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## **Current utilisation patterns for long-acting insulin analogues including biosimilars among selected Asian countries and the implications for the future**

Short title: **Long-acting insulin analogues across Asia**

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## Abstract

**Introduction:** Prevalence rates for diabetes mellitus continue to rise, which coupled with increasing costs of complications, has appreciably increased expenditure in recent years. Poor glycaemic control including hypoglycaemia enhances complication rates and associated morbidity, mortality and costs. Consequently, needs to be addressed. Whilst the majority of patients with diabetes have type 2 diabetes, a considerable number of patients with diabetes require insulin to help control their diabetes. Long-acting insulin analogues were developed to reduce hypoglycaemia associated with insulin and help improve adherence, which can be a concern. However, there considerably higher costs have impacted on their funding and use especially in countries with affordability issues. Biosimilars can help reduce the costs of long-acting insulin analogues thereby increasing available choices. However, the availability and use of long-acting insulin analogues can be affected by limited price reductions versus originators and limited demand-side initiatives to encourage their use. Consequently, we wanted to assess current utilisation rates for long-acting insulin analogues, especially biosimilars, and the rationale for patterns seen, across multiple Asian countries ranging from Japan (high-income) to Pakistan (lower-income) to inform future strategies. **Methodology:** Multiple approaches including assessing utilization and prices of insulins including biosimilars among six Asian countries and comparing the findings especially with other middle-income countries. **Results:** Typically, there was increasing use of long-acting insulin analogues among the selected Asian countries. This was especially the case enhanced by biosimilars in Bangladesh, India, and Malaysia reflecting their perceived benefits. However, there was limited use in Pakistan due to issues of affordability similar to a number of African countries. The high use of biosimilars in Bangladesh, India and Malaysia was helped by issues of affordability and local production. The limited use of biosimilars in Japan and Korea reflects limited price reductions and demand-side initiatives similar to a number of European countries. **Conclusions:** Increasing use of long-acting insulin analogues across countries is welcomed adding to the range of insulins available, which increasingly includes biosimilars. A number of activities are needed to enhance the use of long-acting insulin analogue biosimilars in Japan, Korea and Pakistan.

## 1. Introduction

Diabetes is a growing public health priority across countries (1-7). It was estimated in 2019 that there were 463 million adults worldwide with diabetes mellitus (1, 2, 8). This represents 9.3% of the world's population aged 20 to 79 years (1). Prevalence rates are expected to grow to 578 million in 2030 unless addressed (1), helped by rising incidence rates (2). Since 1990, incident cases of diabetes mellitus have increased worldwide by over 100%, rising to 22.94 million in 2017 (2), with this trend expected to continue. South-East Asia and the Western Pacific are no exceptions with prevalence rates for diabetes mellitus expected to rise by 74% and 31% respectively from 2019 to 2030 (1). The top ten countries with the highest number of patients with diabetes mellitus world-wide include Bangladesh, India, and Pakistan, with this situation likely to continue (1). These countries also have a high number of patients with undiagnosed diabetes (1). The second highest mortality rate due to diabetes in any Region of the world is in South-East Asia including Bangladesh and India at over one million people in 2019 (1), which is an increasing concern that needs addressing.

Diabetes is associated with appreciable morbidity, mortality and costs, with costs enhanced by the cost of complications (1, 8-15), adding to the urgency to improve detection and management of these patients. Annual global expenditure on patients with diabetes is currently estimated at US\$760 billion, expected to rise to US\$825 billion by 2030 (1). Others have suggested a higher global economic burden when including both direct and indirect costs (16, 17). Combined global costs were estimated at US\$1.3 trillion in 2015 rising to an estimated US\$2.1 to US\$2.5 trillion by 2030, equating to 2.2% of Gross Domestic Product (GDP) (9, 10). The cost of complications is exacerbated by the fact that diabetes is currently among the leading causes of blindness, and associated implications, as well as non-traumatic lower-extremity amputations worldwide, with patients with diabetes also at a greater risk of end-stage renal disease and cardiovascular diseases (1, 8). Cardiovascular conditions currently account for the greatest cause of morbidity and mortality among patients with diabetes (1, 18, 19).

Consequently, patients with diabetes must be carefully managed (20). This includes addressing poor glycaemic control which increases morbidity, mortality and costs (21-23). Whilst only a minority of patients with diabetes are receiving insulin, which can be up to 40% of patients with diabetes in low- and middle-income countries (LMICs) (24-26), long-acting insulin analogues were developed to reduce the risk of hypoglycaemia, including nocturnal hypoglycaemia. In addition, increase patient convenience and adherence through reduced number of injections (8, 27-30). As a result, long-acting insulin analogues along with other treatment approaches can help address concerns with hypoglycaemia across Asia and the Western Pacific (22, 30-33). This is important with estimated rates of hypoglycaemia up to 3.5–3.6 events/month among patients with type 1 diabetes (T1DM) and 2.2–3.7 among those with type 2 diabetes (T2DM) (31, 34, 35). These patient benefits are recognised by long-acting insulin analogues currently the most prescribed insulin in upper-middle and high-income countries (36). In addition, annual world-wide sales of long-acting insulin glargine could potentially reach US\$9.26 billion by 2025 (37). Global sales of insulin detemir were US\$2.7 billion in 2015 and growing at 7.5% per year (38), with global sales of insulin degludec rising 1.8 fold to US\$1.11 billion in 2017 versus 2016 (39). Growing sales of insulin detemir and degludec are enhanced by studies suggesting improved cost-effectiveness versus insulin glargine; however, this is not always the case (40-44).

However, there are concerns that long-acting insulin analogues can be appreciably more expensive than Neutral Protamine Hagedorn (NPH) and other standard insulins impacting on their availability and funding within healthcare systems (5, 36, 45, 46). This is important as there are concerns with the routine availability and funding of insulins and other treatments for diabetes across a number of low- and middle-income countries (LMICs) (1, 36, 46, 47). The affordability of medicines a key issue among a number of Asian countries including Bangladesh, India and Pakistan (48-50) (Table 1). Affordability and access to medicines can also be an issue in the private sector in Malaysia with its lack of price controls compared with the public sector; however, patients are generally unwilling to pay for medicines for chronic conditions preferring to attend clinics in public healthcare facilities where medicines are heavily subsidized (51-53).

These concerns with the additional costs of long-acting insulin analogues, alongside concerns with the extent of the clinical benefit in practice between the different insulin preparations, is reflected by long-acting insulin analogues currently not reimbursed in a number of countries. These include African and South American countries (5, 45, 54-56). In addition, long-acting insulin analogues are currently not listed in the World Health Organization Essential Medicines List (WHO EML) (54)..

