Report for the 2021 WHO Expert Committee on Selection and Use of Essential Medicines on recent insulin price trends in a sample of countries (including but not necessarily limited to low- and middle-income countries), exploring key issues and suggestions for the future to enhance utilisation and funding for long-acting insulin analogues given current concerns

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1. Executive Summary

There are growing prevalence rates for diabetes worldwide, increasing morbidity and mortality. Morbidity and mortality rates are enhanced by the complications associated with diabetes, which include coronary vascular disease, as well as by hypoglycaemia. This urgently needs to be addressed exacerbated by the recent COVID-19 pandemic.

Long-acting insulin analogues were developed to reduce hypoglycaemia, especially nocturnal hypoglycaemia, as well as enhance patient convenience and address concerns with adherence to insulin regimes in practice. Recent systematic reviews, including Cochrane Reviews and the Lancet Commission on Diabetes, have endorsed their use, and this is reflected in their increased prescribing across multiple countries. Long-acting insulin analogues are now the principal insulin prescribed in upper-middle and high-income countries. Despite this, long-acting insulin analogues are still not listed in the WHO EML although they are included in the latest WHO Standard Treatment Guideline (STG) for diabetes.

There have been concerns with the higher acquisition costs of long-acting insulin analogues versus standard insulins such as NPH insulins, which has affected their reimbursement and funding in public healthcare systems especially among middle- and lower-income countries (LMICs). However published studies have now demonstrated their cost-effectiveness, with a number of studies demonstrating that their higher acquisition costs can be offset by lower complication rates, including hypoglycaemia, and associated costs.

The launch of biosimilars offers the opportunity to further lower the costs of long-acting insulin analogues to benefit all key stakeholder groups. Their availability has enhanced their use among Asian countries including Bangladesh, India and Malaysia, as well as among European countries. However, we are aware that the originator company has proactively lowered its prices of insulin glargine 100IU/ml to reduce the attractiveness of the biosimilar market. In addition, especially across Europe, promoted the patented 300IU/ml formulation (Toujeo®) enhanced by a number of publications suggesting lower rates of hypoglycaemia and improved patient convenience with the 300IU/ml formulation. This needs addressing as this has reduced the attractiveness of the biosimilar insulin glargine market in a number of European countries, with potential long-term consequences.

There are also still concerns among a number of African countries and Brazil regarding listing and funding of long-acting insulin analogues, including biosimilars, in the first place within their public healthcare systems. However, this is beginning to change in Brazil and some African countries, with this trend likely to continue as more biosimilars are launched with lower prices. Greater pro-activity is still needed though to enhance the use of long-acting insulin analogues to the benefit of all patients and healthcare systems. This includes potentially enhancing local production of the analogues, which builds on initiatives in Brazil generally with insulins and Malaysia with biosimilar insulin glargine, as well as additional education of key local decision makers regarding the role and value of long-acting insulins to address any remaining concerns. This is especially important post the COVID-19 pandemic with its impact on adversely affecting identification and management of patients with non-communicable diseases including diabetes.

In conclusion, as acquisition costs fall and evidence grows regarding the beneficial impact of long-acting insulin analogues on patient outcomes, demonstrated by increasing utilisation rates across countries, it becomes more difficult to exclude long-acting insulin analogues from national and WHO EMLs. The next step is for the WHO to re-look at their listing in the EML as prices fall, and subsequently align the EML with the WHO treatment guidelines for diabetes. Alongside this, seek ways to achieve additional price reductions for biosimilar insulin glargine to nearer that of NPH and other insulins where there are still concerns. This can potentially be achieved by facilitating local production of biosimilars among African and South American countries, as well as instigating educational and other activities to enhance the future use of biosimilars. Activities can also include only listing long-acting insulin analogues and strengths on EMLs where biosimilars exist as well as introducing quality targets surrounding the prescribing of biosimilars. Such tactics are also recommended in countries where utilisation of biosimilars are reduced by ongoing pricing and marketing tactics by originator companies. As a result, continue to expand the attractiveness of the biosimilar market to the future advantage of patients, physicians and healthcare systems.

1. Introduction including the rationale for the project

Diabetes is a priority disease area with prevalence rates growing across countries (1-3). In 2019, there were an estimated 463 million people worldwide with diabetes, with the vast majority (80%) in low-income and middle-income countries (LMICs) (4, 5), with these prevalence rates expected to grow. This growth will be fuelled by rising incident cases, which increased by over 100% between 1990 and 2017, and continuing (5).

Across Africa, there is an estimated 15.9 to 19 million people with diabetes (6, 7), with prevalence rates likely to reach 34.2 million in sub-Saharan Africa alone by 2040, and potentially up to 42 to 47 million people are likely to have diabetes across Africa by 2045 (6-8). Currently in Bangladesh, an estimated 7 million adults (6.9%) have diabetes (9), with some authors suggesting that prevalence rates will be as high as 13.0% of the population by 2030 unless addressed (10). In Europe approximately 59 million people are currently estimated to have diabetes, with these rates predicted to rise to 68 million by 2045 unless addressed (11).

These growing prevalence rates will increase the worldwide economic burden of diabetes to between US$2.1 to US$2.5 trillion by 2030, equating to 2.2% of Gross Domestic Product (GDP) (12). In 2015, the cost of diabetes 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 of costs being direct costs including the costs of medicines (13). These costs are estimated to increase to between US$35 to US$33 billion and US$59 to 32 billion (1.1% to 1.8% GDP) by 2030 unless addressed (13). The overall costs of diabetes are enhanced by associated complications, exacerbated by poor glycaemic control and adherence to treatments including insulins (9). Complications include renal disease, potentially leading to dialysis and transplantations, diabetic feet ulcerations potentially resulting in lower extremity amputations, complications with eyes potentially leading to blindness, as well as a greater risk of heart attacks and strokes (4). Diabetes is currently among the leading causes of non-traumatic lower extremity amputation and blindness worldwide, with patients also at greater risk of cardiovascular disease (4). Diabetes also reduces patients' quality of life; consequently, it needs to be carefully managed (1, 13-17). In Africa, morbidity and mortality associated with NCDs including diabetes and its complications is likely to exceed those associated with infectious diseases by 2030 unless addressed (18). In view of this, it is important that patients with diabetes should be increasingly carefully managed, which includes reducing the risk of complications including hypoglycaemia.

Long-acting insulin analogues were developed to reduce the risk of hypoglycaemia, especially nocturnal hypoglycaemia, as well as enhance patient convenience thereby improving adherence rates, which can be a concern (4, 11, 19-21). A number of studies have demonstrated patient benefits of either long-acting insulin glargine or insulin detemir versus Neutral Protamine Hagedorn (NPH), although there have been concerns with appreciably higher acquisition costs and limited differences in patient benefits in some studies (20, 22-25). This perceived improvement in patient care with long-acting insulin analogues is reflected by the fact that their use now exceeds that of standard insulins such as NPH insulins among upper-medium and high-income countries (26). In addition, within the insulin market, expenditure on long-acting insulin analogues is growing. The insulin glargine market was valued at US$3.88 billion in 2018, and is envisaged to reach US$9.26 billion by 2025. This will be helped by growing sales of patented 300 IU/ml insulin glargine (Toujeo® – Gla-300) offsetting increasing sales of biosimilars, although others have suggested lower overall sales (27, 28). Alongside this, sales of insulin detemir were US$2.7 billion in 2015 and growing at 7.5% per year (29). There is also increased prescribing of insulin degludec, enhanced by studies demonstrating its cost-effectiveness compared with other long-acting insulin analogues (30-33). As a result annual sales of insulin degludec were US$1.11 billion in 2017, up 1.8 fold from 2016 (34). Overall, the global insulin market was valued at US$24 billion in 2018 and is envisaged to grow at a compounded rate of 4.9% over the next few years (35).

Concerns with considerably higher acquisition costs of long-acting insulin analogues versus standard insulins such as NPH in some markets, coupled with concerns with their overall cost-effectiveness, have resulted in issues with their use and funding in some countries (1, 23, 26, 36-40). However, this is not universal with studies showing 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 (41-44). These various concerns and issues are reflected in current considerations regarding the inclusion of long-acting insulin analogues in the World Health

Organization's Essential Medicines List (WHO EML) (45). This is different to current WHO standard treatment guideline (STG) which does include long-acting insulin analogues. However, we are now seeing recent systematic reviews including those from the Cochrane Centre as well as the Lancet Commission on Diabetes now endorse the use of long-acting insulin analogues, and this will grow (4, 20).

These issues are different to the inclusion of short-acting insulin analogues within EMLs and STGs, although here to there have been concerns regarding the extent of clinical benefits seen with very short-acting insulin analogues versus regular human insulins (46).

The costs of long-acting insulin analogues can be reduced with increasing availability and use of lower cost biosimilars, which should enhance their listing and funding within public healthcare systems where there are currently concerns with their role and value. However, we are aware there have only been limited price reductions for biosimilar insulin glargine in some countries versus the originator as well as concerns with switching patients between originators and biosimilars due to different devices between the formulations and the potential for hypoglycaemia (47-50). Sales of patented insulin glargine 300IU/ml Gla-300) are also increasing in view of potentially reduced rates of hypoglycaemia (28). These combined factors have reduced the attractiveness of biosimilar long-acting insulin analogues in a number of countries, reduced potential savings from biosimilar availability as well as reduced the potential of listing biosimilar insulin glargine in National EMLs where this is currently not the case.

Concerns with different devices between the originator and biosimilar insulin glargine potentially increasing rates of hypoglycaemia resulted in, for instance, low use of insulin glargine biosimilars (9%) among diabetologists in the UK in 2017 (51). Some European health authorities are also currently advising against switching between originator and biosimilar insulin glargine despite publications demonstrating similar effectiveness and safety between them (52-55) in view of these concerns, further limiting their utilisation. However, this is not universal with some commissioning groups in England achieving utilisation rates of 53.3% in December 2018 for biosimilar insulin glargine out of the total insulin glargine market (56). In addition, in the US usage of the biosimilar reached over 40% of the total insulin glargine public market by 2018 (47).

The first priority within a country should be to ensure that NPH insulin and other similar basal insulins, along with other medicines listed in the WHO EML, are readily accessible and available to all citizens. In addition, there is the necessary equipment and facilities for rapid diagnosis of patients with diabetes as well as for patients to routinely monitor their insulin levels at home to prevent complications. This is before considering the potential availability and funding of more expensive long-acting insulin analogues given the morbidity and mortality associated with diabetes (57). We are aware that there are issues with access and availability of insulin and monitoring equipment among a number of LMICs, which urgently needs addressing (1, 26, 58). However, this is beginning to change. We are also aware that long-acting insulin analogues are now widely available and prescribed in a number of countries including LMICs to help minimise the risk of nocturnal hypoglycaemia and improve patient comfort (4), endorsed for instance by the Lancet Commission on Diabetes (4). However, issues of affordability and value still persist (26, 40, 59, 60). Consequently, the development of lower cost biosimilars for insulin glargine and detemir should help address concerns with their costs and perceived value. Recent reviews have confirmed the safety and effectiveness of long-acting biosimilar insulin analogues (54, 55, 61, 62), coupled with the potential for considerable cost savings (63). However, concerns with switching still remain (49, 51, 53).

