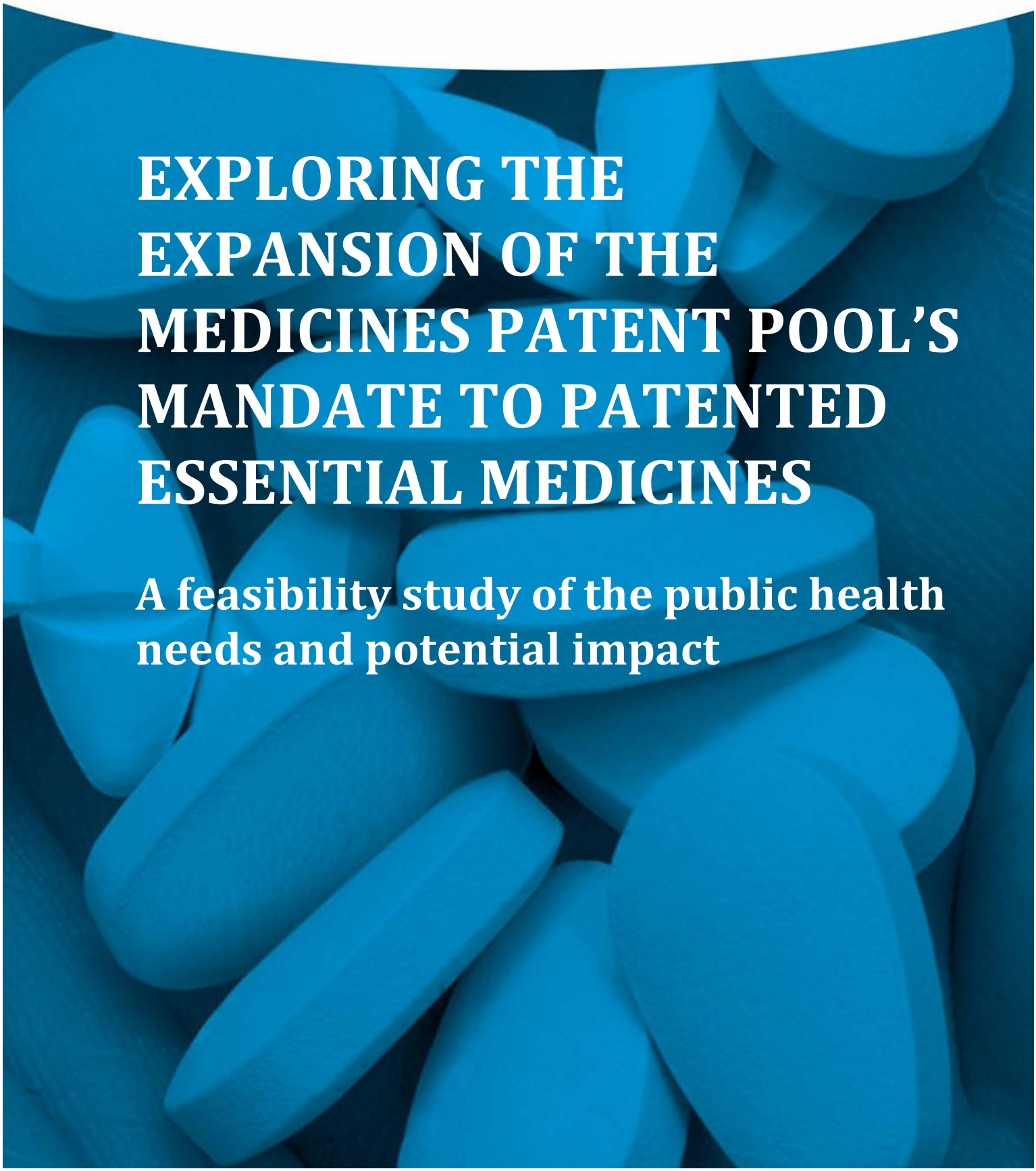
medicines patent pool



EXPLORING THE EXPANSION OF THE MEDICINES PATENT POOL'S MANDATE TO PATENTED ESSENTIAL MEDICINES

A feasibility study of the public health needs and potential impact

4 Patented medicines that the WHO Expert Committee considered as having relevant clinical benefits but needing additional data*: Case study on novel medicines for type 2 diabetes*

4.1 Background

The WHO Expert Committee considers applications for inclusion in the EML on the basis of public health relevance, safety, efficacy and comparative cost-effectiveness. For some medicines, the Committee may consider that the available evidence is not strong enough to recommend immediate inclusion, but that additional evidence may justify inclusion in the future if such evidence confirms the benefits shown in earlier data. One such case can be seen in the SGLT2 inhibitors, a novel class of medicines for the treatment of type 2 diabetes.

The 2017 WHO Expert Committee considered a review of second-line treatments for type 2 diabetes and highlighted the SGLT2 inhibitors in view of their clinical benefit as second-line therapy and mortality-reducing effect in patients at high risk of cardiovascular events.[1] The Committee indicated that more clinical data were needed before this class of medicines could be reconsidered for addition to the list.