Having said this, we are aware there have been published studies which have shown that the higher acquisition costs of the long-acting insulin analogues can potentially be offset by savings from diabetes-associated complications including hypoglycaemia (57-60).

Biosimilars offer the potential for appreciably lower costs for biological medicines thereby improving their opportunities for reimbursement and funding where there have been concerns with affordability and value in the first place (61-64). For instance in Denmark, expenditure on adalimumab fell by 82.8% in late 2018 with a switch from the originator to biosimilars at considerably lower prices (65). However, we are aware that price reductions for biosimilars can be more limited. For instance in Korea, current regulations only advocate a 20% price reduction for biosimilars versus originators (66). In Japan, a 30% price reduction is advocated for biosimilars versus originators (66). In addition, there has been more limited price reductions for biosimilar adalimumab among other European countries (67).

Biosimilar insulin glargine, the first long-acting insulin analogue biosimilar, has been shown to have similar effectiveness and safety to the originator in a number of studies including those conducted in Japan (68-72). However, there can be concerns with the extent of price reductions versus originators in practice as seen in the United Kingdom, which may impact on future use in practice (73-76). There have also been concerns generally with the effectiveness and safety of biosimilars across countries, which can reduce their use in the absence of demand-side measures encouraging their use (66, 77, 78).

Asian countries include Bangladesh, India and Pakistan where family members becoming ill can have catastrophic consequences (79-82), contrasting with Japan and Korea.

Consequently, the primary objective of this study is to suggest future activities that could be introduced across Asia to enhance availability and use of biosimilar long-acting insulin analogues among pertinent patients given ongoing challenges. As a result, increase treatment choices that can be available to patients to benefit their care. This will build on an initial assessment of current utilisation and expenditures for insulins and long-acting insulin analogues, including biosimilars, among selected Asian countries. These include Bangladesh, India and Pakistan where family members becoming ill can have catastrophic consequences (79-82), contrasting with Japan and Korea (14, 66). In addition, the rationale behind any utilisation patterns seen. Potential future activities include those to enhance reimbursement and funding of long-acting insulin analogues in the first place if this is an issue, building on the findings of Ewen *et al.* (2019) and other LMICs including African countries (36, 46, 83). Fulfilling the objective also includes suggesting potential additional policies that could be introduced by Governments and others to lower the prices of biosimilar long-acting insulin analogues to enhance their access and affordability. This is because we are aware that competition can lower biosimilar prices, similar to the situation for oral generics across countries (84-86). This should again benefit all key stakeholder groups given the rising prevalence of diabetes and its complications, and potential low cost-of-goods for biosimilar insulin glargine (65, 84, 87, 88).

## **2. Methodology**

We adopted a mixed approach. This included briefly documenting the current situation regarding diabetes in Bangladesh, India, Japan, Korea, Malaysia and Pakistan based on published data. Subsequently, collect utilisation and expenditure data for insulins in general, and long-acting insulin analogues in particular, and the subsequent rationale for any patterns seen (89). We specifically focused on insulin glargine among the long-acting insulin analogues as there are biosimilars for insulin glargine across the studied countries. The Asian countries chosen provided a range of countries to be able to provide comprehensive future advice. The range was based on their population size, economic status, the extent of universal healthcare, level of co-payments, promotion of biosimilars, geographies as well as differences in the extent of financial consequences when family members become ill (Table 1) (66, 90-94). Population data as well as data on the Gross Domestic Product (GDP) were taken from the latest OECD data (95). The only exception was South Korea where the latest World Bank data was used (94).

The data collection approach among the selected Asian countries was opportunistic. The approach used in each country was adapted depending on the availability and access to pertinent data within each country as well as its situation. Since originator or biosimilar long-acting insulin analogues can

be dispensed in private community pharmacies or drugs stores in Bangladesh, India, Malaysia and Pakistan, we included data on current utilisation and expenditure patterns as well as prices for long-acting insulin analogues, including biosimilars, from a range of such facilities across these countries. We have used this approach before in these countries when national datasets were not routinely available (90-92, 96). We included a range of pharmacies and locations in Bangladesh as community pharmacies and drug stores are the principal source for insulins in Bangladesh (97). The situation is different in India with Government hospitals dispensing insulins free-of-charge. Consequently, we were principally interested in pricing data in India and comparing this with hospital procurement data, and not necessarily interested in ensuring a comprehensive location of pharmacies. Community pharmacies in Malaysia and Pakistan were purposely selected for this study based on access to the co-authors. The intention, certainly in Malaysia, was to provide an impression of the current situation with insulins typically provide free-of-charge in hospitals. The situation was different in Pakistan as we were able to access comprehensive utilisation and expenditure data.

Similar to previous projects, impressions of patterns and prices were provided when no other robust data sets were available to document changes in the utilisation and prices of insulin glargine as well as other insulin preparations. That is, if other information sources were unavailable due to issues of local culture and confidentiality since we were not paying personnel for their time (90-92). This data for community pharmacies and drug stores in Bangladesh and India was supplemented with utilisation and expenditure data from hospitals. In Korea and Pakistan, the MIDAS-IQVIA International database was also used to provide data on utilisation and expenditure patterns. These data sets are seen as robust, and are a principal source for utilisation and expenditure data within and across countries (98-101). In the case of Korea, this builds on our recent study with infliximab biosimilar (66). Pertinent pricing data was converted to US\$ for comparative purposes using current exchange rates (<https://www.xe.com/currencyconverter/>).

Suggestions for potential ways forward to enhance funding and utilisation of biosimilar long-acting insulin analogues was provided by the senior-level co-authors and some of the community pharmacists. These mimic previous studies undertaken by the co-authors in this and related areas, which include analysis of policies to enhance the rational use of medicines including biosimilars and generics as well as pricing policies generally, which involved direct contact with key stakeholder groups (92, 102-108).

Ethical approval for this study was not required according to national legislation and institutional guidelines in line with previous studies in similar circumstances (90-92, 96, 104, 109). However where pertinent, all pharmacists freely provided the requested information having been given the opportunity to refuse to take part if wished. This is similar to previous studies of this nature conducted among community pharmacies and drug stores across Asia and wider (90-92, 96).

### **3. Results**

We will report on each country initially in terms of prevalence rates and key aspects of managing patients with diabetes before looking separately at utilisation, costs and expenditures for different insulins especially long-acting insulin analogues and their biosimilars (Table 2). This will build on a summary of the key characteristics of each country (Table 1). We have also included in Table 1 data from five African countries with similar GDP characteristics and challenges with funding long-acting insulin analogues to aid discussions on potential next steps to enhance funding of long-acting insulin analogues where pertinent are currently funded within their public healthcare systems. These five African countries were purposely selected to provide exemplars based prior knowledge.