In view of this, there is a need to assess current utilisation of long-acting insulin analogues across countries particularly Central and Eastern European (CEE) countries as well as LMICs where there are resource issues regarding both biologicals as well as long-acting insulin analogues to guide future policies. In addition, investigate the extent of current price reductions and other activities from both originator and biosimilar companies to enhance their affordability and use especially among LMICs. This potentially includes any 'evergreening' and other activities by originator companies to reduce the attractiveness of the biosimilar market. Examples of 'evergreening' tactics in other situations include the launch of different devices for the treatment of asthma as well as the development of longer-acting oral formulations and intra-muscular formulations of anti-psychotics to improve compliance and reduce recurrences (64-67). In addition, escitalopram versus citalopram, pregabalin versus gabapentin and esomeprazole versus omeprazole (68-72).

Alongside this, there is a recognised need to explore the potential rationale for any changes seen in utilisation patterns of insulins, including long-acting insulin analogues, across countries in recent years to provide exemplars. In addition, help to develop guidance on future activities that could be introduced by key stakeholder groups across countries to enhance future availability and use of biosimilar long-acting insulin analogues to the benefit of all key stakeholder groups. This includes addressing current gaps in the EML.

This report is focused on long-acting insulin analogues as there has typically been greater controversy surrounding their use in view of the considerable price differential that has been seen in practice between long-acting insulin analogues and regular/ pre-mixed insulins in some countries, which has resulted in calls for their disinvestment (37, 59, 60). In addition, as mentioned, concerns with switching patients between originators and biosimilars due to different devices between the formulations and the potential for increasing hypoglycaemia (47-50). Alongside this, the activities of the originator company to promote still patented formulations, including potentially 'evergreening' tactics with the launch of Gla-300, to reduce the attractiveness of the biosimilar market.

2. Methodology

The research principally concentrated on long-acting insulin glargine 100 IU/ ml as this was typically the only long-acting insulin biosimilar available across countries, expenditure on insulin glargine is appreciable and potentially reaching up to US$9.26 billion worldwide by 2025 (27), and there have been controversies surrounding its use with calls for disinvestment in some countries (37). Alongside this, annual sales of insulin detemir were US$2.7 billion in 2015 and growing at 7.5% per year (29) and annual sales of insulin degludec were already US$1.11 billion in 2017, up 1.8 fold from 2016 (34). These growth rates further endorse the need to critically examine ways to increase the prescribing of lower cost biosimilar long-acting insulin analogues across countries, especially where there have been concerns with the funding and use of long-acting insulin analogues in the first place. Increased prescribing of biosimilar insulin glargine should increase competition and potentially lower prices, as well as enhance the attractiveness of the biosimilar market for other long-acting insulin analogues as they lose their patents. This should benefit all key stakeholder groups.

A mixed approach was used to collect utilisation and expenditure data on insulins in general, and insulin glargine in particular, and the subsequent rationale for the patterns seen. The data collected depended on its availability and access across countries, as well as the situation within countries. Alongside this, determine potential ways to enhance future listing, funding and use of long-acting insulin analogues including biosimilars where currently these are not available/ not routinely funded and used within public healthcare systems to the benefit of all key stakeholders.

Europe included both Western European and CEE countries as they constitute a range of countries with different economic powers, geographies and populations (73) in order to robustly compare and contrast the different approaches to long-acting insulin analogues and biosimilar insulin glargine preparations. CEE countries were chosen as there has been appreciably lower utilisation of originator biologic medicines among these countries versus Western European countries in view of their high costs and associated high patient co-payments (74-76). Consequently, there should be greater potential for biosimilars of long-acting insulin analogues among CEE countries. However, this remains to be seen.

Among the European countries, the principal focus will be on reimbursed utilisation and expenditure data from 2014 or later onwards. Data from health authority and health insurance company databases were principally used as they have robust data sets which are regularly audited (73, 77, 78). Consequently, these databases provide a reliable source for comparing utilization and expenditure data across countries (77). The exception in Europe is Kosovo where the data is based on imports. This is because formal reimbursement of medicines has not started yet in Kosovo; hopefully, by the end of 2021 or the first quarter of 2022. We have used this approach in Kosovo in previous studies (79, 80). Data from Malta is also based on import data for the national healthcare system with all Maltese nationals with diabetes are entitled to free treatment through the public health care system according to the conditions set out in the national formulary.

Utilisation data was first broken down into Defined Daily Doses (DDDs) to aid comparisons between countries. DDDs are a well-recognised measure for comparing utilisation patterns between countries (81, 82), and have been used in multiple publications when assessing utilisation and expenditure patterns across disease areas and countries (73, 83-88). DDD data will be collated and changed into percentages to aid comparisons between countries given appreciable differences in population sizes among the European countries. Expenditure data remained in the local currency, without conversion to either Euros or US$ where pertinent, as the principal focus of this research especially in Europe was on differences in reimbursed prices over time between the originator and the different biosimilars as percentages rather than actual price levels. However, price data has been collected for a number of African and Asian countries for comparative purposes especially where long-acting insulins are currently not reimbursed.

The Asian countries chosen included Bangladesh, India, Korea, Malaysia and Pakistan. The countries again provided a range of countries based on their population size, economic status, extent of universal healthcare, geography, level of co-payments, as well as financial consequences when family members become ill (89-91). Pricing and utilization data was also included from a range of South American and African countries since typically long-acting insulin analogues are not routinely listed or reimbursed within the public healthcare systems in a number of these countries or recommended in national treatment guidelines (1, 59, 60, 92), although this is changing. Since originator or biosimilar long-acting insulin analogues in these countries are typically dispensed in private community pharmacies or drugs stores, or in private hospitals, feedback from physicians, pharmacists and key personnel working within pharmacies, combined with local knowledge, was used to provide information on utilisation and prices of the different insulin glargine preparations together with changes in recent years and any rationale. We have used this approach before when national datasets are not routinely available (89-91, 93). Similar to previous projects, impressions were provided from physicians and pharmacists when no Ministry of Health or other robust data sets were available to document changes in utilisation and prices of insulin glargine as well as other insulin preparations in recent years. That is, if other information sources were unavailable due to issues of confidentiality and local culture since we were not paying physicians or pharmacy personnel for their time (89-91). This data for community pharmacies and drug stores has been supplemented with utilisation and expenditure data from hospitals where available. The hospitals were typically selected to provide a representation of the situation within a country.

In addition in Brazil, Korea and Pakistan, data was extracted from the MIDAS-IQVIA International database as well as government sources to provide current data on utilization and expenditure patterns. In the case of Korea, this builds on a recent study with infliximab biosimilar (94).

3. Findings including insulin glargine

We will first consolidate the findings from Africa before discussing those from Asia, South America and Europe This reflects the fact that published studies have shown generally limited listing of long-acting insulin analogues among Africa countries versus higher use in upper-middle- and high-income countries.

3.1 Africa

Typically among African countries, there is limited or no utilisation of long-acting insulin analogues due to cost differentials, issues of affordability and lack of listing within the EMLs of a number of African countries. This will remain until prices of long-acting insulin analogues approach those of standard insulins such as NPH insulin.

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

African countries where long-acting insulin analogues are currently not contained within national EMLs include Eswatini, Malawi, South Africa, Uganda, and Zambia. The situation is different in other African countries including Kenya, Namibia, Nigeria, and Zimbabwe. However, even in these countries there is limited use of long-acting insulin analogues due to issues of affordability. The situation may change as the price of long-acting insulin analogues falls with increasing availability of biosimilars as well as studies emphasising their patient benefits, especially given the extent of hypoglycaemia and its consequences across Africa. However, this remains to be seen.

Within Eswatini, the only insulins currently available within the public healthcare system include soluble insulins, isophane, zinc insulins and insulin plus isophane (30/70), all at 100IU/ ml (95). Insulin protaphane whilst not listed is stocked in some government hospitals including the Mbabane Government hospital and Army clinics. However, there are frequent stock-out of medicines within public facilities in Eswatini, especially for NCDs, with patients guided towards private pharmacies to purchase their medicines with associated issues of co-payment and affordability (96). Insulin glargine is though available within private hospitals in Eswatini. Prices of insulin protaphane 5 x 3ml pensets within the wholesalers in Eswatini are Rand 633.00, with insulin glargine 100IU/ml 17% higher at R727 for a 5 x 3ml penset (similar DDD). This is encouraging compared with the situation in South Africa (Table 1), with reductions in the price of insulin glargine towards soluble and isophane insulin potentially enhancing listing and funding in the public healthcare system in Eswatini combined with educational activities promoting the value of long-acting insulin analogues to key Government decision makers.

Within Malawi, despite up to 60% of healthcare being provided by public facilities, funded via taxation and donations from international partners, with 37% of care provided by the Christian Health Association of Malawi (CHAM) (97), patients are typically referred to private pharmacies to purchase their medicines if these are currently unavailable in public facilities (97, 98). This is a concern with a recent paper finding that standard insulin 100 IU/mL (10 mL) was only available among 25.0% of surveyed public hospitals and 36.4% of surveyed CHAM facilities (97). However, utilisation data from public facilities is very variable in Malawi and packs dispensed within leading hospitals can also be variable, i.e., in Queen Elizabeth Central Hospital 6059 packs of INSUGEN® regular, NPH or biphasic were dispensed in 2015 rising to 8780 in 2017 before falling to 5522 in 2019, and rising to 5200 between January to June 2020. In the future, it may be that appreciably lowering the costs of long-acting insulin analogues via biosimilars may enhance their listing and use in Malawi in the future.

Currently, long-acting insulins are unavailable within the public healthcare system in South Africa due to concerns with higher costs than basal/ NPH insulins and no perceived clinical advantage (60). Having said this, costs of long-acting insulin analogues have come down in price in the public hospitals in recent years with greater competition and the availability of biosimilars (Table 1). These continued price reductions should enhance future listing and use within the public system, with cost considerations a key issue in South Africa given their desire to maintain universal healthcare (99). This is emphasised in the ministerially appointed South African National Essential Medicines List Committee which recently reviewed long-acting insulin analogues for use among tertiary and quaternary care facilities (60). The Committee stated that consideration of a therapeutic grouping of intermediate-acting and long-acting insulin analogues, coupled with respective pooled procurement/tendering, may potentially assist with access to these analogues at affordable prices in the future (60). Alongside this, additional research may still be needed to determine whether long-acting insulin analogues reduce the risk of long-term diabetic complications in practice, building on existing publications. However, the current 2.8-fold difference between intermediate-acting analogues and biosimilar insulin glargine (DDD basis for 5 pens) arising from successful procurement practices limits their listing in the national EML.

Table 1 - Current prices among public hospitals in South Africa (in SA Rand)

INSULIN TYPE	TRADE NAME	EML status *	PRICE**
Intermediate-acting (human)	Protaphane HM, 100 iu/ml, disposable pen (5x3ml)	EML	R164.10
Intermediate-acting combined with fast-acting	Actraphane HM 30/70, 100 iu/ml, disposable pen (5x3ml)	EML	R164.10
Glargine, long-acting insulin analogue biosimilar	Optisulin 100 iu/ml x 3ml cartridges; pens provided free of charge	NON-EML	R92.08 for one pen; R460.40 for 5 pens
Glargine, long-acting insulin analogue	Lantus 100 iu/ml, vial (1x10ml)	NON-EML	R534.57
Detemir, long-acting insulin analogue	Levemir 100 iu/ml, disposable pen (5x3ml)	NON-EML	R639.20

NB: * EML = Essential medicine list; ** Contract price in SA Rand listed on contract circular RT297-2019 (Accessed 7 February 2021). Available at: http://www.treasury.gov.za/divisions/ocpo/ostb/bidders/CMD%2024%20RT297-2019.pdf

Currently in Uganda, long-acting insulin analogues such as insulin glargine are not listed in the Ugandan EML. This is seen as problematic among physicians in view of the high rates of hypoglycaemia currently in Uganda. The lack of listing of long-acting insulin analogues in Uganda limits their use in practice in Uganda with issues of affordability a major concern (100). This also applies to other medicines to treat patients with diabetes and its complications, along with diagnostic tests. These concerns have resulted in calls for medicines within the EML, as well as diagnostic tests, to be readily accessible and available in public healthcare facilities across Uganda (100-102).