This case study will consider the current challenges with treatment of type 2 diabetes in low- and middle-income countries (LMICs) and the potential for the MPP to play a role in accelerating access to new treatments.

4.2 Burden of disease in low- and middle-income countries

Diabetes represents a major cause of illness, causing five million deaths worldwide in 2015.[2] The number of people living with diabetes is expected to increase from 415 million in 2015 to 642 million by 2040.[2] In countries included in past MPP licences, the prevalence is estimated to reach 200 million people in the next 15 years (see appendix).

Diabetes and deaths due to high blood glucose are now more common in LMICs than in high-income countries (Figure 1),[3] and diabetes represents a greater disease burden globally (in terms of disease-adjusted life years) than tuberculosis or malaria.[4]

While it is estimated that about half of diabetes cases in LMICs are undiagnosed,[5] its impact is significant. The prevalence of diabetes has quadrupled worldwide since 1980, and continues to rise particularly in LMICs (Figure 1).[3,6,7] It is estimated that diabetes will cause more than US$1.1 trillion economic losses in LMICs in 2030.[8]

Figure 1. Evolution in the proportion of the population living with diabetes, by country income category, 1980-2012. It is estimated that approximately 90% of cases are type 2 diabetes.

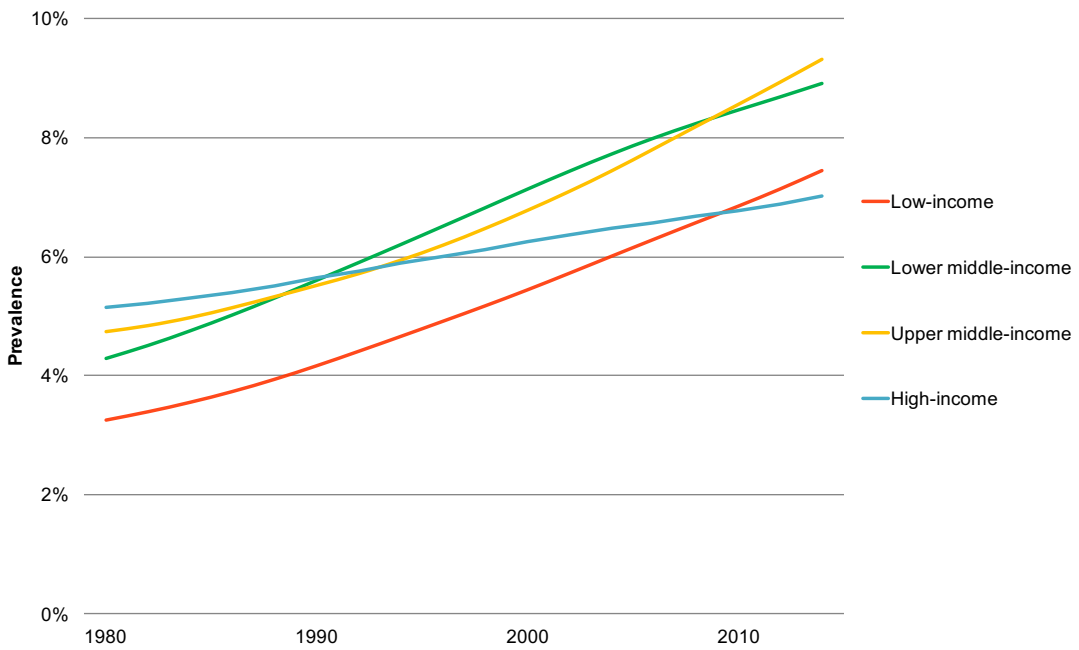


Figure adapted from the World Health Organization's Global report on diabetes, 2016.[3] *World Bank lending groups used for income categories.*

The three main types of diabetes are termed type 1 diabetes (T1D), type 2 diabetes (T2D), and gestational diabetes (diabetes arising during pregnancy). T2D represents more than 90% of global diabetes and is the focus of this chapter.[6] In all types of diabetes, the levels of blood sugar are raised, which, if uncontrolled over time, can lead to many serious and life-threatening complications.