We will subsequently report on key issues regarding insulins, including long-acting insulin analogues, in each Asian country separately in view of the different approaches to collecting utilisation, pricing and expenditure data. Following this, consolidate the findings to provide future guidance. Suggestions for the future will be based on the considerable experience of the co-authors from across multiple countries and continents including African and Asian countries.

Table 1 – Key characteristics among the chosen African and Asian countries

Country	Population	GDP/ Capita	Healthcare status/ co-payments
Bangladesh	156,186,882	\$3,900	<ul style="list-style-type: none"> <li>• Some medicines provided free-of-charge in public hospitals. Otherwise, high levels of co-payment (92, 97)</li> <li>• An appreciable number of households in Bangladesh are forced to sell their assets or borrow money each year to fund treatments (110)</li> <li>• Biosimilars have the potential to lower costs and increase utilisation (97)</li> </ul>
Botswana	2,209,208	\$16,900	<ul style="list-style-type: none"> <li>• Provides universal healthcare through primary healthcare centres and hospitals (111)</li> <li>• However, there can be concerns with the current management of patients with diabetes (112-114)</li> <li>• Long-acting insulin analogues are currently not available within the public healthcare systems. Substantial price reductions will enhance their chances of funding within the public system (76)</li> </ul>
Ghana	26,908,262	\$4,400	<ul style="list-style-type: none"> <li>• There is health insurance in Ghana which covers the majority of the costs of patients with diabetes (76)</li> <li>• Long-acting insulin analogues are currently not reimbursed in Ghana despite being on the Ghanaian Essential Medicines List limiting their use in practice until prices substantially fall (76, 115)</li> </ul>
India	1,266,883,598	\$6,700	<ul style="list-style-type: none"> <li>• India is striving towards universal healthcare with insulins provided free of charge in Government hospitals (36, 116, 117)</li> <li>• However, there is still substantial co-payments for medicines for patients in ambulatory care, with potentially catastrophic consequences for families when members become ill (81, 91)</li> </ul>
Japan	126,702,133	\$38,900	<ul style="list-style-type: none"> <li>• Typically high co-payment levels</li> <li>• However, good quality care with affordability less of an issue until recently - helping to enhance usage of biosimilars (118, 119)</li> </ul>
Kenya	46,790,758	\$3,400	<ul style="list-style-type: none"> <li>• Typically high co-payment levels (46, 96)</li> <li>• High co-payments eased via Access schemes within cardiovascular diseases including diabetes (120, 121); however, this is not universal</li> <li>• Whilst long acting insulin analogues are listed in the Kenyan Essential Medicines List, appreciable price reductions are needed to enhance utilisation given current high costs (46, 122)</li> </ul>
Korea	50,924,172	\$31,846.2	<ul style="list-style-type: none"> <li>• Universal healthcare instigated in 1989, with good access reflected by funding an appreciable number of medicines for orphan diseases versus neighbouring countries (123)</li> <li>• Currently limited demand-side measures encouraging the prescribing of generics and biosimilars versus originators (66, 124). However, this may change as resource pressures grow</li> </ul>
Malaysia	30,949,962	\$27,200	<ul style="list-style-type: none"> <li>• Public healthcare system providing universal healthcare. However, there can be concerns with long waiting times in ambulatory care (125)</li> </ul>

			<ul style="list-style-type: none"> <li>Medicines including insulins provided free-of-charge within public hospitals, with costs moderated by comprehensive procurement systems(76)</li> </ul>
Nigeria	186,053,386	\$5,900	<ul style="list-style-type: none"> <li>High co-payments with potentially catastrophic consequences when family members become ill (126, 127)</li> <li>The costs of medicines to treat patients with diabetes and its complications can be as high as 90% of total costs, much of which will be out-of-pocket (128, 129)</li> <li>Limited utilisation of long-acting insulin analogues including biosimilars with high costs versus standard insulins (83)</li> </ul>
Pakistan	201,995,540	\$5,100	<ul style="list-style-type: none"> <li>High patient copayments with potentially catastrophic consequences for families when members become ill (80, 82, 90)</li> <li>This applies to patients with diabetes (76, 82)</li> </ul>
South Africa	54,300,704	\$13,500	<ul style="list-style-type: none"> <li>South Africa has universal healthcare with approximately 80% of the population using public healthcare facilities (130)</li> <li>There are concerns with the management of patients with diabetes in South Africa including adherence to prescribed medicines (6, 131)</li> <li>Currently though long-acting insulin analogues are not listed within the South Africa Essential Medicines List due to considerably higher costs than procured insulins and concerns with the extent of healthgain versus current procured insulins (56, 76)</li> </ul>

### 3.1 Prevalence rates and the management of diabetes among the selected Asian countries

Table 2 consolidates the baseline information regarding current prevalence rates and the management of patients with diabetes among the six selected Asian countries.

Table 2 – Prevalence rates and management of patients with diabetes among six Asian countries

Country	Prevalence and management of patients with diabetes mellitus
Bangladesh	<ul style="list-style-type: none"> <li>Up to 8.4 million adults currently have diabetes mellitus, representing 8.1% of the adult population, with prevalence rates expected to increase to 15.0 million by 2045 unless addressed (1, 132)</li> <li>Patients with diabetes paid an average of 35,385 BDT (US\$454) per year for their medicines versus only 1609 BDT (US\$21) for those without diabetes (Islam et al. - 2017) (133).</li> <li>Government hospitals in Bangladesh typically only fund NPH and other similar insulins until funds run out. In addition, private hospitals do not typically stock medicines for out-patients, which includes long-acting insulin analogues (97)</li> <li>Consequently, patients prescribed long-acting insulin analogues need to purchase them directly from community pharmacies and drug stores subject to 100% co-payment (97)</li> <li>However, there are hardship funds available in some hospitals to help cover the costs of insulin treatment for the very poor if needed</li> </ul>
India	<ul style="list-style-type: none"> <li>It was estimated that 65 million people in India had diabetes in 2016, up from 26.0 million in 1990, and growing (134), exacerbated by high prevalence rates of prediabetes (135).</li> <li>Ewen <i>et al.</i> (2019) found that prices of insulins in the public sector in India and Pakistan ranged from US\$5 for human insulins for 10mls of 100IU/ml to US\$33 for a similar amount of long-acting insulin analogues (36).</li> </ul>