Currently, prices for insulin glargine vary between $15 - $35/ pen in Uganda depending on whether this is a biosimilar or originator, and whether hospital or community pharmacy, with adolescents with diabetes typically requiring 2 pens/ month. This compares with current prices of 1000IU (i.e., 10ml of 100IU/ml) within the healthcare system of approximately $8-10 for soluble insulin, NPH insulin at $9-10, with premixed at $10-15, with each 10ml vial lasting approximately 25 – 30 days. It is believed that prices of biosimilar insulin glargine would need to fall to nearer those of premixed insulin on a monthly basis, e.g., reduction of 50% or more, to be considered for listing in the National EML and more widely used.

Currently within Zambia, stock-outs of insulins listed in the EML among public facilities are a concern with patients having to principally purchase their insulin from private pharmacies subject to 100% co-payment (40). However, there are concerns with the routine availability of insulins within private pharmacies in Zambia, with prices typically higher than international reference prices (103). To address this, the Government in the Republic of Zambia has been routinely purchasing insulins listed in the Zambian EML. This includes protaphane as its longer acting insulin, with currently no purchasing of long-acting insulin analogues including biosimilar insulin glargine as these are currently not listed in the Zambian EML due to issues of affordability and value (40, 103). Usage of insulin protaphane has increased within the University Teaching Hospitals in Lusaka in recent years reflecting increasing prevalence rates. Usage has grown from 4130 vials in 2018, 9631 vials in 2019 and 3888 vials up to June 2020, with this growth rate likely to continue. It is believed that prices of long-acting insulins, 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.

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

Currently, insulin glargine is available within the public healthcare system in Botswana alongside short, intermediate acting and pre-mixed insulins including Humalog® (1); however, there is principally limited or no use within the public system. Long-acting insulin analogues are also available in the private system. Appreciably lowering the prices of long-acting insulin analogues with biosimilars towards those of NPH and other similar insulins would appreciably enhance their use within the public health system in Botswana.

Long-acting insulin analogues are also available within the healthcare system of Cameroon. However, access to insulins and monitoring equipment is a major issue with high co-payment levels outside of sponsored programmes such as the 'Changing Diabetes in Children' (CDiC) initiative (104, 105). There are though concerns with glycaemic control among children enrolled in the CDiC programme with often 3 or more insulin injections per day (106). Long-acting insulin analogues could help; however, prices would need to appreciably fall through biosimilars to enhance their use.

Two long-acting insulin analogues, insulin glargine and detemir, have been approved by the Ghanaian FDA, with long-acting insulin analogues currently listed in the Ghanaian EML (26, 107). However, these are currently not included in the Ghanaian STGs nor currently reimbursed within the National Health Insurance (NHI) Scheme due to their higher costs, severely limiting their prescribing within the public healthcare system in practice (92, 108). This is reflected by increased use of soluble, isophane and premixed insulins within one leading public hospital in Ghana, rising from 8883 10ml 100IU/ml units in 2018 to 7468 by mid-year 2020. In addition in 2020, only 4 units of 3ml 100IU/ml insulin glargine were dispensed. 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, with this increase expected to continue, with currently no prescribing of long-acting insulin analogues. Appreciably lowering the price of long-acting insulin analogues will enhance access and affordability given ongoing funding concerns in Ghana. This is reflected by Novo Nordisk offering insulin free to children to improve their care under its CDiC initiative in Africa (109).

Concerns with the diagnosis of diabetes in Kenya, combined with issues of affordability with often catastrophic consequences when family members become ill, has resulted in a number of initiatives in recent years (1, 110-112). This includes the Base of Pyramid (BoP) aiding diagnosis as well as established a ceiling price of KSh 500–600 (US$5) for insulin Mixtard® insulin in participating hospitals and surrounding pharmacies, equating to a two thirds price reduction (111). Consequently, there has been very variable availability and use of long-acting insulin analogues in Kenya despite their availability in the public system. Utilisation of long-acting insulin analogues in Kenyatta National Hospital (KNH) rose to between 3.4% to 3.6% of total insulin use in recent years from 0.51% in 2015 despite falling insulin use during this period, with patients purchasing supplies in community pharmacies. However, their use is typically not seen outside of leading tertiary hospitals due to issues of affordability. Consequently, it is envisaged that prices of long-acting insulins including biosimilars will need to appreciably fall before there is any appreciable use in Kenya in the future.

Overall, a wide range of insulins, including soluble and long-acting insulins, are currently available to the public via PHCs financed by the Government of the Republic of Namibia (1). However, tempered by issues of affordability.

The situation is different in Nigeria where the cost of care is typically out-of-pocket, resulting in potentially high co-payment levels for medicines for patients (113). This is particularly important in Nigeria with studies suggesting that the costs of medicines to treat patients with diabetes can range from 72.3% to 90% of total costs, typically out-of-pocket (114, 115). Standard insulins such as premixed insulin and long-acting insulin analogues, insulin glargine, are currently contained in the Nigerian EML. However, concerns with affordability and availability, especially insulin glargine, affects their use in practice (1).

Among three hospitals in Northern Nigeria, utilisation of insulin glargine ranged from 50 to 100 packs of 5x3ml 100IU/ml, with prices per pack ranging from N3600 to N4300. Among 11 community pharmacies surveyed, an average of 75 packs of insulin glargine were dispensed during the year, which was typically the originator. It is likely that prices of long-acting insulin analogues will also need to appreciably fall in Nigeria with increasing availability of biosimilars to enhance their use given current high patient co-payment levels.

Long-acting insulin analogues have been listed in the Essential Medicines List/ Standard Treatment Guidelines of Zimbabwe since 2015 (EDLIZ 7th and 8th editions) (116). This includes both insulin glargine and insulin detemir. However, availability within central provincial and district public hospitals is erratic and inconsistent, exacerbated by their higher costs versus standard insulins. Consequently, the most accessible and prescribed insulins in Zimbabwe currently include the short, intermediate and

biphasic insulins in 10ml vials. Prices of long-acting insulin analogues will have to appreciably fall via biosimilars to enhance their use in the future.

3.2 Asia

There is generally increasing use of long-acting insulin analogues in Asia including Bangladesh and India, with this trend expected to continue.

3.2.1 Bangladesh

Within hospitals in Bangladesh, there is variable use of long-acting insulin analogues reflecting the fact that among public hospitals, standard insulins are typically provided free-of-charge until monies and supplies run out; however, this is not universal. Once this happens, patients typically purchase their insulins directly from pharmacies and drug stores with 100% co-payment. This is the situation for patients attending private hospitals with typically no purchasing of medicines directly in these hospitals.

The prescribing of long-acting insulin analogues among hospital personnel in Bangladesh can be as high as 50% of total insulins, driven principally by endocrinologists. However, this is not universal although physicians who are not endocrinologists are now increasing their prescribing of long-acting insulin analogues. This is principally insulin glargine among the long-acting insulin analogues. Affordability though remains a key consideration with a study published in 2017 documenting that diabetes with diabetes paid an average of 35,385 BDT (US$454) per year for their medicines versus only 1609 BDT (US$21) for those patients without diabetes (117).

The increased prescribing by physicians of long-acting insulin analogues in Bangladesh is reflected by their increased dispensing in community pharmacies and drug stores, reaching 50% or higher of insulins dispensed in recent years. This is principally insulin glargine, with biosimilars increasingly dispensed in view of cost differences (Table 2).

Table 2 – Current prices for a range of different insulin glargine preparations among pharmacies in Bangladesh

Manufacturer	Packs (100IU/ml insulin glargine)	Typical selling price in pharmacies and drug stores (local currency)
Lantus (Sanofi-Aventis)	100IU/Ml 3ML Pen, 5 X 3ml pen	1220, 6100 BDT
Abasaglar	100IU/Ml - 3ML Pen	1085 BDT
Glarine	100IU/Ml - Pen, 5 x 3ml pens	950, 4750 BDT
Larsulin	100IU/ML - 3ML Vial and Pen Cartridge	600 BDT

Prices have remained stable in recent years. However, a minority of pharmacies reported both increases and decreases in prices up to 13.8%.

3.2.2 India

There has been an increase in the prescribing of insulin glargine among five surveyed hospitals in India until recently, reaching over 80,000DDDs in 2019 in one hospital. This is typically a biosimilar with prices (expenditure/ DDD) generally stable over the years at 60 INR/ DDD in these five hospitals apart from a modest increase in 2017 followed by a fall. This is different to the findings of Ewen et al (2019) who found no human insulin was available in their surveyed provincial and district public hospitals in India and only short-acting insulin was in stock in the teaching hospital in the state capital surveyed (26). This may reflect growing awareness among physicians of the patient benefits with long-acting insulin analogues enhanced by lower procured prices (expenditure/ DDD).

There were though differences in the prices of the different insulin glargine preparations in 2020 among 207 community pharmacies surveyed. The most consistent price for Lantus® 100IU/ml 3 mls

was 722INR, with the cheapest biosimilar at 382INR/3mls, which was the most consistent price for biosimilars and similar to the procured price for biosimilars among the hospitals. There have though been changes in the prices of both the originator and biosimilars in recent years in India, with a maximum of 20% in any one year. The current price difference between originator and biosimilar insulin glargine in India may well have facilitated increased prescribing of biosimilars within hospitals in India in recent years where typically insulins are provided free of charge until funds run out as part of moves towards universal healthcare (26, 118, 119).

3.2.3 Korea

There are currently limited differences in the public price of insulin glargine 100IU/ml between the originator and biosimilars in Korea, ranging from price reductions of 0.27% to 5.0% between the originator and the biosimilar depending on the preparation prescribed (120).

In view of this, coupled with currently limited demand-side measures in Korea (94, 121), there is currently only limited utilisation of biosimilar insulin glargine in Korea. However, usage has grown from a low of 0.95% of total insulin glargine preparations in 2017 up to 4.7% in 2019, with further growth expected.

3.2.4 Malaysia

Typically within the university hospitals in Malaysia, there is appreciable prescribing of long-acting insulin analogues at between 50-70% of all insulins dispensed. This is typically insulin glargine biosimilars, which can account for up to 90% of all long-acting insulin analogues dispensed. This high rate among the public hospitals in Malaysia is facilitated by procurement practices including the government's preferentially purchasing of generics and biosimilars from Malaysian companies where possible (122), with biosimilar insulin glargine now manufactured in Malaysia to a high standard (123-125).

Since insulins are available free of charge among public hospitals in Malaysia, there is currently limited dispensing of biosimilars among community pharmacies in Malaysia although there is limited dispensing of the originators at 100% co-pay. Originator Lantus® is currently priced 10 to 20% higher than the biosimilar to try and enhancing dispensing in community pharmacies.

Overall, it is envisaged that price reductions for biosimilar insulin glargine versus originator prices in Malaysia, enhanced by local manufacturing, has enhanced their use potentially serving as a model to other countries.

