflects issues of affordability in Uganda, which is a major issue [147]. Currently, prices for insulin glargine for patients within the healthcare system in Uganda vary between US$15 - $35/pen depending on whether this is a biosimilar or originator, and whether at a hospital or community pharmacy. We have seen similar prices in other LMICs [44,92]. Typically, adolescents with diabetes require 2 pens/month, with overall costs considerably higher than US$8-10 for soluble insulin, NPH insulin at $9-10, with premixed insulin at $10-15 all at 1000 IU (i.e., 10 ml of 100 IU/ml) with each 10 ml vial lasting approximately 25–30 days.

Overall, it is believed that prices of biosimilar insulin glargine would need to fall appreciably for listing of long-acting insulin analogues in the National EML and more widely used. Addressing these challenges should though improve the care of patients with diabetes mellitus in Uganda and reduce the complications in patients with diabetes requiring insulin [150]. Improving caretaker involvement and other factors including a variety of insulin preparations available should help address key issues such as adherence to insulin therapy, further improving the care of patients with diabetes in Uganda and reducing associated morbidity and mortality [151].

Zambia: Similar to other African countries, there are concerns with the management of patients with diabetes mellitus in Zambia to reduce complications as well as address stock-outs of short, intermediate and longer-acting insulins common among public facilities [97,152]. Stock-outs among public facilities are a major challenge to patients in Zambia as this necessitates them having to either purchase their insulin from private pharmacies subject to 100% co-payment or through insurance schemes [97]. Having said this, there are concerns with the routine availability of short and intermediate-acting insulins within private pharmacies in Zambia, with prices typically higher than international reference prices, which also needs to be addressed [121].

To help with the availability of insulins within public healthcare facilities, the government of the Republic of Zambia has been routinely purchasing insulins listed in the Zambian EML. This includes protaphane as its longer acting insulin alongside both short and more intermediate-acting insulins. There has been no purchasing of long-acting insulin analogues including biosimilar insulin glargine as these are currently not listed in the Zambia EML due to issues of affordability and value [97,121]. We are also aware that in Zambia, there are initiatives in place for patients to receive free or subsidized insulins through the national health insurance scheme operationalised in 2020 to address issues of access, affordability and availability and we will be following this up in future research projects [7,153].

Usage of insulin protaphane within the University Teaching Hospitals in Lusaka has increased in recent years from 4130 vials in 2018, 9631 vials in 2019 and 3888 vials up to June 2020, with this growth rate likely to continue. Overall, it is believed that prices of long-acting insulin analogues, including biosimilar insulin glargine, would need to be close to those of insulin protaphane for insulin glargine to be prescribed and funded within the public healthcare system in Zambia. This is similar to a number of other African countries.

DISCUSSION

We believe this is the first study to document current utilisation patterns of long-acting insulin analogues across Africa and the rationale for either no or limited use within the different public healthcare systems. The first step within African countries is to ensure that patients with T1DM and T2DM are treated well, which includes enhancing access to pertinent treatments [4,7]. In the case of patients with T2DM, which represent the vast majority of patients with diabetes in Africa, activities should include improving diagnosis as well as aggressive early management with appropriate oral medicines to prevent progression to diabetes requiring insulin for management [4]. It is likely that mobile technologies will be increasingly used across Africa to help improve the management of patients with diabetes mellitus and associated complications especially given some of the concerns with monitoring patients with NCDs arising from the recent COVID-19 pandemic [115,154]. Mobile technologies can be used to provide education to patients with diabetes to improve their self-care as well as monitor their status including their HbA1c levels, adherence levels to prescribed medicines, weight and lifestyle changes [154,155]. In addition, appointment reminders as lockdown pressures ease [156].

However, if patients require insulin for their management, we are seeing global sales of long-acting insulin analogues increasing with worldwide sales of long-acting insulin glargine potentially rising to US$9.26 billion by 2025, with, as mentioned, worldwide sales of long-acting insulin detemir at US$2.7 billion in 2015 and growing at 7.5% per year [76, 157]. Utilisation of long-acting insulin analogues now exceeds that of human insulins among upper-middle and high-income countries and we are also seeing the growing use of long-acting insulin analogues in countries such as Bangladesh as well as lower income Central and Eastern European countries [39,75,92,95,102]. This reflects their perceived role with reducing rates of hypoglycaemia versus standard insulins such as NPH insulins as well as improving patient convenience. There are though ongoing controversies surrounding the benefits of long-acting insulin analogues as seen in the recent Cochrane Review by Hemmingsen et al. (2021) [77]. However, countered to some extent by the recent systematic review combined with a network analysis by Tricco et al. (2021) [78]. This is accentuated in Africa by the fact that compartive studies between NPH insulins and long-acting insulin analogues have typically been undertaken in high-income countries with very different circumstances to patients with diabetes in LMICs including those in Africa.