	<ul style="list-style-type: none"> <li>Insulins are currently provided free of charge to government hospitals in India as part of general moves towards universal healthcare (36, 116, 117)</li> </ul>
Japan	<ul style="list-style-type: none"> <li>Whist prevalence rates for diabetes mellitus have been growing in Japan in previous years, rates are currently stable (136, 137)</li> <li>Among adults, prevalence rates were 7.9% in 2019, lower than a number of other Asian countries (138, 139)</li> <li>It is currently considered there is good access to care for patients with diabetes mellitus in Japan (14)</li> </ul>
Korea	<ul style="list-style-type: none"> <li>The prevalence of diabetes mellitus has grown in Korea in recent years, increasing from 9.6% of the population in 2007-2009 to 10.8% in 2016-2017 (140, 141)</li> <li>Among adults aged 20 to 79 years, the prevalence rate for diabetes mellitus in 2019 was 9.2% (138).</li> <li>It is currently considered there is good access to care for patients with diabetes mellitus in Korea. However, there can be concerns with the quality of care for patients with diabetes in some regions in Korea (15, 142)</li> </ul>
Malaysia	<ul style="list-style-type: none"> <li>Prevalence rates of prediabetes and diabetes were high at 19.6% among residents in Penang, Malaysia, in late 2017 (143)</li> <li>The overall prevalence rate for diabetes in Malaysia in 2019 was 16.8% among adults aged 20 to 79 years (138).</li> </ul>
Pakistan	<ul style="list-style-type: none"> <li>Ewen <i>et al.</i> (2019) found that prices of insulins in the public sector in India and Pakistan ranged from US\$5 for human insulins for 10mls of 100IU/ml to US\$33 for a similar amount of long-acting insulin analogues (36).</li> <li>There has been a 69.5% increase in the total utilisation of insulin in Pakistan from 2014 to 2019, with a 151.2% increase in expenditure as a result of increasing utilisation of long-acting insulin analogues including insulin glargine (Table 3). This increasing utilisation of insulin reflects increasing prevalence rates for diabetes mellitus in Pakistan in recent years (138, 144).</li> </ul>

Table 3 - Changes in utilisation and expenditure on total insulins in Pakistan from 2014 to 2020

	2014		2019		2020 (Jan to June)	
	Utilisation	Expenditure	Utilisation	Expenditure	Utilisation	Expenditure
Total Insulin	8251000	3990784000	13988000	10061008000	13988000	11263813000
% insulin Glargine	1.46	10.68	1.83	9.75	1.97	9.59

NB: Expenditure in local currency – PKR

### 3.2 Bangladesh

There was considerable variation in the prescribing of the different insulin preparations among the five surveyed public and private hospitals and institutions in Bangladesh (Table 4). This reflects considerable variations generally with endocrinologists more likely to prescribe long-acting insulin analogues versus non-endocrinologists. Non-endocrinologists are more likely to prescribe standard insulins such as premixed insulins especially when they are provided free-of-charge in Government hospitals. However, we are now also seeing growing prescribing of long-acting insulin analogues among these physicians reflecting their perceived value in reducing rates of hypoglycaemia as well as improving patient convenience and adherence.

Table 4 - Range of insulin prescribing patterns among the five surveyed hospitals in Bangladesh

	% long-acting insulins vs. other insulins	% insulin glargine vs other total long-acting insulin analogues	% insulin glargine among different presentations	
			Originator	Biosimilar (various)
Public Hospital (Medical Colleges and University)	10-15% up to 45 – 50%	20-30% up to 70 – 80% (majority)	30% up to 60-70%	30-40% up to 70%
Private Hospital (Chattogram Maa-O-Shishu Medical College)	15 - 20%	70 – 90%	2%	98%
Private Teaching Hospital (BIRDEM)	20-25%	50-60%	60%	40%

NB: The %s in each category refer to the % out of total utilisation in that category.

Insulin glargine is increasingly the biosimilars (Table 4). This reflects appreciable price differences between the originator and biosimilars in Bangladesh (Table 5) coupled with high co-payment levels.

Table 5 - Typical selling prices for different insulin glargine preparations among 58 pharmacies and drug stores in Bangladesh

Manufacturer	Packs (100IU/ml insulin glargine)	Typical selling price in pharmacies and drug stores (local currency)
Insulet®	3ml vial	600 BDT (US\$7.08)
Larsulin®	3ml Vial and Pen Cartridge	600 BDT (US\$7.08)
Vibrenta®	3ML Vial and Pen Set	600 BDT (US\$7.08)
Glarine®	Single 3ml Pen; 5 x 3ml pens	950 BDT (US\$11.21), 4750 BDT (US\$56.05)
Abasaglar®	Single 3ml Pen; 5 x 3ml pen cartridges	1085 BDT (US\$12.80) to to 3617 BDT (US\$42.68)
Lantus® ( Sanofi-Aventis)	Single 3ml Pen, 5 X 3ml pens	1220 BDT (US\$14.40), 6100 BDT (US\$72.00)

Overall, 167 pharmacies took part from across Bangladesh divided into four groups, giving a response rate of 66.8%. A similar wide-range of patterns (Table 4) was seen in the dispensing patterns for the different insulins among the various community pharmacies and drug stores. Table 6 contains the details of dispensing patterns among 76 of the 82 pharmacies in Group One. The categories for the percentages of each insulin dispensed (analogue or other insulin preparation) were divided into four, e.g, 0 to 30%, 31 – 50%, etc., for ease of understanding and comparisons between the years, with the actual number of pharmacies for each category and insulin converted to percentages for comparative purposes.

Table 6 – Dispensing patterns of different insulin preparations among 76 pharmacies and drug stores in Bangladesh (Group One)

% Dispensed	2019		2020	
	Other insulins	Analogues	Other insulins	Analogues
0 - 30%	14.5	30.3	15.8	26.3
31 - 50%	38.2	31.6	42.1	27.6
51 - 70%	32.9	34.2	32.9	42.1
71% and above	14.5	3.9	9.2	3.9
<b>Total</b>	<b>100%</b>	<b>100%</b>	<b>100%</b>	<b>100%</b>

NB: Analogues are principally long-acting insulin analogues including originators and biosimilars. 2020 is up to early December 2020. Figures represent %s dispensed

Overall, long-acting insulin analogues were the principal insulin dispensed in nearly 50% of the community pharmacies surveyed in Group One in 2020, up from 2019 (Table 6). The biosimilars were the principal insulin glargine dispensed in over 50% of these pharmacies surveyed in 2020, reaching over 80% in 12.7% of those surveyed in 2020 (Table 7). The pharmacies were again broken down into different categories to compare dispensing patterns. In this case, eight categories were adopted to enhance comparisons between the years. Again, there was considerable variation in the dispensing patterns among the various pharmacies taking part depending on a number of issues including affordability and trust in the biosimilars versus originators.