3.2.5 Pakistan

Whilst there has been a 69.5% increase in the utilisation of insulins in Pakistan from 2014 to 2019, with a 151.2% increase in expenditure, utilisation of insulin glargine still remains low at 1.97% of total insulins in 2020. This reflects issues of affordability with insulins generally, and for long-acting insulin analogues in particular, despite good availability of the different insulins as a result of co-payment issues (89, 126, 127).

Currently biosimilars (Basagine®) are 20.5% cheaper than the originator among community pharmacies in Pakistan, similar to the findings of Ewen et al (2019) (26). However, typically the originator is generally dispensed with concerns generally with the quality of generics in Pakistan (128). Issues regarding the quality of biosimilars, coupled with greater price reductions, need to be addressed in Pakistan given currently high patient co-payment levels before there is appreciable use of long-acting insulin analogues in Pakistan.

3.3 South America and Canada

We do see differences among the South American countries regarding the utilisation of long-acting insulin analogues as these have not traditionally been funded in the public healthcare system in Brazil due to concerns with higher costs and limited clinical differences from basal insulins (37, 59); however, this is changing.

Currently insulins in Argentina are bought by the various Provinces, e.g., PRODIABA in the province of Buenos Aires, to help with their costs for patients due to bulk purchasing. For certain insurance members, especially those with high membership, there can also be appreciable discounts up to further enhance affordability and use. However, there are currently limited price reductions for biosimilar insulin glargine versus originators in Argentina, i.e., up to a maximum of 3%, impacting on their use in practice.

In Brazil, the Ministry of Health fund NPH and other human insulins 100 IU/ mL (39), with their use within the public healthcare system increasing from 5.61DDDs/1000 inhabitants/ day (DIDs) in 2009 to 9.04 DIDs in 2017 (129), with this growth is continuing. However, expenditure/ DDD fluctuated between 2009 and 2017 at between US$0.17 to US$0.57 (2017 exchange rates) influenced by negotiations and other factors between various pharmacy providers (129). However, due to concerns with higher costs and perceived modest additional patient benefits, the National Health Technology Agency (CONITEC) recommended that long-acting insulin analogues should not be incorporated into the Brazilian NHS. Consequently, patients had to fully fund the costs of the analogues themselves if these were recommended by physicians unless there was a successful court case (37). Some States though in Brazil had recently included medicines with higher costs such as insulin glargine within their healthcare system provided patients meet agreed criteria to reverse the increasing costs of law suits (130, 131). However, recently the Ministry of Health changed its advice for patients with Type 1 diabetes (T1DM) (59, 129), although this is conditional on the costs of the analogues being equal to or less than the NPH insulin pens and prescribed according to the guidelines established by the Ministry of Health (132). This has affected their use in practice.

Throughout these deliberations, patients can still purchase insulins, including long-acting insulin analogues and their biosimilars, directly from private pharmacies if they so wish although this is subject to 100% co-payment. Consequently, private pharmacies are important for purchasing and distributing insulin glargine in Brazil, with growing trends seen in recent years. Currently, maximum consumer prices (PMC) for biosimilar insulin glargine are 51.5% lower than the originator. However, the originator company has offered extensive discounts limiting the differences in prices between originators and biosimilars and thereby the dispensing of biosimilars. This is a concern long-term as it will discourage competition in the biosimilar market for insulin glargine and potentially lower prices. In addition, discourage other manufacturers from launching biosimilars of other long-acting insulin analogues once they lose their patents.

This contrasts with Uruguay where there has been considerable growth in the utilisation of long-acting insulin analogues in recent years although from a low base. This reflects their perceived value. Utilisation of insulin glargine and detemir rose by 345.8% between 2014 and 2019 from a total of 3825 DDDs to 21900 DDDs in the public system (FNR - Fondo Nacional de Recursos) with this trend continuing. However, the share of insulin glargine has gradually decreased from 77.9% of total long-acting insulins in 2014. There are currently no biosimilar insulin glargine preparations in Uruguay, reflected by the fact that expenditure/ DDD for insulin glargine has remained constant over time at 51.84 Uruguayan Peso/ DDD. However, this may change as the long-acting insulin market becomes more attractive and attracts biosimilars at lower prices.

Basaglar® insulin glargine biosimilar accounted for 7.8% of all insulin glargine dispensed between July 2018 and June 2018 among the various Provinces in Canada (133). It is envisaged these rates will increase with ongoing demand-side measures to enhance the prescribing of biosimilars in the public health system in Canada (134, 135). However, price differentials may need to increase from 21.1% currently (133) to accelerate this.

3.4 Europe

There has typically been growing utilisation and expenditure on long-acting insulin analogues as a percentage of total insulins among the European countries in recent years (Table 3), reflecting their increasing value to treat patients with diabetes requiring insulin. Interestingly, there was no apparent difference in utilisation rates between Western European and CEE countries with the highest utilisation of long-acting insulin analogues versus total insulins seen among CEE countries including Estonia and Latvia. This compares well with Catalonia where the prescribing of long-acting insulin analogues reached 55.2% of total insulins in 2020, with expenditure accounting for 63.2% of total expenditure on insulins. This is different to the situation with other biological medicines such as the anti-TNFs where

there could be considerable differences in utilisation rates between the countries, with typically low use among CEE countries (74, 76).

Table 3 – Percentage utilisation and expenditure of long-acting insulin analogues versus total insulins across Europe in recent years

	Utilisation			Expenditure		
	Previous two years	Previous year	Latest figure	Previous two years	Previous year	Latest figure
Bosnia and Herzegovina	27.1	35.3	35.5	35.6	42.8	45.1
Bulgaria	19.5	19.6	22.0	30.8	29.9	33.3
Estonia	53.7	55.1	56.5	60.6	62.8	63.0
Hungary	23.1	25.7	27.7	45.5	50.2	53.7
Kosovo				2.0	4.2	4.1
Latvia	29.6	32.4	34.5	36.4	41.4	45.5
Malta	17.9	13.2	40.0	24.1	18.0	32.0
Norway		27.8	31.2			
Poland	8.2	9.5	10.8	10.7	12.2	13.2
Romania				39.5	34.1	31.3
Scotland	26.4	26.6	26.5	35.1	35.3	35.2
Slovenia	18.9	19.0	19.3	25.5	24.1	23.0
Sweden	29.4	31.3	32.9			

The relatively high expenditure on long-acting insulins in Romania in recent years (Table 3) again reflects successful marketing by the originator companies, with insulin glargine one of the top selling medicines in Romania in recent years recently joined by insulin detemir.

There was also variable use of biosimilar insulin glargine among European countries. This reflects considerable marketing activities by the originator company to promote the 300IU/ml formulation (Table 4) among a number of the European countries. This combined with the originator company decreasing its prices appears to have reduced the attractiveness of the 100IU/ml insulin glargine biosimilar market and their subsequent use (Table 5). As a result, no biosimilar insulin glargine is currently marketed in either Albania, Latvia, Malta or Romania, with limited prescribing in Estonia and Norway. There is also currently no biosimilar insulin glargine available in Kosovo due to concerns with its effectiveness and safety versus the originator. Low utilisation of biosimilar insulin glargine in Bulgaria again reflects continued marketing activities by the originator company coupled with currently a lack of physician incentives to preferentially prescribe biosimilars along with limited price difference in practice between the originator and the biosimilar (Table 5) with both reducing their prices over time.

Table 4 – Current utilisation of biosimilar insulin glargine (100IU/ml) and glargine 300IU/ml (Gla-300) versus total insulin glargine in recent years

	% biosimilar 100IU/ml		% 300IU/ml	
	Previous year	Latest figure	Previous year	Latest figure
Albania	0.0	0.0	31.8	45.3
Bulgaria	10.0	11.0		
Bosnia and Herzegovina	4.1	6.2	44.0	52.1
Catalonia	7.8	12.4	26.9	28.1
Estonia	0.7	0.7	49.8	55.4
Hungary	21.7	24.6	52.9	58.0
Italy	18.9	25.0	20.4	30.4
Latvia	0.0	0.0	51.6	51.4
Lithuania	25.5	26.5	37.9	39.0
Norway	6.7	7.2	39.3	44.9
Poland	44.7	44.8	34.6	37.1
Scotland	18.8	19.5	7.4	9.1
Sweden	50.0	72.8	34.7	40.4
Slovenia	14.3	15.7		

The situation in Lithuania contrasts with the other Baltic nations, which may reflect a general trend towards international non-proprietary name (INN) prescribing in Lithuania coupled with ongoing internal reference pricing (136, 137). The low prescribing of biosimilar insulin glargine in Scotland reflects ongoing advice not to switch patients between the originator and a biosimilar; however, new patients should be started on a biosimilar where possible (52, 138). The low use of Gla-300 in Scotland reflects current prescribing restrictions unlike a number of European countries (139).

Table 5 – Selection of price changes among both the originator and biosimilar companies over time across Europe

	Albania	Bulgaria	Estonia	Hungary	Latvia	Lithuania	Malta	Poland	Sweden
% difference originator vs. biosimilar prices									
Launch of the biosimilar	Not applicable	4.7%	16.4%	28.2%	Not applicable	12.30%	Not applicable	24.7%	13.6%
Latest difference	Not applicable	5.7%	7.1%	1.6%	Not applicable	Similar	Not applicable	0.2%	0.6%
% price change over time (from 2014/2015 to 2020)									
Originator	-32.0%	-10.8%	-24.9%	-21.2%	-14.4%	-21.1%	-61.3%	-31.1%	-12.7%
Biosimilar	Not applicable	-11.7%	Stable	1.20%	Not applicable	-6.8%	Not applicable	-6.5%	-1.4%

The growing utilisation of biosimilar in Hungary (Table 4) is welcomed as this was not the case with biosimilars for infliximab and rituximab (140, 141); however, prescribing is moderated by high use of Gla-300 and limited price differences in practice between the originator and biosimilar (now only 1.6%).

The appreciably higher utilisation of biosimilar insulin glargine in Poland in recent years compared with a number of other CEE countries (Table 4) may well be facilitated by a flat reimbursement rate with patients paying the price difference for a more expensive originator (142, 143). Alongside this, the Ministry of Health and the National Health Insurance in Poland are looking to encourage the use of biosimilars to save resources especially as Poland is a leading producer of biosimilars in Europe (142, 144).

The growth in the prescribing of biosimilar 100IU/ml insulin glargine in Italy in recent years probably reflects ongoing regional and national demand-side measures to enhance their prescribing to conserve resources (47, 145); however, moderated by growing utilisation of Gla-300 (Table 4).

Overall, Sweden had the highest biosimilar use among the studied European countries despite growing prescribing of Gla-300 (Table 4). This may reflect a tradition of prescribing of multiple source medicines with compulsory generic substitution coupled with ongoing initiatives to enhance the quality and efficiency of prescribing including biosimilars (87, 146-148). In addition, less concerns with patients being switched to a biosimilar compared with for instance Scotland. Consequently, along with Poland, can serve as exemplars to European countries where there is still limited prescribing of biosimilar insulin glargine.

4. Recommendations for countries to enhance the availability, funding and prescribing of long-acting insulin biosimilars

This section will be divided into two sections, Firstly, suggesting activities to enhance the availability and funding of long-acting insulins in the first place within public healthcare systems where currently these are not available as seen in a number of Africa countries (Box 1).