In T2D, the body becomes resistant to insulin, secretion of insulin becomes impaired, or both.[7,9] The development of T2D is closely associated with overweight and obesity, but there is evidence to suggest that Black, Hispanic, and Asian populations develop risk for diabetes at a lower body mass index than Caucasian populations do.[6,7,10–13]

4.3 Complications of diabetes

The long-term clinical management of T1D and T2D is focused on preventing long-term complications, which include damage to the kidneys, eyes, nerves and cardiovascular system. Diabetes causes up to 55% of all end-stage kidney failure,[3] and 7% of diabetics have damage to the retina severe enough to threaten sight.[14]

Cardiovascular complications are particularly important (and are the key focus of this case study). Diabetes increases the risk of cardiovascular disease,[15] and cardiovascular disease is responsible for more than 70% of deaths in people with T2D.[16]

Compared to people living with diabetes in high-income countries, people living with diabetes in LMICs may have a higher risk of developing complications. For example,

high blood sugar is generally detected later in Africa, suggesting a higher risk of complications at the time of diagnosis.[6,17] In addition, the onset of diabetes is generally earlier in Asians, leading to a higher long-term risk of complications.[18]

4.4 Outline of type 2 diabetes treatment, drug classes, diagnostic methods, and guidelines

4.4.1 Diagnosis and monitoring

T2D is diagnosed by detecting blood glucose levels that are above defined limits, using tests that measure blood glucose directly, or by measuring glycated haemoglobin (HbA1c) levels.

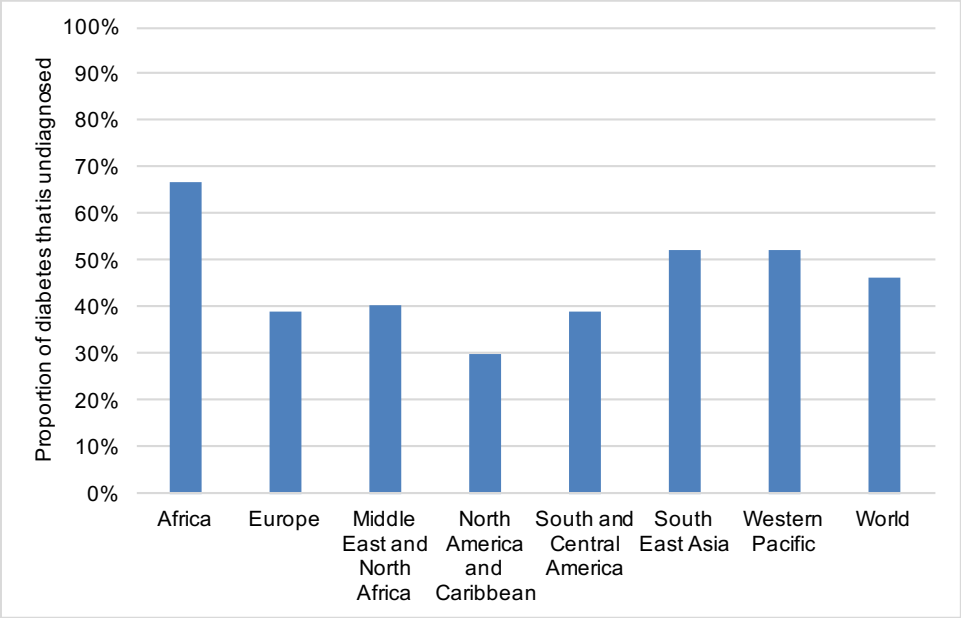
Blood glucose levels are ideally measured by laboratory analysis of a sample of venous blood, but point-of-care capillary blood glucose meters are more convenient and an acceptable alternative.[19] However, these point-of-care devices come with their own challenges for access.[20] HbA1c testing is more convenient in that it does not require the individual to fast before the test. In addition, HbA1c better reflects long-term diabetes control, and point-of-care measurement devices are available. However, HbA1c measurement is more expensive than other modalities.[19,21] A WHO survey found that blood glucose measurement was generally available in primary care settings in more than 90% of upper-middle-income countries and more than 80% of lower-middle-income countries, but only 50% of low-income countries.[22]

T2D is ideally monitored through at least twice-yearly HbA1c measurements or, if not available, blood glucose measurements.[19] In addition to monitoring glycaemic control, it is critical to incorporate complication surveillance, including regular monitoring of kidney function, eye and foot health, and cardiovascular risk factors.[19]

National background papers commissioned to inform this analysis revealed substantial variety in diagnosis and monitoring practices. In Cambodia, the majority of diabetes patients are diagnosed through random blood glucose measurement late in the disease process when complications are already severe. Similarly, in Pakistan,, the proportion of the population screened for diabetes is likely to be less than 5%, and diagnosis is normally preformed using random blood glucose measurement with a point-of-care device. In India, screening is done opportunistically, most often with a point-of-care blood glucose meter. However, in Peru blood glucose screening is part of standard cardiovascular screening done for patients more than 40 years of age.

The IDF estimates that 47% of diabetes is undiagnosed globally, with regional rates of undiagnosed diabetes ranging from a low of 30% in North America and the Caribbean to a high of 67% in Africa (Figure 5).[2]

Figure 5. Percentage of diabetes that is undiagnosed, by region.