Table 7 - Dispensing patterns of different insulin glargine preparations among 79 of the 82 pharmacies and drug stores 2019 and 2020

% of Pharmacies	2019		2020	
	Originator	Biosimilar	Originator	Biosimilar
0-20	16.5	6.3	16.5	6.3
21-30	7.6	12.7	13.9	16.5
31-40	16.5	12.7	24.1	13.9
41-50	21.5	19.0	10.1	8.9
51-60	16.5	25.3	8.9	22.8
61-70	11.4	6.3	16.5	12.7
71-80	8.9	7.6	8.9	6.3
81-100	1.3	10.1	1.3	12.7
<b>Total</b>	<b>100</b>	<b>100</b>	<b>100</b>	<b>100</b>

NB: Figures are percentages

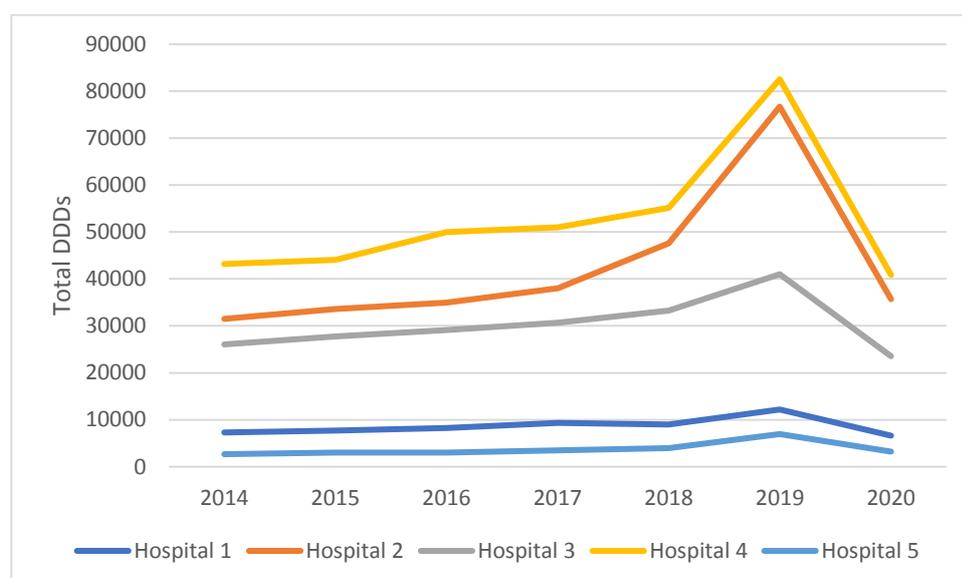
Overall, among the 167 pharmacies and drug stores surveyed across the four groups, typically there was no change in the prices of the various insulin glargine preparations between 2020 and 2019. However, price rises were seen in a minority of pharmacies (10.8%) in 2020 vs. 2019, with the greatest price increases seen for the biosimilar insulin glargine preparations (11.3% vs. 10.3%). Price reductions were also seen in a minority of surveyed pharmacies and drug stores (9.8%), greatest for the originator (13.8%).

The findings from the different hospitals, pharmacies and drugs stores taking part (Tables 3 to 6) suggests increasing prescribing of long-acting insulin analogues in Bangladesh in recent years, which is principally insulin glargine. This is increasingly biosimilar insulin glargine reflecting issues of affordability and price differences between the various insulin glargine preparations (Table 4).

### 3.3. India

In India among five purposely selected government hospitals, biosimilar insulin glargine Glaritus® is typically the only insulin glargine 100IU/ml dispensed. There has been an increase in the prescribing of insulin glargine in all these five hospitals in recent years (Figure 1); however, falling during 2020 with changes in procurement.

Figure 1 – Total annual utilisation of insulin glargine (DDDs) among 5 Government hospitals in India



The increasing use of long-acting insulin analogues (insulin glargine) may well reflect a growing awareness of the patient benefits with long-acting insulin analogues, and is different to the findings of Ewen *et al.* (2019). These authors found no insulin, including human insulin, was available in their surveyed provincial and district public hospitals in India whilst only short-acting insulin was in stock in the one teaching hospital in the state capital (36).

Prices (expenditure/ DDD) were generally stable for insulin glargine (typically the biosimilar) in these five surveyed Government Hospitals. Prices were 60 INR (US\$0.82)/ DDD between 2014 to 2016 before rising to 70.0 INR (US\$0.96)/DDD in 2017. Prices subsequently fell to 50.93 INR (US\$0.70)/DDD in 2018 and 2019 before increasing to 61.6 INR (US\$0.84)/ DDD in 2020.

We also saw differences in the prices of the different insulin glargine preparations in India in 2020 among 207 community pharmacies surveyed (Table 8). Prices for Glaritus® (biosimilar insulin glargine) were typically similar in price to current procurement prices in the five surveyed Government hospitals (on a DDD basis). These ranged from 382INR (US\$5.24) to 650INR (US\$8.92)/3mls, with 382INR (\$5.24)/3mls the most consistent price among the 207 pharmacies surveyed. This compares to 722INR (US\$9.91)/ 3mls (100IU/ml) as the most consistent price for the originator. The price differences among the community pharmacies surveyed reflects differences in the purchasing power and incentives among the various manufacturers and pharmacy groups.

Table 8 - Price ranges for insulin glargine 100UI/ml 3mls among community pharmacies in India in 2020

Insulin Glargine preparation	Price range	Most consistent price
<b>Originator</b>		
Lantus®	649 - 750 INR (US\$8.90 - 10.29)	722 INR (US\$9.90)
<b>Biosimilars</b>		
Basaglar®	565 - 605 INR (US\$7.75 - 8.30)	605 INR (US\$8.30)
Basalog®	500 - 750 INR (US\$6.86 - 9.67)	555 INR (US\$7.61)
Basugine®	590 - 594 (US\$8.09 -8.15)	594 INR (US\$8.15)
Glaritus®	382 - 650 (US\$5.24 - 8.91)	382 INR (\$5.24)