Box 1 – Strategies to enhance the listing of long-acting insulin analogues in EMLs and STGs where currently not listed

- Collate ongoing evidence to support the listing of long-acting insulin analogues within EMLs in countries where there are concerns - building on the Lancet Commission on Diabetes and Cochrane reviews (4, 20), and actively communicate such findings
- Seek ways to enhance the listing and affordability of long-acting insulin analogues especially among African and South American countries. This includes potential ways to reduce the price difference between NPH and other insulins and long-acting insulin analogues, and could include enhancing local production of insulin glargine 100IU/ml (through for instance SADC and East African groups in Africa) coupled with pan-country procurement programmes. Ideally, long-acting insulin analogues via biosimilars or lower cost originators should be no more than 30% to 50% above NPH and other insulins on a daily (DDD) basis
- Make sure that only long-acting insulin analogues where biosimilars are available are listed in national EMLs and STGs to encourage competition and lower prices among biosimilars. This has worked well in other markets, e.g., adalimumab in Europe (148, 149)
- Once listed - ensure consistency between country EMLs and STGs given current concerns in for instance Ghana
- In addition:
    - Potentially 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
    - Once listed, monitor patients prescribed long-acting insulin analogues and subsequently broadcast findings to cement their future use - building on existing published studies

Secondly, documenting potential ways to enhance the utilisation of biosimilar insulin glargine once listed/ reimbursed to improve the attractiveness of the biosimilar market for insulin glargine and follow-on biosimilars to combat potentially ‘evergreening’ and other activities by originator companies (Box 2).

Box 2 – Potential activities to enhance the prescribing and dispensing of biosimilar insulin glargine

Educational initiatives

- Educate patients where pertinent regarding similar effectiveness and safety between originator and biosimilar long-acting insulin analogues, and actively disseminate any findings from current studies to avoid/ reduce any nocebo effect (150)
- Instigate additional research activities where pertinent to further demonstrate potential advantages including cost-effectiveness of long-acting insulins including biosimilars versus NPH and other basal insulins where concerns still exist. Lower cost biosimilars can help improve their cost-effectiveness and enhance access/ availability/ usage of long-acting insulin analogues in suitable patients where there are still concerns
- Work with patients to ensure they are familiar with the different pens/ devices in case of switching between different insulin glargine preparations (and other long-acting insulin biosimilars when they become available) to minimise any perceived risk of increased hypoglycaemia with different devices for insulin glargine 100IU/ml, e.g., Scotland vs. Sweden
- Work with patient organisations to reduce any misinformation about biosimilars for long-acting insulin analogues to facilitate greater use especially where resources/ co-payments are a continued issue

Prices/ competition activities

- Only potentially list biosimilars on national formulary lists/ essential medicine lists. If difficult, seek ways to limit the prescribing of 300IU/ml insulin glargine building on prescribing restrictions and their impact in Scotland as well as the success of prescribing restrictions in other disease areas (85, 151-153)
- Concurrent with this, encourage greater discounts from biosimilar manufacturers to enhance future prescribing of biosimilar insulin glargine (100IU/ml) – with such activities potentially necessary to (i) address issues of affordability where there are still concerns; (ii) address any financial issues with educating patients about the different devices (iii) reverse current trends in the preferential prescribing of Gla-300 vs. biosimilar insulin glargine (100IU/ml). This could be achieved by:
    - Expanding tendering/ procurement activities. This could be via tendering groups as seen in Europe with the formation e.g., Beneluxa group as well as in South America with new medicines for hepatitis C (154-157)
    - Potentially instigate regional production of long-acting insulins building on recent developments in Malaysia and Brazil with its production of human insulin (158)
- Introduce prescribing targets/ goals (quality indicators) for initiating patients on a biosimilar vs. an originator analogue as well as potentially switching targets to a biosimilar provided suitable educational support is in place to address concerns with patients switching between different devices where these still exist
- Make sure there is consistency/ agreement between recommendations for long-acting insulin analogues in National EMLs and STGs – addressing concerns seen for instance in Ghana

References

1. Godman B, Basu D, Pillay Y, Almeida P, Mwita JC, Rwegerera GM, et al. Ongoing and planned activities to improve the management of patients with Type 1 diabetes across Africa; implications for the future. Hospital practice. 2020;48(2):51-67.
2. Kibirige D, Lumu W, Jones AG, Smeeth L, Hattersley AT, Nyirenda MJ. Understanding the manifestation of diabetes in sub Saharan Africa to inform therapeutic approaches and preventive strategies: a narrative review. Clinical Diabetes and Endocrinology. 2019;5(1):2.
3. da Rocha Fernandes J, Ogurtsova K, Linnenkamp U, Guariguata L, Seuring T, Zhang P, et al. IDF Diabetes Atlas estimates of 2014 global health expenditures on diabetes. Diabetes research and clinical practice. 2016;117:48-54.
4. Chan JCN, Lim LL, Wareham NJ, Shaw JE, Orchard TJ, Zhang P, et al. The Lancet Commission on diabetes: using data to transform diabetes care and patient lives. Lancet. 2021;396(10267):2019-82.
5. Liu J, Ren Z-H, Qiang H, Wu J, Shen M, Zhang L, et al. Trends in the incidence of diabetes mellitus: results from the Global Burden of Disease Study 2017 and implications for diabetes mellitus prevention. BMC public health. 2020;20(1):1415.
6. Godman B, Basu D, Pillay Y, Mwita JC, Rwegerera GM, Anand Paramadhas BD, et al. Review of Ongoing Activities and Challenges to Improve the Care of Patients With Type 2 Diabetes Across Africa and the Implications for the Future. Frontiers in pharmacology. 2020;11(108).
7. International Diabetes Feceration. IDF Africa Members. 2019. Available at URL: https://idf.org/our-network/regions-members/africa/members/25-south-africa.html.
8. Hamid S, Groot W, Pavlova M. Trends in cardiovascular diseases and associated risks in sub-Saharan Africa: a review of the evidence for Ghana, Nigeria, South Africa, Sudan and Tanzania. The aging male. 2019:1-8.
9. Afroz A, Zhang W, Wei Loh AJ, Jie Lee DX, Billah B. Macro- and micro-vascular complications and their determinants among people with type 2 diabetes in Bangladesh. Diabetes & metabolic syndrome. 2019;13(5):2939-46.
10. Bhuyan KC, Fardus J. Factors Responsible for Diabetes Among Adult People of Bangladesh. Am J Biomed Sci & Res. 2019; 2(4): 137-42.
11. Ceriello A, deValk HW, Guerci B, Haak T, Owens D, Canobbio M, et al. The burden of type 2 diabetes in Europe: Current and future aspects of insulin treatment from patient and healthcare spending perspectives. Diabetes research and clinical practice. 2020;161:108053.
12. Bommer C, Sagalova V, Heesemann E, Manne-Goehler J, Atun R, Bärnighausen T, et al. Global Economic Burden of Diabetes in Adults: Projections From 2015 to 2030. Diabetes Care. 2018;41(5):963-70.
13. Atun R, Davies JI, Gale EAM, Barnighausen T, Beran D, Kengne AP, et al. Diabetes in sub-Saharan Africa: from clinical care to health policy. The lancet Diabetes & endocrinology. 2017;5(8):622-67.
14. Pastakia SD, Pekny CR, Manyara SM, Fischer L. Diabetes in sub-Saharan Africa - from policy to practice to progress: targeting the existing gaps for future care for diabetes. Diabetes Metab Syndr Obes. 2017;10:247-63.
15. Tusa BS, Weldesenbet AB, Gemada AT, Merga BT, Regassa LD. Heath related quality of life and associated factors among diabetes patients in sub-Saharan countries: a systemic review and meta-analysis. Health and quality of life outcomes. 2021;19(1):31.
16. Rwegerera GM, Moshomo T, Gaenamong M, Oyewo TA, Gollakota S, Rivera YP, et al. Health-related quality of life and associated factors among patients with diabetes mellitus in Botswana. Alexandria Journal of Medicine. 2018;54(2):111-8.
17. Hayes A, Arima H, Woodward M, Chalmers J, Poulter N, Hamet P, et al. Changes in Quality of Life Associated with Complications of Diabetes: Results from the ADVANCE Study. Value in Health. 2016;19(1):36-41.
18. Mudie K, Jin MM, Tan, Kendall L, Addo J, Dos-Santos-Silva I, et al. Non-communicable diseases in sub-Saharan Africa: a scoping review of large cohort studies. J Glob Health. 2019;9(2):020409.
19. Pedersen-Bjergaard U, Kristensen PL, Beck-Nielsen H, Nørgaard K, Perrild H, Christiansen JS, et al. Effect of insulin analogues on risk of severe hypoglycaemia in patients with type 1 diabetes prone to recurrent severe hypoglycaemia (HypoAna trial): a prospective, randomised, open-label, blinded-endpoint crossover trial. The lancet Diabetes & endocrinology. 2014;2(7):553-61.
20. Semlitsch T, Engler J, Siebenhofer A, Jeitler K, Berghold A, Horvath K. (Ultra-)long-acting insulin analogues versus NPH insulin (human isophane insulin) for adults with type 2 diabetes mellitus. The Cochrane database of systematic reviews. 2020;11:Cd005613.