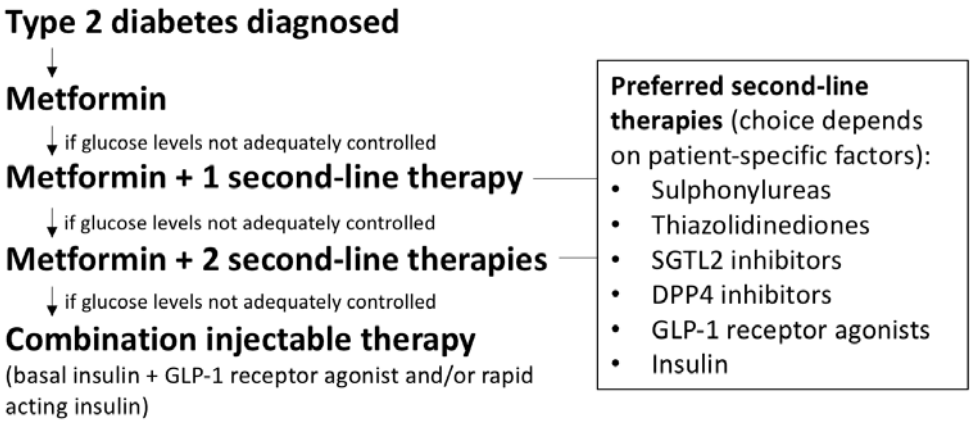
Data from IDF Atlas, split by IDF region.[2]

4.4.2 Treatment of Type 2 Diabetes

While we focus on pharmaceutical interventions, it is important to note that interventions to promote a healthy lifestyle may be as or more important in controlling the type 2 diabetes epidemic at the population level. The WHO *Global action plan for the prevention and control of NCDs*, for example, proposes numerous policy options for member states aimed at promoting healthy eating and exercise.[23]

US and European treatment guidelines advocate starting treatment with metformin as soon as T2D is diagnosed (unless contraindications are present), along with dietary changes and exercise.[24,25]

Figure 6. Summary of pharmacological treatment guidelines for T2D (American Diabetes Association).



Current guidelines offer six classes of drugs as options for second-line treatment if and when metformin monotherapy fails (Figure 6). These six classes are sulphonylureas,

thiazolidinediones, SGLT2 inhibitors, DPP4 inhibitors, GLP1As, and insulin. Of these, the first two and insulin are therapies that have been in use for decades, while SGLT2 inhibitors, DPP4 inhibitors, and GLP1As have been brought to market in the last decade.

While in general guidelines leave the choice between the classes of second-line treatment down to patient-specific considerations,[24,26] in patients with known cardiovascular disease, second-line agents that showed cardiovascular benefits in trials should be prioritized: the SGLT2 inhibitors canagliflozin and empagliflozin and the GLP1A liraglutide.[24] After second-line therapy with one of these drug classes fails, current guidelines recommend adding another of these classes as a third medication.[24,26] US guidelines recommend that in patients who have markedly high blood glucose levels at diagnosis be treated with metformin and a second-line agent from the start.[24]

GLP1As and insulins require subcutaneous injections and cold chain and may therefore be less suitable for large-scale use in resource-poor settings. Other challenges with insulin include the need for more regular blood glucose monitoring, a high risk of hypoglycemic events (in which blood sugar drops too low) and a weight-gain effect. Some GLP1As require injection only once weekly and have weight-reducing effects. The development of an oral GLP1A (currently in phase 3) may also contribute to making this class of antidiabetic medicines more suitable for scale-up in resource-limited settings in the future.[27]

Thiazolidinediones have been the subject of multiple controversies surrounding potential dangers of increasing heart attacks and bladder cancer,[28,29] although the evidence for these risks is controversial.[7,30] Nevertheless, they confer an increased risk of bone fractures when used in women[31] and increase the risk of developing heart failure.[32] In high-income countries, thiazolidinediones are not commonly used,[33–36] and national background papers commissioned to inform this study suggested that they are used little in LMICs, despite their low price. They are also not included in the WHO EML.

Sulphonylureas (SUs) are the only class of oral second-line medicine for type 2 diabetes currently included in the WHO EML. SUs can cause hypoglycemic events and weight gain and may contribute to beta-cell failure. However, in combination with metformin, SUs are the most widely used drug class in LMICs due to their low price and long period of clinical experience.[7] Data on sulphonylureas' cardiovascular effects are equivocal with some studies showing increased, and some decreased, risk.[37,38] A recent meta-analysis found that SUs conferred an increased risk of severe hypoglycemia compared to newer agents.[39] Aside from being unpleasant for patients and diminishing medication adherence,[40] episodes of severe hypoglycemia are linked to a significantly increased risk of cardiovascular events and mortality in patients with T2D.[41]

Based on the WHO Expert Committee's highlighting of SGLT2 inhibitors, we have focused on this class for the purposes of this feasibility analysis. SGLT2 inhibitors are a novel class of medicines used as second-line therapy for T2D. This class currently includes empagliflozin, canagliflozin and dapagliflozin.