There are also concerns across Africa with the appreciably higher price of long-acting insulin analogues versus NPH and other insulins, and issues of affordability even with NPH and other insulins [39]. This is reflected in the variable listing of long-acting insulin analogues on national EMLs across Africa (Table 2), building on the lack of listing in the current WHO EML [123]. Even if listed on national EMLs, there can be concerns with their funding due to current high prices as seen in Ghana where long-acting insulin analogues are not currently listed in the NHIS or in their STGs despite listing in their EML. In addition, limited use in Cameroon, Kenya, Namibia, Nigeria and Zimbabwe despite long-acting insulin analogues being listed in their EMLs. The high prices for long-acting insulin analogues are exacerbated by the fact that, as mentioned, the insulin market is dominated by 3 manufacturers

who between them account for up to 96% of the global market by volume and up to 99% by value [41-44].

Based on our findings, coupled with ongoing activities in other countries especially other LMICs, we believe that a number of concurrent activities are needed to enhance the listing and funding of long-acting insulin analogues across Africa, including their biosimilars, to expand available choices. These include multiple activities to help obtain low cost biosimilar insulin glargine through for instance increasing competition as well as studies demonstrating the benefits of long-acting insulin analogues among African patients. Following this, educational activities to enhance their use especially if there are differences in pens and devices between different long-acting insulin analogue presentations [158]. As seen in South Africa and other African countries, appreciably lowering procured prices for biosimilar insulin glargine will improve their chances for listing in national EMLs [96].

As mentioned, potential activities to enhance the availability of low cost biosimilar insulin glargine within public healthcare systems across Africa include increased competition to potentially lower the prices of long-acting insulin analogue biosimilars as seen with biosimilars in other situations [89,159]. This can potentially be achieved by:

a) Governments/procurement agencies building on the WHO prequalification initiative to enhance imports of long-acting insulin analogue biosimilars from other LMICs including Bangladesh, China, India and Malaysia [44,46,92,107].

b) Governments/procurement agencies working with traditional insulin manufacturers and others to make long-acting insulin analogues available at lower prices, building on initiatives in Cameroon, Kenya and Nigeria, as well as Biocon's 'Mission 10 cents' initiative for recombinant human insulin (rh-insulin) [47-49,51,57,59,160]. This is potentially challenging given the current monopoly among the three principal insulin manufacturers currently accounting for up to 99% of the value of the global insulin market; however, potentially facilitated by purchasing consortia building on initiatives across Europe [44,161,162].

c) Governments (especially across regions) seeking to produce biosimilar insulin glargine within Africa. Biocon already supplies insulin analogues, including biosimilar insulin glargine, to a number of African countries, and was instrumental in developing appreciable manufacturing capabilities in Malaysia in addition to providing low cost recombinant human insulins in Tanzania [59,107,163]. The progression of consortia such as the East African Community consortia, which advocated increased local production of essential equipment and medicines to address future shortages arising from the COVID-19 pandemic as well as the South African Development Community (SADC), provide a forum for such discussions [115,164,165]. Such discussions can build on ongoing existing country initiatives regarding a 'GMP road Map' for Africa, which is now being progressed in a number of African countries including Ghana [116,166,167].

d) Similar to this, key government personnel within groups such as West African Groups, East African Community consortia and the South African Development Community (SADC) can unite to push for low prices for biosimilar insulin glargine [116,164,165], building on current successes in South Africa with their procurement practices for insulin. This also builds on current initiatives with purchasing consortia across Europe [161,162].

e) Governments/Ministries of Health should seek to only list biosimilars (of proven quality) on EMLs, e.g. biosimilar insulin glargine 100 IU/ml on national EMLs/health insurance lists, and not originators to further enhance competition among biosimilar manufacturers. Ideally, biosimilar long-acting insulin analogues should be no more than 30% to 50% more expensive than NPH and other insulins on a daily basis, especially with patients in a number of African countries struggling to fund standard insulins