21. McGovern A, Tippu Z, Hinton W, Munro N, Whyte M, de Lusignan S. Comparison of medication adherence and persistence in type 2 diabetes: A systematic review and meta-analysis. Diabetes, obesity & metabolism. 2018;20(4):1040-3.
22. Horvath K, Jeitler K, Berghold A, Ebrahim SH, Gratzer TW, Plank J, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. The Cochrane database of systematic reviews. 2007(2):Cd005613.
23. Waugh N, Cummins E, Royle P, Clar C, Marien M, Richter B, et al. Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation. Health technology assessment. 2010;14(36):1-248.
24. Tricco AC, Ashoor HM, Antony J, Beyene J, Veroniki AA, Isaranuwatchai W, et al. Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systematic review and network meta-analysis. BMJ. 2014;349:g5459.
25. Pérez-Maraver M, Caballero-Corchuelo J, Boltana A, Insa R, Soler J, Montanya E. Comparison of human insulin and insulin analogues on hypoglycaemia and metabolic variability in type 1 diabetes using standardized measurements (HYPO score and Lability Index). Acta diabetologica. 2013;50(4):529-35.
26. Ewen M, Joosse HJ, Beran D, Laing R. Insulin prices, availability and affordability in 13 low-income and middle-income countries. BMJ global health. 2019;4(3):e001410.
27. Zion Market Research. Insulin Glargine Market: by Type (Pre-filled Syringe and Single Dose Vial), by Application (Type 1 Diabetes and Type 2 Diabetes), by Distribution Channel (Hospital Pharmacy, Online Sales, Retail Pharmacy and Other Distribution Channels): Global Industry Perspective, Comprehensive Analysis and Forecast, 2018 – 2025. 2019. Available at URL: https://www.zionmarketresearch.com/report/insulin-glargin-market.
28. Taylor P. Lantus sales decline as competition heats up at Sanofi. 2016. Available at URL: http://www.pmlive.com/pharma_news/lantus_sales_decline_as_competition_heats_up_at_sanofi_929619.
29. PMLive. Levemir. Available at URL: http://www.pmlive.com/top_pharma_list/pharmaceutical_products/levemir.
30. Cheng AYY, Wong J, Freemantle N, Acharya SH, Ekinci E. The Safety and Efficacy of Second-Generation Basal Insulin Analogues in Adults with Type 2 Diabetes at Risk of Hypoglycemia and Use in Other Special Populations: A Narrative Review. Diabetes therapy. 2020;11(11):2555-93.
31. Thalange N, Gundgaard J, Parekh W, Tutkunkardas D. Cost analysis of insulin degludec in comparison with insulin detemir in treatment of children and adolescents with type 1 diabetes in the UK. BMJ open diabetes research & care. 2019;7(1):e000664.
32. Evans M, Moes RGJ, Pedersen KS, Gundgaard J, Pieber TR. Cost-Effectiveness of Insulin Degludec Versus Insulin Glargine U300 in the Netherlands: Evidence From a Randomised Controlled Trial. Adv Ther. 2020;37(5):2413-26.
33. Russel-Szymczyk M, Valov V, Savova A, Manova M. Cost-effectiveness of insulin degludec versus insulin glargine U100 in adults with type 1 and type 2 diabetes mellitus in Bulgaria. BMC endocrine disorders. 2019;19(1):132-.
34. PharmaLive. NOVO NORDISK 2018: STRUGGLING AGAINST THE TIDE. 2018. Available at URL: https://www.pharmalive.com/novo-nordisk-2018-struggling-against-the-tide/.
35. Research and Markets. $24 Billion Insulin Markets - Global Intelligence Database 2012-2018 & 2019-2023. 2019. Available at URL: https://www.globenewswire.com/news-release/2019/05/29/1856512/0/en/24-Billion-Insulin-Markets-Global-Intelligence-Database-2012-2018-2019-2023.html.
36. Home PD, Bolli GB, Mathieu C, Deerochanawong C, Landgraf W, Candelas C, et al. Modulation of insulin dose titration using a hypoglycaemia-sensitive algorithm: insulin glargine versus neutral protamine Hagedorn insulin in insulin-naïve people with type 2 diabetes. Diabetes, obesity & metabolism. 2015;17(1):15-22.
37. Caires de Souza AL, de Assis Acurcio F, Guerra Junior AA, Rezende Macedo do Nascimento RC, Godman B, Diniz LM. Insulin glargine in a Brazilian state: should the government disinvest? An assessment based on a systematic review. Applied health economics and health policy. 2014;12(1):19-32.
38. Marra LP, Araujo VE, Oliveira GC, Diniz LM, Guerra Junior AA, Acurcio FA, et al. The clinical effectiveness of insulin glargine in patients with Type I diabetes in Brazil: findings and implications. Journal of comparative effectiveness research. 2017;6(6):519-27.
39. Almeida P, Silva TBC, de Assis Acurcio F, Guerra Junior AA, Araujo VE, Diniz LM, et al. Quality of Life of Patients with Type 1 Diabetes Mellitus Using Insulin Analog Glargine Compared with NPH Insulin: A Systematic Review and Policy Implications. The patient. 2018;11(4):377-89.

40. Kalungia CA, Mwale M, Sondashi IS, Mweetwa B, Yassa P, Kadimba G. Availability of Essential Antihypertensive and Antidiabetic Medicines in Public Health Facilities in Lusaka District, Zambia. Medical Journal of Zambia 2017; 44 (3): 140-8.
41. Lee TY, Kuo S, Yang CY, Ou HT. Cost-effectiveness of long-acting insulin analogues vs intermediate/long-acting human insulin for type 1 diabetes: A population-based cohort followed over 10 years. British journal of clinical pharmacology. 2020;86(5):852-60.
42. Alemayehu B, Speiser J, Bloudek L, Sarnes E. Costs associated with long-acting insulin analogues in patients with diabetes. The American journal of managed care. 2018;24(8 Spec No.):Sp265-sp72.
43. Gordon J, Evans M, McEwan P, Bain S, Vora J. Evaluation of insulin use and value for money in type 2 diabetes in the United kingdom. Diabetes therapy : research, treatment and education of diabetes and related disorders. 2013;4(1):51-66.
44. Gururaj Setty S, Crasto W, Jarvis J, Khunti K, Davies MJ. New insulins and newer insulin regimens: a review of their role in improving glycaemic control in patients with diabetes. Postgrad Med J. 2016;92(1085):152-64.
45. World Health Organization - Model List of Essential Medicines. 21st List 2019. Available at URL: https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?ua=1.
46. Fullerton B, Siebenhofer A, Jeitler K, Horvath K, Semlitsch T, Berghold A, et al. Short-acting insulin analogues versus regular human insulin for adult, non-pregnant persons with type 2 diabetes mellitus. The Cochrane database of systematic reviews. 2018;12(12):Cd013228.
47. Godman B, Allocati E, Moorkens E, Kwon H-Y. Can local policies on biosimilars optimize the use of freed resources – experiences from Italy. Generics and Biosimilars Initiative Journal (GABI). 2020; 9 (4). Available as URL: http://gabi-journal.net/can-local-policies-on-biosimilars-optimize-the-use-of-freed-resources-experiences-from-italy.html.
48. Greater Glasgow and Clyde. Medicines Update - Prescribing Medicines by Brand. 2020. Available at URL: http://www.ggcprescribing.org.uk/blog/prescribing-medicines-brand/
49. Greener M. Why isn't the NHS making the most of biosimilar insulin? Prescriber August 2019: 21-24.
50. Aladul MI, Fitzpatrick RW, Chapman SR. Healthcare professionals' perceptions and perspectives on biosimilar medicines and the barriers and facilitators to their prescribing in UK: a qualitative study. BMJ open. 2018;8(11):e023603.
51. Chapman SR, Fitzpatrick RW, Aladul MI. Knowledge, attitude and practice of healthcare professionals towards infliximab and insulin glargine biosimilars: result of a UK web-based survey. BMJ open. 2017;7(6):e016730.
52. Lothian Formulary. 6.1.1 Insulins. 2020. Available at URL: https://www.ljf.scot.nhs.uk/LothianJointFormularies/Adult/6.0/6.1/6.1.1/Pages/default.aspx.
53. Heinemann L, Carter AW. Will Biosimilar Insulins Be Cheaper? Diabetes technology & therapeutics. 2017;19(9):513-5.
54. Yamada T, Kamata R, Ishinohachi K, Shojima N, Ananiadou S, Nom H, et al. Biosimilar vs originator insulins: Systematic review and meta-analysis. Diabetes, obesity & metabolism. 2018;20(7):1787-92.
55. Blevins TC, Barve A, Raiter Y, Aubonnet P, Athalye S, Sun B, et al. Efficacy and safety of MYL-1501D versus insulin glargine in people with type 1 diabetes mellitus: Results of the INSTRIDE 3 phase 3 switch study. Diabetes, obesity & metabolism. 2020;22(3):365-72.
56. Agirrezabal I, Sánchez-Iriso E, Mandar K, Cabasés JM. Real-World Budget Impact of the Adoption of Insulin Glargine Biosimilars in Primary Care in England (2015-2018). Diabetes Care. 2020;43(8):1767-73.
57. Perumal-Pillay VA, Suleman F. Selection of essential medicines for South Africa - an analysis of in-depth interviews with national essential medicines list committee members. BMC health services research. 2017;17:17.
58. Beran D, Laing RO, Kaplan W, Knox R, Sharma A, Wirtz VJ, et al. A perspective on global access to insulin: a descriptive study of the market, trade flows and prices. Diabetic medicine. 2019;36(6):726-33.
59. CONITEC - Ministry of Health Brazil. Insulinas análogas de ação prolongada para o tratamento de diabetes mellitus tipo I. December 2018. Available at URL: http://conitec.gov.br/images/Consultas/Relatorios/2018/Relatorio_InsulinasAnalogas_AcaoProlongada_DM1_CP81_2018.pdf.
60. Department of Health Republic of South Africa. National Essential Medicines List Committee (NEMLC) - TERTIARY AND QUATERNARY LEVEL ESSENTIAL MEDICINES LIST Reviewed Items.

2020. Available at URL: http://www.kznhealth.gov.za/pharmacy/Tertiary-quaternary-level-essential-medicine-recommendations_January2020.pdf.
61. Lamb YN, Syed YY. LY2963016 Insulin Glargine: A Review in Type 1 and 2 Diabetes. BioDrugs. 2018;32(1):91-8.
62. Tieu C, Lucas EJ, DePaola M, Rosman L, Alexander GC. Efficacy and safety of biosimilar insulins compared to their reference products: A systematic review. PloS one. 2018;13(4):e0195012.
63. Heinemann L. Biosimilar Insulin and Costs: What Can We Expect? Journal of diabetes science and technology. 2015;10(2):457-62.
64. Keramatian K, Chakrabarty T, Yatham LN. Long-Acting Injectable Second-Generation/Atypical Antipsychotics for the Management of Bipolar Disorder: A Systematic Review. CNS Drugs. 2019;33(5):431-56.
65. Olagunju AT, Clark SR, Baune BT. Long-acting atypical antipsychotics in schizophrenia: A systematic review and meta-analyses of effects on functional outcome. The Australian and New Zealand journal of psychiatry. 2019;53(6):509-27.
66. Godman B PM, Miranda J, Barbui C et al. Can authorities take advantage of the availability of generic atypical antipsychotic drugs:? Findings from Sweden and potential implications. Journal of Pharmaceutical Health Services Research 2013;4:139-50.
67. McCabe H, Godman B, Kurdi A, Johnston K, MacBride-Stewart S, Lennon J, et al. Prescribing trends of inhaler treatments for asthma and chronic obstructive pulmonary disease within a resource-constrained environment in the Scottish national health service: findings and implications. Expert review of respiratory medicine. 2019;13(7):679-89.
68. Alkhafaji AA, Trinquart L, Baron G, Desvarieux M, Ravaud P. Impact of evergreening on patients and health insurance: a meta analysis and reimbursement cost analysis of citalopram/escitalopram antidepressants. BMC medicine. 2012;10:142-.
69. Vernaz N, Haller G, Girardin F, Huttner B, Combescure C, Dayer P, et al. Patented drug extension strategies on healthcare spending: a cost-evaluation analysis. PLoS Med. 2013;10(6):e1001460.
70. Godman B, Kurdi A, McCabe H, Johnson CF, Barbui C, MacBride-Stewart S, et al. Ongoing initiatives within the Scottish National Health Service to affect the prescribing of selective serotonin reuptake inhibitors and their influence. Journal of comparative effectiveness research. 2019;8(7):535-47.
71. Godman B, Kurdi A, McCabe H, MacBride-Stewart S, Leporowski A, Hurding S et al. Ongoing activities to influence the prescribing of proton pump inhibitors within the Scottish National Health Service: their effect and implications. Generics and Biosimilars Initiative Journal (GaBI Journal). 2018;7(4):142-51.
72. Godman B, Wilcock M, Martin A, Bryson S, Baumgärtel C, Bochenek T, de Bruyn M. Generic pregabalin; current situation and implications for health authorities, generics and biosimilars manufacturers in the future. GaBI Journal. 2015;4(3):125-35.
73. Godman B, Hill A, Simoens S, Kurdi A, Gulbinovič J, Martin AP et al. Pricing of oral generic cancer medicines in 25 European countries; findings and implications. Generics and Biosimilars Initiative Journal (GaBI Journal). 2019;8(2):49-70.
74. Baumgart DC, Misery L, Naeyaert S, Taylor PC. Biological Therapies in Immune-Mediated Inflammatory Diseases: Can Biosimilars Reduce Access Inequities? Frontiers in pharmacology. 2019;10:279.
75. Putrik P, Ramiro S, Kvien TK, Sokka T, Pavlova M, Uhlig T, et al. Inequities in access to biologic and synthetic DMARDs across 46 European countries. Annals of the rheumatic diseases. 2014;73(1):198-206.
76. Kostic M, Djakovic L, Sujic R, Godman B, Jankovic SM. Inflammatory Bowel Diseases (Crohn s Disease and Ulcerative Colitis): Cost of Treatment in Serbia and the Implications. Applied health economics and health policy. 2017;15(1):85-93.
77. Vogler S, Schneider P. Assessing Data Sources for Medicine Price Studies. International journal of technology assessment in health care. 2019;35(2):106-15.
78. Garuoliene K, Godman B, Gulbinovic J, Schiffers K, Wettermark B. Differences in utilization rates between commercial and administrative databases: implications for future health-economic and cross-national studies. Expert review of pharmacoeconomics & outcomes research. 2016;16(2):149-52.
79. Robertson J, Iwamoto K, Hoxha I, Ghazaryan L, Abilova V, Cvijanovic A, et al. Antimicrobial Medicines Consumption in Eastern Europeand Central Asia – An Updated Cross-National Study and Assessment of QuantitativeMetrics for Policy Action. Frontiers in pharmacology. 2019;9(1156).