In general, the benefits of SGLT2 inhibitors compared to other oral second-line T2D drug classes are their weight-reducing effect, and mortality-reducing effects for patients

with high cardiovascular risk profiles,[42] notably described in the EMPA-REG trial for empagliflozin[43] and in the CANVAS trial for canagliflozin[H].[44] These benefits for patients with cardiovascular risks were highlighted by the WHO EML Committee, and are also reflected in the recently updated guidelines of the American Diabetes Association, which recommend that second-line therapy in patients with known cardiovascular disease should be treated with SGTL2 inhibitors or liraglutide (a GLP-1 agonist).[24]

The SGLT2 inhibitors' main side-effects are associated with their mechanism of action (increased excretion of glucose in the urine), a higher rate of urogenital infections, and a risk of dehydration due to increased passage of urine (osmotic diuresis). [42],[45] There are concerns that canagliflozin (but not empagliflozin or dapagliflozin) confers an increased risk of amputation, although the exact causal link is unclear.[46] Assessments by the UK National Institute for Health and Care Excellence (NICE) found that overall, SGLT2 inhibitors were superior to the SUs, thiazolidinediones, and DPP4 inhibitors in terms of quality-adjusted life years gained through treatment, although inferior to GLP1As (which are currently limited to injectable formulations).[47–49]

DPP4 inhibitors and GLP1As, with drugs in both classes under patent protection (see section 6), could also potentially be candidates for MPP licensing, and parts of the impact analysis described later in this chapter may also apply to those classes.

4.4.3 Availability and affordability of medicines for diabetes.

In a 2015 WHO survey, the standard first-line medicine for T2D, metformin, was reported to be generally available in the public sector in approximately 40% of low-income countries and more than 70% of lower-middle-income countries. The availability of SUs, the most commonly used second-line drug class, was lower. It was generally available in the public sector in only 15% of low-income countries and 67% of lower-middle-income countries .[50] A survey by the International Diabetes Federation found that T2D medicines were available for purchase in approximately half of low-income countries and 48–89% of middle-income countries (depending on the drug class), but that full government provision of T2D medicines was very low.[51]

A survey of 30 countries undertaken by Health Action International (HAI) assessed affordability of treatments and found that metformin and sulphonylureas were both available and affordable in 28% of cases in low-income countries and 23% of cases in middle-income countries[I].[52] Although the prices offered for metformin and sulphonylureas are in general low,[53] mark-ups within the supply chain and other supply chain problems contribute substantially to a lack of availability and affordability.[6,52]

National background papers commissioned as part of this analysis identified a number of illustrative examples in relation to the new T2D medicines, namely the DPP4 inhibitors, SGLT2 inhibitors, and GLP1As:

[H] A trial on the cardiovascular and renal effects of dapagliflozin (DECLARE-TIMI58) is ongoing,[56] and a real-world analysis that has found cardiovascular benefit for dapagliflozin is described below.

[I] Medicines were considered available and affordable when they were available 80% of the time or more, and a monthly supply cost no more than the equivalent of one day's wages for the lowest-paid government worker or were available for free in the public sector.

- In Pakistan, SGLT2 inhibitors are not registered and not available and GLP1As are registered but expensive. An estimated 10% of patients eligible for triple therapy with DPP4 inhibitors receive it, and less than 5% of those eligible for triple therapy with GLP1As receive the treatment.
- In India, teneligliptin, a DPP4 inhibitor that was one of the earlier DPP4 inhibitors to go off patent, has become widely used, as other DPP4 inhibitors were less affordable. Teneligliptin is little-known outside of India and Japan. While SGLT2 inhibitors are becoming more popular due to their weight loss effect, DPP4 inhibitors entered the market earlier and are thus still more commonly prescribed and are more affordable. However, the significant majority of Indians pay for medicines out-of-pocket.[54] GLP1 agonists are used only in a few specialist centres due to their high price.
- In Cambodia, less than 1% of those that could benefit from SGLT2 inhibitors or DPP4 inhibitors receive them, and GLP1As are not available.
- In Tanzania, some SGLT2 inhibitors and DPP4 inhibitors were available, but only in the private sector, and at a high price.

In summary, while data are limited, available information suggests that newer second-line medicines are generally not widely available in LMICs (DPP4 inhibitors being an exception in a few countries). Second-line medicines may be accessible in the private market in some countries, but their prices can be prohibitive for many.

Table 1. Prices and registration status for medicines for type 2 diabetes, as reported in national background papers.