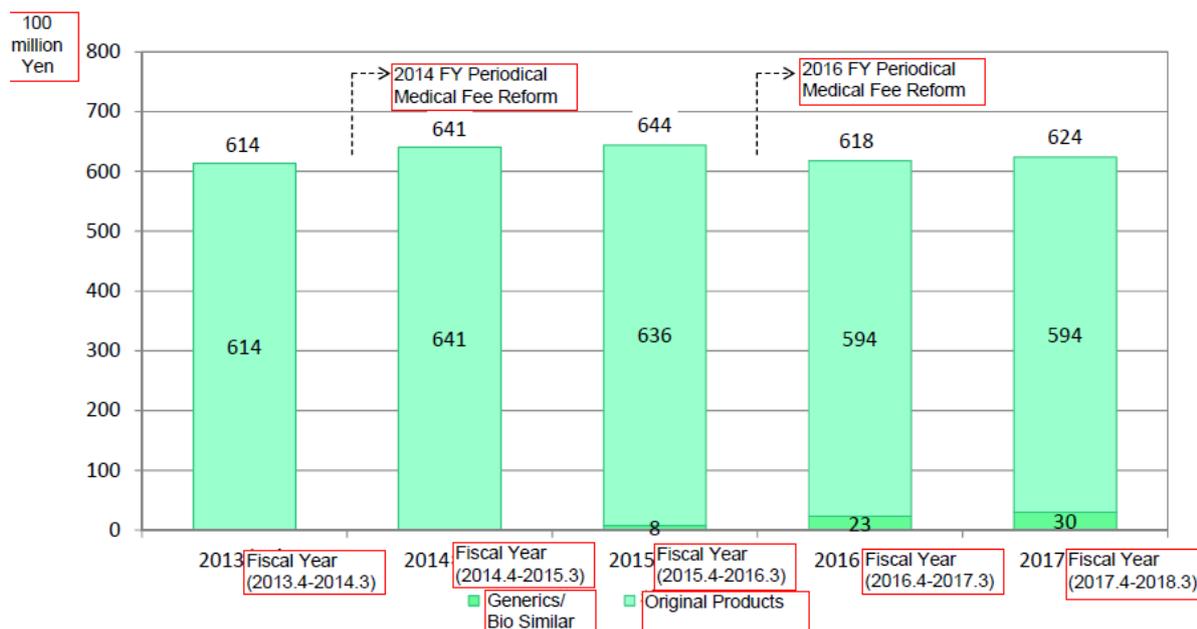
Whilst there have been changes in prices for both the originator and biosimilar insulin glargine preparations among the surveyed community pharmacies between 2016 and 2020 in India, similar to the situation in Bangladesh (Section 3.2), appreciable price differences still exist between the originator and some of the biosimilars (Table 7). It is likely this price difference may have resulted in increased prescribing of biosimilar insulin glargine among government hospitals in India in recent years with insulins provided free of charge.

### 3.4 Japan

The uptake of biosimilars has typically been lower in Japan versus a number of high-income countries including Western European countries (62, 66, 67, 78, 145-148). This is reflected by the fact that in 2017, the biosimilar market in Japan accounted for just 5% of the global biosimilar market, appreciably less than 13% of the total global biologics market in 2017 (149). A number of factors can account for this lower uptake (150). These include the fact that whilst biosimilars are currently priced 30% lower than originators they can end up being more expensive for patients under current regulations, physicians and pharmacists are generally unfamiliar with biosimilars and there are concerns with the effectiveness and safety of biosimilars (66, 149, 151, 152).

The total insulin market has been reasonably steady in Japan in recent years (Figure 2) reflecting stable prevalence rates (Table 2). There has also been limited use of biosimilar insulins in recent years in Japan, similar to other disease areas (153). However, it is envisaged that usage of biosimilars for insulin glargine will start growing with sustainability of the current healthcare system becoming an increasing issue for the Government and co-payments an increasing issue for patients (118). In addition, greater confidence in biosimilars (119). Utilisation of biosimilars has been tempered though among patients receiving subsidies for intractable diseases (154)..

Figure 2 – National Health Insurance Expenditure on Insulins in Japan 2013 to 2017



### 3.5 South Korea

We currently see limited differences in the public price of originator and biosimilar insulin glargine preparations in South Korea in recent years. These range from a price reduction of 0.27% to 5.0% between the originator and the biosimilar at US\$ 9.04 vs 8.59 and US\$9.02 per unit depending on the preparation prescribed (Table 9) (155).

In view of this, coupled with currently limited demand-side measures in Korea to influence physician prescribing including biosimilars (66, 124), there has only been limited utilisation of biosimilar insulin glargine in Korea (100IU/ml) in recent years. However, usage is growing from a low of 0.95% of total insulin glargine preparations in 2017 up to 4.7% in 2019, with further growth expected. This would

mirror utilisation patterns of infliximab, rituximab and trastuzumab biosimilars at 9.05%, 12.89% and 13.93% respectively of total use for these three biological medicines in their second year of market entry (156).

**Table 9 – Percentage utilisation and expenditure on biosimilar insulin glargine versus total insulin glargine in South Korea 2017 to 2019**

Insulin glargine	2017		2018		Price(USD)	2019	
	Share(%)		Share(%)			utilization	expenditure
	utilization	expenditure	utilization	expenditure			
<b>Originator</b>							
Lantus solosta	99.05	99.21	97.5	97.82	9.04	95.28	95.93
<b>Biosimilars</b>							
Basa glaquick pen	0.95	0.79	2.42	2.12	9.02	2.89	2.55
Glazia prefilled pen	NA	NA	0.08	0.07	8.59	1.83	1.52

### 3.6 Malaysia

Within the university hospitals in Malaysia, there is considerable prescribing of long-acting insulin analogues at between 50-70% of all insulins dispensed. This rate of prescribing is typically higher than seen among a range of hospitals in Bangladesh (Table 3). Similar to India though, biosimilars account for an appreciable proportion of long-acting insulin analogues dispensed in government hospitals, up to 90%. This appreciable utilisation of biosimilar insulin glargine is enhanced by procurement practices for public hospitals in Malaysia. These are based on the government preferentially purchasing generics and biosimilars from Malaysian companies where possible, procurements based on International Non-Proprietary Names (INN), and the increasing production of biosimilar insulin glargine in Malaysia manufactured to a high standard (93, 157-159).

Since insulins are available free of charge among public hospitals in Malaysia (Table 1), there is currently limited dispensing of biosimilar insulin glargine among seventeen community pharmacies surveyed throughout Malaysia (Box 1). Most pharmacies typically dispense the originator for patients wishing to purchase insulin glargine as they are generally willing to cover the full costs themselves (Box 1).

**Box 1 – Current situation regarding insulin glargine (100IU/ml) among twelve community pharmacies in Malaysia**

- **Originator**
  - Available in 13 out of the 17 pharmacies surveyed
  - Sales price ranged from 53.6 – 75.00 Malaysian Ringgits (US\$13.23 – 18.52)/dispensed preparation (3mls 100IU/ml)
  - No change in the selling price 2020 vs. 2019 in 8/ 13 pharmacies where data was available; 0-20% higher in one; 0 – 20% lower in four
- **Biosimilar**
  - Not sold or unavailable in 16 out 17 pharmacies in 2019 and 15 out of 17 pharmacies in 2020
  - When sold, the sales price ranged from 50 – 60 (US\$12.34 – 14.81) Malaysian Ringgits/dispensed preparation
  - Where sold – typically only a minority of biosimilar insulin glargine dispensed (below 40% of all insulin glargine preparations)

### 3.7 Pakistan

There has also been an 69.5% increase in the total utilisation of insulin in Pakistan from 2014 to 2019, with a 151.2% increase in expenditure as a result of increasing utilisation of long-acting insulin analogues including insulin glargine (Table 3). This increasing utilisation in insulin reflects increasing prevalence rates for diabetes mellitus in Pakistan in recent years (138, 144). However, utilisation of insulin glargine as a percentage of total insulin still remains low at just 1.97% in 2020, higher though

for expenditure (9.6% of total expenditure in 2020). This low utilisation of insulin glargine is likely due to issues of affordability, exacerbated by issues generally surrounding the affordability of even standard insulins such as NPH insulins among patients with diabetes in Pakistan despite the availability of different insulins among community pharmacies in Pakistan, although their availability can be variable (36, 48, 82, 90).