80. Jakupi A, Godman B, Martin A, Haycox A, Baholli I. Utilization and Expenditure of Anti-cancer Medicines in Kosovo: Findings and Implications. PharmacoEconomics - open. 2018;2(4):423-32.
81. WHO. WHO Collaborating Centre for Drug Statistics Methodology. ATC/ DDD Index. Available at URL: https://www.whocc.no/
82. WHO. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC Classification and DDD Assignment. 2017. Available at URL: https://www.whocc.no/filearchive/publications/2017_guidelines_web.pdf
83. Godman B, Shrank W, Andersen M, Berg C, Bishop I, Burkhardt T, et al. Policies to enhance prescribing efficiency in europe: findings and future implications. Frontiers in pharmacology. 2010;1:141.
84. Moon JC, Godman B, Petzold M, Alvarez-Madrazo S, Bennett K, Bishop I, et al. Different initiatives across Europe to enhance losartan utilization post generics: impact and implications. Frontiers in pharmacology. 2014;5:219.
85. Voncina L, Strizrep T, Godman B, Bennie M, Bishop I, Campbell S, et al. Influence of demand-side measures to enhance renin-angiotensin prescribing efficiency in Europe: implications for the future. Expert review of pharmacoeconomics & outcomes research. 2011;11(4):469-79.
86. Godman B, Petzold M, Bennett K, Bennie M, Bucsics A, Finlayson AE, et al. Can authorities appreciably enhance the prescribing of oral generic risperidone to conserve resources? Findings from across Europe and their implications. BMC medicine. 2014;12:98.
87. Godman B, Shrank W, Andersen M, Berg C, Bishop I, Burkhardt T, et al. Comparing policies to enhance prescribing efficiency in Europe through increasing generic utilization: changes seen and global implications. Expert review of pharmacoeconomics & outcomes research. 2010;10(6):707-22.
88. Godman B, Bishop I, Finlayson AE, Campbell S, Kwon HY, Bennie M. Reforms and initiatives in Scotland in recent years to encourage the prescribing of generic drugs, their influence and implications for other countries. Expert review of pharmacoeconomics & outcomes research. 2013;13(4):469-82.
89. Godman B, Haque M, Islam S, Iqbal S, Urmi UL, Kamal ZM, et al. Rapid Assessment of Price Instability and Paucity of Medicines and Protection for COVID-19 Across Asia: Findings and Public Health Implications for the Future. Frontiers in Public Health. 2020;8(744).
90. HAQUE M, Kumar S, Charan J, Bhatt R, Islam S, Dutta S, et al. Utilisation, availability and price changes of medicines and protection equipment for COVID-19 in India: findings and implications Short title: COVID-19 and price changes of treatments in India. Frontiers in pharmacology. 2021;11(1822).
91. Haque M, Islam S, Iqbal S, Urmi UL, Kamal ZM, Shuvo SA et al. Availability and price changes of potential medicines and equipment for the prevention and treatment of COVID-19 among pharmacy and drug stores in Bangladesh; findings and implications. Bangladesh Journal of Medical Science 2020; 19 Special Issue on Covid19: S36-S50
92. Ministry of Health Republic of Ghana. Ghana Standard Treatment Guidelines (2nd edition). 2017. Available at URL: https://www.moh.gov.gh/wp-content/uploads/2020/07/GHANA-STG-2017-1.pdf.
93. Sefah I, Ogunleye O, Essah D, Opanga S, Rizvi N, Wamaitha A, et al. Rapid assessment of the potential paucity and price increases for suggested medicines and protection equipment for COVID-19 across developing countries with a particular focus on Africa and the implications. Frontiers in pharmacology. 2021;11(2055).
94. Kim Y, Kwon H-Y, Godman B, Moorkens E, Simoens S, Bae S. Uptake of Biosimilar Infliximab in the UK, France, Japan, and Korea: Budget Savings or Market Expansion Across Countries? Frontiers in pharmacology. 2020;11(970).
95. Government of the Kingdom of Swaziland Ministry of Health, the US President's Emergency Plan for AIDS Relief, USAID, and Strengthening Pharmaceutical Systems (SPS) Program. Standard Treatment Guidelines and Essential Medicines List of Common Medical Conditions in the Kingdom of Swaziland. 2012. Available at URL: https://apps.who.int/medicinedocs/documents/s22119en/s22119en.pdf.
96. Ncube NBQ, Knight L, Bradley HA, Schneider H, Laing R. Health system actors' perspectives of prescribing practices in public health facilities in Eswatini: A Qualitative Study. PloS one. 2020;15(7):e0235513.
97. Khuluza F, Haefele-Abah C. The availability, prices and affordability of essential medicines in Malawi: A cross-sectional study. PloS one. 2019;14(2):e0212125.
98. Pillay Y, Manthalu G, Solange H, Okello V, Hildebrand M, Sundewall J, et al. Health benefit packages: moving from aspiration to action for improved access to quality SRHR through UHC reforms. Sexual and reproductive health matters. 2020;28(2):1842152.

99. Meyer JC, Schellack N, Stokes J, Lancaster R, Zeeman H, Defty D, et al. Ongoing Initiatives to Improve the Quality and Efficiency of Medicine Use within the Public Healthcare System in South Africa; A Preliminary Study. Frontiers in pharmacology. 2017;8:751.
100. Obakiro SB, Kiyimba K, Napyo A, Kanyike AM, Mayoka WJ, Nnassozi AG, et al. Appropriateness and affordability of prescriptions to diabetic patients attending a tertiary hospital in Eastern Uganda: A retrospective cross-sectional study. PloS one. 2021;16(1):e0245036.
101. Kibirige D, Atuhe D, Kampiire L, Kiggundu DS, Donggo P, Nabbaale J, et al. Access to medicines and diagnostic tests integral in the management of diabetes mellitus and cardiovascular diseases in Uganda: insights from the ACCODAD study. Int J Equity Health. 2017;16(1):154.
102. Birabwa C, Bwambale MF, Waiswa P, Mayega RW. Quality and barriers of outpatient diabetes care in rural health facilities in Uganda - a mixed methods study. BMC health services research. 2019;19(1):706.
103. Kaiser AH, Hehman L, Forsberg BC, Simangolwa WM, Sundewall J. Availability, prices and affordability of essential medicines for treatment of diabetes and hypertension in private pharmacies in Zambia. PloS one. 2019;14(12):e0226169-e.
104. Lontchi-Yimagou E, Mapa-Tassou C, Dehayem MY, Essi MJ, Saji J, Takogue R, et al. The effect of free diabetes care on metabolic control and on health-related quality of life among youths with type 1 diabetes in Cameroon. BMJ open diabetes research & care. 2017;5(1):e000397.
105. Claude Mbanya J, Aschner P, Chan JCN, Jose Gagliardino J, Saji J. Self-monitoring of blood glucose (SMBG) and glycaemic control in Cameroon: Results of the International Diabetes Management Practices Study (IDMPS). Diabetes research and clinical practice. 2017;126:198-201.
106. Djonou C, Tankeu AT, Dehayem MY, Tcheutchoua DN, Mbanya JC, Sobngwi E. Glycemic control and correlates in a group of sub Saharan type 1 diabetes adolescents. BMC research notes. 2019;12(1):50.
107. Ministry of Health Republic of Ghana. Ghana National Drugs Programme (GNDP) - Essential Medicines List. 7th Edition. 2017. Available at URL https://www.moh.gov.gh/wp-content/uploads/2020/07/GHANA-EML-2017.pdf.
108. Ghana National Health Insurance Medicine list 2018. Avaiable at URL: http://www.nhis.gov.gh/files/2018%20NHIS%20ML.pdf.
109. Premium Times. Diabetes: Novo Nordisk to offer free insulin to children in Nigeria, Ghana. 2020. Available at URL: https://www.premiumtimesng.com/health/426147-diabetes-novo-nordisk-to-offer-free-insulin-to-children-in-nigeria-ghana.html.
110. Mbui JM, Oluka MN, Guantai EM, Sinei KA, Achieng L, Baker A, et al. Prescription patterns and adequacy of blood pressure control among adult hypertensive patients in Kenya; findings and implications. Expert review of clinical pharmacology. 2017;10(11):1263-71.
111. Shannon GD, Haghparast-Bidgoli H, Chelagat W, Kibachio J, Skordis-Worrall J. Innovating to increase access to diabetes care in Kenya: an evaluation of Novo Nordisk's base of the pyramid project. Glob Health Action. 2019;12(1):1605704.
112. Oyando R, Njoroge M, Nguhiu P, Sigilai A, Kirui F, Mbui J, et al. Patient costs of diabetes mellitus care in public health care facilities in Kenya. The International journal of health planning and management. 2020;35(1):290-308.
113. Fadare JO, Enwere OO, Adeoti AO, Desalu OO, Godman B. Knowledge and Attitude of Physicians Towards the Cost of Commonly Prescribed Medicines: A Case Study in Three Nigerian Healthcare Facilities. Value in health regional issues. 2020;22:68-74.
114. Fadare J, Olamoyegun M, Gbadegesin BA. Medication adherence and direct treatment cost among diabetes patients attending a tertiary healthcare facility in Ogbomosho, Nigeria. Malawi Med J. 2015;27(2):65-70.
115. Mutyambizi C, Pavlova M, Chola L, Hongoro C, Groot W. Cost of diabetes mellitus in Africa: a systematic review of existing literature. Global Health. 2018;14(1):3.
116. Ministry of Health and Child Care Zimbabwe. EDLIZ 7TH EDITION 2015. Available at URL: http://www.mdpcz.co.zw/wp-content/uploads/2018/10/EDLIZ.pdf
117. Shariful Islam SM, Lechner A, Ferrari U, Laxy M, Seissler J, Brown J, et al. Healthcare use and expenditure for diabetes in Bangladesh. BMJ global health. 2017;2(1):e000033-e.
118. Sood N, Wagner Z. JAMA Health Forum. India's Historic Effort to Expand Health Insurance to Individuals Living Below the Poverty Line. 2020. Available at URL: https://jamanetwork.com/channels/health-forum/fullarticle/2763530.
119. Reddy KS. Health Care Reforms in India. Jama. 2018;319(24):2477-8.
120. HIRA. Updates of the NHIS drug list for reimbursement 2020. Available at URL: http://www.hira.or.kr/bbsDummy.do?pgmid=HIRAA030014050000.