Medicine	Lowest available price per unit (USD)			
	Cambodia	Pakistan	Peru	Tanzania
Metformin 500mg*	$0.02†	$0.01†	$0.13†	$0.004†
Metformin 850mg*	N	$0.01†	$0.02†	N
Sulphonylureas				
Glibenclamide 5mg	$0.02†	$0.01†	$0.02†	$0.003†
Gliclazide 30mg*	$0.15†	$0.03†	$0.70**	N
Pioglitazone 15mg	N	$0.01†	$1.45†	N
SGLT2 Inhibitors				
Canagliflozin 100mg	N	N	$2.05	$2.23
Empagliflozin 10mg	Limited donations by originator	N	$2.38	N
Dapagliflozin 5mg	Limited donations by originator	N	$1.81	N
DPP4 Inhibitors				
Saxagliptin 2.5mg	N	N	$1.63	N
Sitagliptin 50mg	N	$0.09†	$2.68	$0.80
Linagliptin 5mg	N	N	$1.40	N
Vildagliptin 50mg	N	$0.14†	$0.77	$0.69
GLP1 agonists				
Liraglutide 18mg in 3mL vial	N	N	$109.50	N

***Standard-release formulation. **extended-release formulation. † – generic. N: – not registered or not available. Assumed 1 Pakistani rupee = 0.0095 US dollars, 1 Tanzanian shilling = 0.000445 US dollars. For Tanzania, maximum retail price for dispensaries and health centers used, as reported by the Medical Stores Department.[55]**

4.5 T2D medicines and the WHO Expert Committee.

In 2017, the WHO Expert Committee reviewed all second-line T2DM treatment classes for potential inclusion in the EML. The Committee highlighted that "SGLT-2 inhibitors have shown a relevant clinical benefit as second-line therapy in patients at high risk of cardiovascular events, with a reduction in overall mortality, but [more] data are needed to confirm this finding".[1] While the Committee did not add any new antidiabetic medicines to the EML, the favorable conclusion with regard to SGLT2 inhibitors in particular suggests the potential for inclusion in future EMLs if and when further data become available.

Further data on the cardiovascular effects of SGLT2 inhibitors in trials and real-world settings will become available over the next two to three years. Multiple large trials are underway to further elucidate the effect of SGLT2 inhibitor therapy on cardiovascular and renal disease. These trials are expected to be completed in the next three years, and include the DECLARE-TIMI58, Dapa-HF, and Dapa-CKD trials for dapagliflozin, the CREDENCE trial for canagliflozin, and the EMPEROR trials for empagliflozin.[56–61] In addition, real-world data are beginning to emerge: the EASEL study, published in November 2017, retrospectively analysed a cohort of over 25,000 patients using SGLT2

inhibitors,[62] finding reductions in the rate of cardiovascular events and all-cause mortality comparable to those seen in Phase III trials.

4.6 Inclusion in national essential medicines lists (NEMLs).

A 2014 study found that second-line medicines for T2D, with the exception of sulfonylureas, were included in NEMLs of only about a tenth or less of LMICs surveyed.[63] We did not find SGLT2 inhibitors included in any of the NEMLs we were able to review. Government representatives, in discussions with the MPP, identified high costs as one of the reasons these treatments may not have been included. One health technology assessment mentioned by one government consulted concluded that at currently available prices they were not considered cost-effective.

4.7 Patent landscape for SGLT2 inhibitors

The main product patents on SGLT2 inhibitors expire between 2023 and 2025 and have been filed or granted in many of the LMICs for which it was possible to collect information, including those with significant manufacturing capacity such as India, China, South Africa, Brazil, and Thailand. Several secondary patents may also delay further competition for these products in countries in which patents have been granted. Table 4 also includes patent data for the DPP4 inhibitors and the GLP1As showing a similar pattern. It should be noted, however, that for DPP4 inhibitors a number of generics have already entered the market in some countries (e.g. India, Pakistan) and there has been significant patent litigation around the DPP4 inhibitors sitagliptin, saxagliptin, and vildagliptin in India.[64-66]

Table 4. Patent status of type 2 diabetes drugs in select LMICs and expected expiry dates.

Type 2 diabetes	Expected date of expiry	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM
SGL2 inhibitors															
Canagliflozin															
Canagliflozin product	2024	.	F	F	G	.	G	G	.	.	G	G	G	G	G
Crystalline form of canagliflozin hemihydrate	2027	.	F	G	G	G	G	O	.		G	G	G	G	G
Method of treatment with SGLT inhibitor and a DPP4 inhibitor	2029	.	F	G	.	.	G	O	.	.	G	G	.	.	.
Dapagliflozin															
Dapagliflozin product	2020/2023	.	F	G	G	.	G	G	.	.	G	G	G	G	G
Pharmaceutical formulation of dapagliflozin propanediol monohydrate	2027	.	F	G	G	.	G	O	.	.	G	G	.	G	.
Crystalline dapagliflozin propanediol	2027	.	F	G	G	.	G	O	.	.	G	G	G	G	.
Empagliflozin															
Empagliflozin product	2025	.	F	G	G	.	G	G	.	.	G	F	G	G	G
Crystalline form of empagliflozin	2026	.	F	G	G	.	G	O	.	.	G	G	G	G	G
Combination of empagliflozin and linagliptin.	2028	.	F	G	G	.	G	O	G	.	G	G	G	G	G
DPP4 inhibitors															
Alogliptin															
Alogliptin product patent.	2024	.	F	F	G	.	G	O	G	.	G	F	G	G	G
Method of treating Type II diabetes using alogliptin and pioglitazone	2026	.	F	G	G	.	G	R/A	G	G	G	F	G	G	F
Linagliptin															
Product	2023	.	F	G	G	.	G	G	.	.	G	F	G	G	G