Currently biosimilar (Basagine®) is 20.5% cheaper than the originator among community pharmacies surveyed in Pakistan, which is similar to the findings of Ewen *et al.* (2019) (36), i.e. originator (3ml/10ml) at 1132PKR (US\$7.20), and 3858 PKR (US\$24.54) for one 10ml vial were recorded with the biosimilar (3ml) at 900 PKR (US\$5.73). Despite these price differences, and despite issues of affordability in Pakistan, the originator is typically dispensed among the eleven community pharmacies surveyed with very little dispensing of the biosimilar (Table 1A). There was though very limited dispensing of the 300IU/ml formulation of insulin glargine (originator), with this more concentrated formulation dispensed in only one of the community pharmacies surveyed representing 8.5% of the packs dispensed.

However, there has been a shortage of the originator in recent months increasing the dispensing of the biosimilar (Basagine®).

This limited utilisation of biosimilar insulin glargine in Pakistan at only 3.8% of 100IU/ml packs dispensed (Table 1A) versus Bangladesh, India and Malaysia, may well reflect greater patient and physician confidence in the originator as there have been concerns with the quality of generics in Pakistan (160, 161). Alongside this, currently limited price differences between the originator and the biosimilar in practice and only one biosimilar currently available among the surveyed community pharmacies. This compares with a greater range of biosimilars among the surveyed pharmacists in Bangladesh and India (Tables 5 and 8). As a result, currently no real competition among biosimilar manufacturers in Pakistan and the subsequent implications for lower prices. Enhanced local production, similar to other Asian countries, maybe one way forward to engineer lower prices for biosimilar insulin glargine in Pakistan in the future and increase its use given ongoing issues of affordability in Pakistan (36, 48). However, any biosimilar has to be manufactured to a high standard as seen in Malaysia given concerns with the quality of some of the generics in Pakistan (93, 160, 161).

### **3.8 Suggestions for the future to increase the utilisation of insulin glargine biosimilars**

Different activities will be needed among the different Asian countries to enhance the utilisation of biosimilar long-acting insulin analogues where this is a concern influencing patient and physician choice. The potential strategies will depend on the current use of long-acting insulin analogues in the first place among various countries versus NPH and other insulins. Table 1 illustrates that within Africa, long-acting insulin analogues may be available and listed in the country's essential medicines list. However, usage will only appreciably increase once prices substantially reduce. This is different to the situation within Bangladesh with a similar GDP to most of the chosen African countries (Table 2) (97). Secondly, there can be a need to increase the prescribing of biosimilar insulin glargine (100IU/ml) versus other long-acting insulin analogues including patented insulin glargine 300IU/ml (Toujeo) as well as insulin detemir and degludec to encourage increased competition and low prices (76).

The first step to improve the attractiveness of the market for insulin glargine biosimilar manufacturers is to enhance the reimbursement and funding of long-acting insulin analogues in the first place. Encouragingly, this was mainly an issue in Pakistan among the chosen Asian countries (Section 3.7); however, similar to the chosen African countries (Table 2). Box 2 includes potential ways forward in countries such as Pakistan where there is no or limited funding for long-acting insulin analogues due to issues of affordability. We accept though that the first goal in LMICs such as Pakistan is to ensure patients with T2DM are well managed in the first place and do not require insulin as patients with T2DM currently comprise approximately 90% of patients with diabetes in Asia (162). As a result, reduce their progression to requiring insulin to help control their diabetes to help reduce associated complications. However, once patients require insulin, Box 2 outlines potential ways forward to enhance the potential for patients to be prescribed long-acting insulin analogue biosimilars where this is seen as necessary to help reduce hypoglycaemia.

Box 2 - Potential activities in Pakistan to enhance funding and utilisation of long-acting insulin analogues (biosimilars) where currently limited funding/ use

- Only reimburse/ list biosimilars and not originators even when their prices are reduced, e.g., insulin glargine 100IU/ml on national formulary lists/ essential medicine lists/ hospital formularies, building on activities in India and Malaysia - only undertake this when prices are affordable through increasing competition among biosimilar manufacturers
- Enhance regional production of long-acting insulins building on recent developments in Malaysia with biosimilar insulin glargine and in Brazil with its production of human insulins (93, 163) - in line with suggestions following the recent COVID-19 pandemic to enhance regional production of essential medicines to improve their availability and affordability and reduce potential shortages (164, 165). As a result, reduce the current price gap between long-acting insulin analogues and NPH/ other insulins highlighted in the recent study by Ewen et al (36) to improve future affordability and access
- Concomitant with this, continue educating all key stakeholder groups regarding the clinical benefits of long-acting insulin analogues, building on their perceived benefits endorsed by greater use than NPH and other insulins in upper-middle and high-income countries (36)
- Concurrently, educate key stakeholders of the similar effectiveness and safety between originator and biosimilar long-acting insulin analogues building on current publications, and actively disseminate the findings to avoid/ reduce any nocebo effect (166)
- Instigate additional research regarding the cost-effectiveness of biosimilar insulin glargine vs. NPH and other insulins - building on current studies typically with originator long-acting insulins

We are aware that long-acting insulin analogues are not funded within public hospitals in Bangladesh (Table 2). However, there is growing prescribing and dispensing of long-acting insulin analogues (Tables 4 and 5) which is increasingly biosimilar insulin glargine (Table 7). We expect this trend to continue. The situation is different to India and Malaysia where we have seen growing use of insulin glargine dispensed as biosimilars are funded within the public hospitals. Consequently, the aim in these hospitals and communities is to enhance the prescribing and dispensing of long-acting insulin analogues as biosimilars versus NPH and other insulins to reduce hypoglycaemia and increase adherence where this is pertinent.

Box 3, which builds on the findings to date coupled with input from the senior-level co-authors, suggests potential ways forward to enhance the prescribing of biosimilars once long-acting insulin analogues are routinely available and being prescribed to help contain costs and limit co-payments without compromising care. Additional educational activities combined with a number of demand- and supply-side measures are also needed in Japan and Korea to enhance the prescribing of biosimilar versus originator long-acting insulins given current concerns with biosimilars (66, 149). However, this is changing in Japan as seen with increasing acceptance and use of biosimilar etanercept (119).