121. Kwon HY, Godman B. Drug Pricing in South Korea. Applied health economics and health policy. 2017;15(4):447-53.
122. Government of Malaysia. MALAYSIA'S GOVERNMENT PROCUREMENT REGIME. 2010. Available at URL: https://www.treasury.gov.my/pdf/lain-lain/msia_regime.pdf.
123. Singh S. Biocon's Malaysia Insulin Glargine Manufacturing Facility Receives EU GMP Certification. 2019. Available at URL: https://indiamedtoday.com/biocons-malaysia-insulin-glargine-manufacturing-facility-receives-eu-gmp-certification/.
124. Biocon. Biocon Wins MYR 300 Million Contract for Insulin from MoH, Malaysia. 2017. Available at URL: https://www.biocon.com/biocon-wins-myr-300-million-contract-for-insulin-from-moh-malaysia/.
125. GABI Online. Biocon wins three-year contract to supply insulin in Malaysia. 2017. Available at URL: http://www.gabionline.net/Biosimilars/News/Biocon-wins-three-year-contract-to-supply-insulin-in-Malaysia.
126. Saeed A, Saeed H, Saleem Z, Yang C, Jiang M, Zhao M, et al. Impact of National Drug Pricing Policy 2018 on access to medicines in Lahore division, Pakistan: a pre-post survey study using WHO/HAI methodology. BMJ open. 2020;10(10):e034720.
127. Datta BK, Husain MJ, Asma S. Assessing the relationship between out-of-pocket spending on blood pressure and diabetes medication and household catastrophic health expenditure: evidence from Pakistan. Int J Equity Health. 2019;18(1):9.
128. Khan B, Godman B, Babar A, Hussain S, Mahmood S, Aqeel T. Assessment of active pharmaceutical ingredients in drug registration procedures in Pakistan: implications for the future. Generics and Biosimilars Initiative Journal (GaBI Journal). 2016;5(4):156-63.
129. Dias LLdS, Santos MABd, Osorio-de-Castro CGS. Public financing of human insulins in Brazil: 2009-2017. Revista Brasileira de Epidemiologia. 2020;23.
130. Ministry of Health. PORTARIA CONJUNTA Nº 08, DE 15 DE MARÇO DE 2018. Aprova o Protocolo Clínico e Diretrizes Terapêuticas da Diabete Melito Tipo 1. 2018. Available at URL: http://portalarquivos2.saude.gov.br/images/pdf/2018/marco/19/Portaria-Conjunta-n-8.pdf.
131. Minas Gerais. Deliberação CIB-SUS/MG nº 2359, de 17 de junho de 2010. Dispõe sobre o Protocolo Clínico e Diretrizes Terapêuticas para a utilização de análogo Glargina em portadores de Diabetes Mellitus Tipo 1 (DM1). Available at URL: https://www.saude.mg.gov.br/images/documentos/resolucao_2359.pdf.
132. Ministry of Health, BRASIL. Portaria 19 de 27 de março de 2019. Torna pública a decisão de incorporar insulina análoga de ação prolongada para o tratamento de diabetes mellitus tipo I, no âmbito do Sistema Único de Saúde - SUS. 2-19. Available at URL: http://138.68.60.75/images/portarias/marco2019/dia29/portaria19.pdf.
133. Mansell K, Bhimji H, Eurich D, Mansell H. Potential cost-savings from the use of the biosimilars filgrastim, infliximab and insulin glargine in Canada: a retrospective analysis. BMC health services research. 2019;19(1):827.
134. Siu ECK, Tomalin A, West K, Anderson S, Wyatt G. An Ever-Evolving Landscape: an Update on the Rapidly Changing Regulation and Reimbursement of Biosimilars in Canada. Generics and Biosimilars Initiative Journal (GaBI Journal). 2019;8(3):107-18.
135. Godman B, Allocati E, Moorkens E. Ever-Evolving landscape of biosimilars in Canada; findings and implications from a global perspective. Generics and Biosimilars Initiative Journal (GaBI Journal). 2019;8(3):93-7. DOI: 10.5639/gabij.2019.0803.012.
136. Garuoliene K, Godman B, Gulbinovic J, Wettermark B, Haycox A. European countries with small populations can obtain low prices for drugs: Lithuania as a case history. Expert review of pharmacoeconomics & outcomes research. 2011;11(3):343-9.
137. Godman B, Wettermark B, van Woerkom M, Fraeyman J, Alvarez-Madrazo S, Berg C, et al. Multiple policies to enhance prescribing efficiency for established medicines in Europe with a particular focus on demand-side measures: findings and future implications. Frontiers in pharmacology. 2014;5:106.
138. Greater Glasgow and Clyde. Medicines Update - Semglee® – preferred brand of insulin glargine. 2020. Available at URL: http://ggcprescribing.org.uk/blog/alternatives-insulin-glargine-post-tc/.
139. Scottish Medicines Consortium. Insulin glargine 300 units/mL solution for injection in a pre-filled pen (Toujeo®). 2015. Availabe at URL: https://www.scottishmedicines.org.uk/media/1860/insulin_glargine__toujeo_solostar__abbreviated_final_july_2015_for_website.pdf
140. IQVIA. The Impact of Biosimilar Competition in Europe. 2019. Available at URL: https://ec.europa.eu/docsroom/documents/38461.

141. Harsanyi A, Csanadi M, Marky K, Vincziczki AZ, Kalo Z, Inotai A. Influence of biosimilar infliximab launch on the utilization pattern of biological medicines: the case of Hungary. Expert review of pharmacoeconomics & outcomes research. 2019:1-7.
142. IQVIA. Country Scorecards for Biosimilar Sustainability. 2020. Available at URL: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/country-scorecards-for-biosimilar-sustainability/iqvia-institute-scorecards-appendix-orb2520.pdf?la=en.
143. Kawalec P, Stawowczyk E, Tesar T, Skoupa J, Turcu-Stiolica A, Dimitrova M, et al. Pricing and Reimbursement of Biosimilars in Central and Eastern European Countries. Frontiers in pharmacology. 2017;8:288.
144. Singh V. Top Biosimilar Companies with Approved and Pipeline Products in the US and EU. 2019. Available at URL: https://pharmashots.com/24011/top-biosimilar-companies-with-approved-and-pipeline-products-in-the-us-and-eu/.
145. Bertolani A, Jommi C. Local policies on biosimilars: are they designed to optimize use of liberated resources? Generics and Biosimilars Journal (GaBI). 2020; 9 (4). Available at URL: http://gabi-journal.net/local-policies-on-biosimilars-are-they-designed-to-optimize-use-of-freed-resources.html.
146. Godman B, Persson M, Miranda J, Skiold P, Wettermark B, Barbui C, et al. Changes in the utilization of venlafaxine after the introduction of generics in Sweden. Applied health economics and health policy. 2013;11(4):383-93.
147. Godman B, Wettermark B, Miranda J, Bennie M, Martin A, Malmstrom RE. Influence of multiple initiatives in Sweden to enhance ARB prescribing efficiency following generic losartan; findings and implications for other countries. International journal of clinical practice. 2013;67(9):853-62.
148. Moorkens E, Godman B, Huys I, Hoxha I, Malaj A, Keuerleber S, et al. The expiry of Humira® market exclusivity and the entry of adalimumab biosimilars in Europe: An overview of pricing and national policy measures. Frontiers in pharmacology. 2021;11(1993).
149. Davio K. After Biosimilar Deals, UK Spending on Adalimumab Will Drop by 75%. 2018. Available at URL: https://www.centerforbiosimilars.com/news/after-biosimilar-deals-uk-spending-on-adalimumab-will-drop-by-75.
150. Colloca L, Panaccione R, Murphy TK. The Clinical Implications of Nocebo Effects for Biosimilar Therapy. Frontiers in pharmacology. 2019;10(1372).
151. Furst J, Cizman M, Mrak J, Kos D, Campbell S, Coenen S, et al. The influence of a sustained multifaceted approach to improve antibiotic prescribing in Slovenia during the past decade: findings and implications. Expert review of anti-infective therapy. 2015;13(2):279-89.
152. Godman B, Sakshaug S, Berg C, Wettermark B, Haycox A. Combination of prescribing restrictions and policies to engineer low prices to reduce reimbursement costs. Expert review of pharmacoeconomics & outcomes research. 2011;11(1):121-9.
153. Wettermark B, Godman B, Neovius M, Hedberg N, Mellgren TO, Kahan T. Initial effects of a reimbursement restriction to improve the cost-effectiveness of antihypertensive treatment. Health policy. 2010;94(3):221-9.
154. Eatwell E, Swierczyna A. Emerging voluntary cooperation between European healthcare systems: Are we facing a new future?. Medicine Access@Point of Care 2019; 1-8.
155. O'Mahony JF. Beneluxa: What are the Prospects for Collective Bargaining on Pharmaceutical Prices Given Diverse Health Technology Assessment Processes? PharmacoEconomics. 2019;37(5):627-30.
156. WHO. WHO guideline on country pharmaceutical pricing policies, second edition. Geneva: World Health Organization; 2020. Available at URL: https://apps.who.int/iris/bitstream/handle/10665/335692/9789240011878-eng.pdf.
157. European Commission. DEFINING VALUE IN "VALUE BASED HEALTHCARE". Report of the Expert Panel on effective ways of investing in Health (EXPH). 2019. Available at URL: https://ec.europa.eu/health/sites/health/files/expert_panel/docs/024_defining-value-vbhc_en.pdf.
158. Fiotec. Technology transfer by Ukrainian company for Recombinant Human Insulin production in Farmanguinhos. 2015. Available at URL: https://www.fiotec.fiocruz.br/en/news/2791-technology-transfer-by-ukrainian-company-for-recombinant-human-insulin-production-in-farmanguinhos.

Appendix – Relevant published and submitted papers/ planned papers

Published

- Godman B, Allocati E, Moorkens E, Kwon H-Y. Can local policies on biosimilars optimize the use of freed resources – experiences from Italy. Generics and Biosimilars Initiative Journal (GABI). 2020; 9 (4) (Open Access)

- Godman B. Biosimilars are becoming indispensable in the management of multiple diseases although concerns still exist. Bangladesh Journal of Medical Science. 2021; 20 (1): 5 – 10 (Open Access)

- Godman B. Health authority activities to enhance the quality and efficiency of medicine use and their impact. Adv Hum Biol. 2021;11:11-6 (Open Access)

Submitted

Ongoing efforts to improve the management of patients with diabetes in Bangladesh and the implications – Target Journal – Hospital Practice

Being re-submitted

- Current situation regarding long-acting insulin analogues including biosimilars across countries; findings and implications for the future – Target Journal Frontiers in Public Health – Health Economics (Open Access)

- Biosimilars are essential for sustainable healthcare systems across Europe; however, key issues still remain that need addressing – Target Journal Cost Effectiveness and Resource Allocation (Open Access)

Planned

- Current utilization of long-acting insulin analogues including biosimilars across Europe: findings and implications – Target Journal Hindawi BioMed Research International (Open Access)

- Availability and use of long-acting insulin analogues including biosimilars across Africa; findings and implications – Target Journal Hospital Practice (where we published our Pan-African Type 1 paper)

- Pan Asian Paper – Target Journal CMRO (where we recently published a paper on the management of URTIs among LMICs)

- Availability and Accessibility of Monoclonal Antibodies in Bosnia and Herzegovina; findings and implications – Target Journal - Journal of Research in Pharmacy Practice (Open Access)

- Demand-side measures in Scotland including biosimilars/ insulin glargine; their influence and implications – Target Journal - Journal of Research in Pharmacy Practice (Open Access)