Method of treating type 2 diabetes with combination	2027	.	F	F	F	.	F	F	.	.	F	F	G	.	.
Intermediate and process for preparation	2025	.	F	G	G*	.	.	F	.	.	G	F	.	G	F
Saxagliptin															
Product or salt	2021	.	G	G	.	.	G	G	.	.	G	G	.	G	.
Coated tablet	2025	.	F	G	.	.	G	G	.	.	G	G	G	G	G
Sitagliptin															
Sitagliptin product	2022	.	G	G	G	.	G	G	G	.	G	G	G	G	G
Sitagliptin phosphate and its hydrates	2024	.	F	G	G	.	G	.	F	.	G	G	G	F	G
GLP-1 agonists															
Dulaglutide															
Dulaglutide product	2024	.	G	G	G	.	.	G	.	.	.	.	G	.	.
Exenatide															
Injectable composition	2021	.	F	G	.	.	.	.	.	.	.	.	.	.	.
Method of lowering plasma glucagon with exendin	2020	.	G	G	.	.	.	.	.	.	.	.	.	.	.
Composition for sustained-release of exendin	2025	.	F	G	G	.	.	G	.	.	.	.	.	.	.
Liraglutide															
Liraglutide Product	2017	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Liraglutide Formulation	2025	.	F	G	.	.	.	O	.	.	.	.	.	.	.
Composition of Insulin Degludec	2028	.	F	F	.	.	.	G	.	.	.	.	.	G	.
Albiglutide															
Albiglutide product specifically.	2025/2026	.	F	G	.	.	G	G	G	.	G	.	.	F	G
Method for enhancing GLP-1 activity	2027	.	F	F	G	.	F	F	G	.	G	F	G	G	F
Semaglutide (pipeline medicine)															
Product and composition	2026	.	F	G	.	.	.	G	.	.	.	.	.	G	.

*G – granted. F – filed. R – refused. *Patent terminated in AM, AZ, BY, KG, KZ, MD, TJ and TM. Blank – not filed. ? – no data. ARIPO – African Regional Intellectual Property Organization, EAPO – Eurasian Patent Organization, OAPI – Organization Africaine de la Propriete Intellectuelle.*

4.8 Relevant market analysis

Currently, the originators of empagliflozin and dapagliflozin both have distribution agreements with generic companies in India.[67,68] To our knowledge, no distribution agreements exist for canagliflozin to supply LMICs. At least two generics manufacturers disclose that they have SGLT2 inhibitor products in development on their websites.[69,70]

The global market for T2D medicines is expected to double between 2015 and 2025,[71] and market analysis has identified diabetes as the top therapeutic area in terms of expected growth in emerging markets in the medium term.[72] Originator SGLT2 inhibitors are currently priced at US$19-23 per month on the Indian private market.[73] This stands in contrast to median prices for the oral antidiabetic drugs currently on the WHO EML: gliclazide at $1.33 per month and metformin at $1.94 per month (Table 5).

Dapagliflozin and empagliflozin have significantly lower dosages (10mg and 10-25mg daily, respectively) compared to canagliflozin (100-300mg daily). This suggests that, if manufactured at scale, generic dapagliflozin and empagliflozin may be less expensive to produce.

Table 5. Current global monthly prices for type 2 diabetes medicines (USD).

Description	Buyer median price per month
Gliclazide*	$1.33
Metformin slow-release	$7.13
Metformin immediate-release using 500mg tablets*	$1.94
Metformin immediate-release using 850mg tablets	$1.04
Data from the International Medical Products Price Guide published by Management Sciences for Health.[53] Prices given for representative daily dose in US dollars. Blank – no data. *Included in the 2017 WHO Model List of Essential Medicines.	

4.9 Estimated public health impact

Potential economic and public health impacts of hypothetical MPP licences on SGLT2 inhibitors were estimated using the methodology outlined in Chapter 2 and described in more detail in the appendix. While the estimates outlined in this section apply specifically to the SGLT2 inhibitors, some of the findings may also apply to other new classes of T2D medicines.

The number of patients in countries in past MPP licences that could potentially receive treatment with MPP-enabled generic SGLT2 inhibitors was calculated to reach 1.1–3.3 million, delivering 7–19 million patient-years of treatment, over the seven years leading up to expiry of patent protection.

Based on available data on the impact of SGLT2 inhibitors on mortality among people with high cardiovascular risk,[43,44] we estimated that early access to SGLT2 inhibitors could potentially avert 31,000–126,000 major adverse cardiovascular events (MACE), depending on the scenario (Table 6). This assumed that SGLT2 inhibitors would be used preferentially in T2D patients with higher cardiovascular risk. These estimates are for canagliflozin and empagliflozin only, as there are as yet no published trial data on the impact of dapagliflozin on MACE and mortality (though trials are ongoing). It was also estimated that early access could confer a total of 68,000–275,000 additional QALYs, compared to sulphonylureas, for people living with T2D.