The growing use of lower cost biosimilars will become increasingly important with the global insulin market valued at US\$24 billion in 2018, and currently growing at a compounded rate of 4.9% (167), with the long-acting insulin analogues an increasing proportion (168, 169).

Box 3 – Potential activities to enhance the prescribing and dispensing of biosimilar insulin glargine within public healthcare systems

**Educational initiatives**

- Educate all key stakeholder groups where needed regarding similar effectiveness and safety between originator and biosimilar long-acting insulin analogues to reduce/ avoid potential nocebo effects (166)
- Instigate additional research where needed regarding the cost-effectiveness of biosimilar insulin glargine vs. other long-acting insulins as well as NPH and other insulins, and actively disseminate the findings. This is especially important among LMICs as most studies on the cost-effectiveness of long-acting insulin analogues have been undertaken in high-income countries. Lower cost biosimilars can enhance usage of long-acting insulin analogues where there are concerns with issues of access and affordability
- Work with patients and patient organisations to reduce any misinformation about biosimilars for long-acting insulin analogues to facilitate greater use

**Others include other demand-side activities**

- Introduce target prescribing goals (quality indicators) for starting patients on 100IU/ml biosimilar insulin glargine where possible when prescribing a long-acting insulin analogue - similar to Scotland and other European countries (62, 105, 170)
- Seek to introduce switching targets provided suitable educational support and funding is in place to address potential concerns where these exist – recognising that any quality target must be acceptable to all key stakeholder groups and measurable (171, 172)
- Seek ways to limit the prescribing of patented insulin glargine preparations as well as other patented long-acting insulin preparations through potentially prescribing restrictions and other activities - European health authorities have been successful with instigating prescribing restrictions in the past (173-176)
- Potentially introduce prescribing incentives based on target goals for overall biosimilar prescribing, which could include reduced premiums for increasing use (77, 78, 105)
- In Japan and similar countries, target hospitals and other organisations seeking to save costs as well as sub-groups of patients where biosimilars could help reduce co-payments (149)

**Supply-side activities**

- Reduce any formal national price banding for biosimilars to encourage greater competition and lower prices especially given the envisaged low cost-of-goods for manufacturing biosimilars of long-acting insulin analogues (88)
- Encourage greater discounts/lower prices from companies to enhance the use of biosimilar insulin glargine (100IU/ml) with preference given to biosimilar companies for listing/ funding of long-acting insulin analogues within hospitals – building on activities in India and Malaysia. This could be facilitated by only listing biosimilars rather than originators/ patented long-acting insulin analogues on national formulary lists. Alongside this, potentially delisting originator insulin glargine 100IU/ml and other patented long-acting insulins from formularies/ national lists as familiarity with the biosimilars grows – building on activities with renin-angiotensin inhibitors in Denmark (177)
- Potentially instigate regional production of long-acting insulins building on recent developments in Malaysia to obtain lower prices for biosimilar insulin glargine

**4. Discussion**

We believe this is the first study among multiple Asian countries to assess current utilisation patterns for long-acting insulin analogues, including biosimilars, and the potential rationale for the patterns seen to help improve future analogue use. We should also understand the limitations of emerging LMICs such as the BRIC countries (Brazil, Russia, India and China) (178, 179), and the next eleven nations (180), to increase public investment in higher priced but effective pharmaceuticals. The bottle neck of their affordability lines, and willingness to pay thresholds, in priority areas such as the management of patients with diabetes largely depends upon overall health spending policies and current priority settings, which need to be revised in light of changing morbidity and mortality patterns (181). In this sense, many of the most rapidly developing LMICs nations share comparable challenges, which urgently need to be addressed going forward (182).

It is encouraging to see growing utilisation of long-acting insulin analogues especially in Bangladesh and India given current limited use of these analogues among African countries (Table 2) and Brazil (5, 45, 55, 83). Consequently, this situation can provide guidance and exemplars for the future especially in Pakistan and similar countries (Table 2). Box 2 provides suggestions on potential ways forward to enhance access and funding for long-acting insulin biosimilars in Pakistan to benefit key stakeholder groups given the rising rates of diabetes in the country and associated complications. Ongoing activities in India and Malaysia, especially with local production of biosimilar insulin glargine preparations, can also provide direction to other countries seeking ways to enhance competition among biosimilar manufacturers to help lower future prices. This can build on the WHO prequalification initiative to try and break the monopoly of the three main insulin manufacturers (183, 184). Box 2 also includes additional suggestions to enhance the attractiveness of the biosimilar long-acting insulin analogue market in the first place. We will be following these developments, with the ultimate goal being to increase access and availability of long-acting insulin analogues to all patients to reduce current rates of hypoglycaemia associated with the use of insulin where pertinent, as well as improve adherence rates, to the benefit of all key stakeholder groups. This especially as improved management of insulin-diabetic patients will reduce complication rates, reducing associated morbidity,

mortality and costs. Box 3 provides suggestions to enhance the prescribing and dispensing of biosimilars once these are routinely available and funded within countries. This is important since enhancing the attractiveness of the market for manufacturers of biosimilars for insulin glargine will give manufacturers confidence to develop biosimilars for other long-acting insulin analogues as they lose their patents. This will benefit all key stakeholder groups going forward especially with rising rates of diabetes mellitus with the implications on overall costs including the costs of insulins in the future (185).

We are aware of a number of limitations with this study. These include the fact that we were not able to collect total utilisation and expenditure data from a number of the Asian countries studied, and relied on impressions of changes in utilisation and prices of different insulin preparations, including different insulin glargine preparations, in a number of the Asian countries for the reasons given. In addition, in some of the countries, only a limited number of community pharmacies were surveyed. However, we do not believe that appreciably surveying more pharmacies in these countries would have appreciably altered our findings. Consequently, we believe our findings are robust and provide future guidance to enhance access and utilisation of long-acting insulin analogues across all countries.

## 5. Conclusion

In conclusion, the increasing availability and use of biosimilar insulin glargine should help address concerns with hypoglycaemia as well as adherence to insulins across countries. In addition, generate confidence in their prescribing thereby improving future availability, access and funding of long-acting insulin analogues.

However, there are concerns with access and availability of long-acting insulin analogues including biosimilars in some countries. A range of activities, including potential local production as well as instigating a range of supply- and demand-side measures help increase their use to the benefit of all key stakeholder groups. We will continue to monitor this.

**Conflicts of Interest:** Monami Haque works for Square Toiletries Limited and Karen Koh Pek Khuan works for Friends' Pharmacy. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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