Concurrent with this:

a) WHO Africa and others could seek to expand the remit of the Medicines Patent Pool as well as use of the flexibilities enshrined in the WHO TRIPS agreement to increase access and availability of insulin glargine including biosimilars at affordable prices to enhance their listing and affordability.

b) Pan-African consortia, with the help of WHO Africa, should also seek to ensure where possible consistency in prices for biosimilar insulin glargine across Africa to reduce issues of parallel exportation and other concerns.

c) Ministries of Health and/or physicians' groups should seek to enhance local knowledge of the potential patient benefits with long-acting insulin analogues through clinical trials and real-world evidence studies.

d) Ministries of Health/Physician Groups should ensure consistency between country EMLs and STGs given current concerns in Ghana.

e) Ministries of Health and other key stakeholder groups should work together to ensure the routine availability of biosimilar long-acting insulin analogues among all public health facilities especially hospitals/clinics to enhance competition (and also avoid unnecessary co-pays if patients have to pay for the insulin themselves in community pharmacies).

f) Governments should re-look at key issues such as cumulative mark-ups for medicines within a country, especially for high priority diseases such as diabetes, where there are high patient co-payments as mark-ups have ranged up to 565.8% for insulins among LMICs [112].

Once low cost biosimilar long-acting insulin analogues are routinely available and funded within countries, including listing on country EMLs, there are a number of educational and other initiatives that can be undertaken within African countries to enhance their use These include.

- Key personnel within Ministries of Health and Physician/ Pharmacy Groups should work together to collate ongoing clinical evidence among LMICs to support the continued listing of long-acting insulin analogues within EMLs/ funding within public healthcare systems
- Key physician/pharmacy groups should seek to educate all key stakeholder groups regarding similar effectiveness and safety between originator and biosimilar long-acting insulin analogues as more data becomes available across LMICs including Africa to avoid/reduce any negative nocebo effects [168].

- Physicians and pharmacists (as well as nurse practitioners in primary healthcare clinics) should work with patients to ensure they are familiar with the different pens/devices if this is the case between different long-acting insulin analogues including originators and biosimilars; however, reduced with national procurement practices
- Key Ministry of Health personnel along with physicians and pharmacists should work with patient organisations where pertinent to reduce any misinformation about biosimilars for long-acting insulin analogues to facilitate greater use especially where resources/co-payments are an issue. This includes where pertinent warning patients that devices may be different between originators and biosimilars
- Where pertinent, Ministry of Health personnel could potentially introduce target prescribing goals (quality indicators) for starting suitable patients on 100 IU/ml biosimilar insulin glargine where possible when prescribing a long-acting insulin analogue similar to initiatives among a number of European countries for biosimilars [90,169].
- Physician and Pharmacy Groups should seek to monitor HbA1c and hypoglycaemia rates in patients prescribed long-acting insulin analogues to see if reduced rates of hypoglycaemia/improved control are seen in practice, and subsequently broadcast their findings to enhance future use building on published studies. Concurrent with this, these groups should work with Governments and others to seek ways to enhance the routine availability of strips to improve home monitoring of blood glucose levels given current concerns

We are aware of a number of limitations with this study. These include the fact that we were not able to collect national data on pricing and utilisation of the different insulins outside of South Africa. In addition, we only collected pharmacy data from Nigeria. However, we were able to collect pricing and expenditure data from a number of sources in different countries. In addition, we did not formally test potential prices for long-acting insulin analogue biosimilars (insulin glargine) to be considered for inclusion in national EMLs where this is currently an issue as well as for increased funding and usage. Despite these limitations, we believe our findings are robust providing direction for the future.

CONCLUSION

There are continuing concerns with the growing prevalence rates of diabetes mellitus across Africa including patients requiring insulin and the implications for future morbidity and mortality. Hypoglycaemia is an increasing concern enhancing complication rates, and long-acting insulin analogues can potentially address this. However, the considerably higher costs of these analogues versus NPH and other insulins has appreciably limited their utilisation and funding in practice across Africa including listing on national EMLs. Biosimlar long-acting insulin analogues can potentially enhance future listing on EMLs and funding of these analogues; however, prices will need to appreciably fall to achieve this alongside increasing evidence of their benefits among patients in Africa.

CONFLICTS OF INTEREST AND FUNDING

The authors declare they have no competing interests.

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