In addition to the potential for wider use as a second-line treatment, SGLT2 inhibitors could be of use as a third-line treatment. Most patients need a new line of treatment added every few years until they are eventually switched to insulin therapy.

These impacts in MACE events and QALYs were found with conservative assumptions regarding rates of diagnosis and market uptake in low, medium and high uptake scenarios (see appendix for details).

Table 6. Estimated public health impact of MPP licensing of SGLT2 inhibitors.

		SGLT2 inhibitors
Assumed duration of impact		7 years
Number of patients treated with MPP-enabled product	Low	up to 1.1 million
	Med	up to 2.2 million
	High	up to 3.3 million
Total major adverse cardiovascular events averted	Low	31,000-43,000
	Med	59,000-83,000
	High	89,000-126,000
Total QALYs gained	Low	68,000-94,000
	Med	132,000-181,000
	High	199,000 – 226,000

QALY – quality-adjusted life year.

4.10 Estimated economic impact

The economic impact calculation estimated the theoretical savings possible through the purchase of more affordable quality-assured generic versions of the medicines instead of procurement of the same quantity of originator product. The assumed quantity purchased, per year, was based on projected disease burden and assumptions regarding rate of diagnosis, access to healthcare, and market penetration. Estimated savings were US$0.9–3.1 billion, depending on the uptake scenario and medicine.

4.11 Conclusions

The global burden of T2D is considerable and prevalence in countries in past MPP licences is estimated to reach 200 million people in the next 15 years. In addition to representing a significant health burden, diabetes causes substantial economic losses in LMICs, and financial burden for patients. For example, in India, people with T2D and low incomes spend between a quarter and a third of their income on diabetes care.[74]

Metformin is the recommended treatment for first-line treatment. The only oral second-line treatment currently included in the EML is associated with weight gain, a risk of severe hypoglycemic events,[39] and possibly an increased risk of stroke.[38] Newer types of antidiabetic medicines have potential benefits. Among these benefits, and depending on the class, are the weight-reducing effect, the lower rate of severe hypoglycaemia, and the cardiovascular mortality benefit demonstrated by SGLT2-inhibitors, which was highlighted by the WHO's Expert Committee.[1]

From discussions with diabetes clinicians and national background papers commissioned by the MPP, it is clear that, with few exceptions, these medicines are generally not being used in LMICs because they are altogether unavailable or affordable only to few patients who pay for them out-of-pocket. Without licences, it is unlikely that generic competitors will be able to enter markets in many countries before patents expires. However, when generic market entry becomes possible, prices of SGLT2 inhibitors could become more affordable and this may facilitate their inclusion in national reimbursement schemes, at least for patients at high risk of cardiovascular events.

Our modelling suggested that MPP licensing of SGLT2 inhibitors could extend access to 1.1–3.3 million people, delivering 7–19 million patient-years of treatment. Treatment at these levels would avert an estimated 31,000–126,000 cases of major adverse cardiovascular events, confer 68,000–275,000 additional QALYs. It should be noted, however, that these figures would be highly sensitive to the rate of market uptake for MPP-enabled generics and the number of countries covered by licences.

In terms of public health impact, we focussed on cardiovascular complications and QALYs. However, multiple other potential effects of affordable SGLT2 inhibitors were not captured in this analysis, including benefits gained through delaying or avoiding complications such as visual impairment, kidney disease, and diabetic foot disease. As insulin use brings a slew of challenges for patients and is associated with its own access challenges in poor countries,[75] delaying the need for insulin could be another important benefit of SGLT2Is. The economic impact estimated in this analysis derives only from savings on the cost of medicines and did not consider other benefits to the patient and indirect wider benefits to economies.

Aside from SGLT2Is, GLP1As and DPP4 inhibitors are gaining popularity in high-income country contexts and are under patent protection. DPP4 inhibitors appear to be available as generics in a few countries and some are currently the subject of patent disputes in India. GLP1As would likely become more attractive as an option for LMICs if and when the oral GLP1A in development is approved.

Optimal management of diabetes in the long term requires well-organised multidisciplinary care. Broader access to novel medicines would only be one piece in a package of strategies in LMICs. Interventions to promote healthier diets and exercise are likely to be particularly important and are considered cost-effective.[76]

Multiple factors pose challenges for treating diabetes in LMICs. T2D is typically insidious in its development. Without screening, it can present at a stage where serious complications are already present. Diagnostic modalities, though significantly more affordable than in some other diseases, can nevertheless be unaffordable or unavailable for other reasons.[20] Without improvements in diagnosis and access to diabetes care more generally, any newly available diabetes medicine will have limited impact at the population level. Current treatment access even to the first-line therapy (metformin) remains low in certain countries and increased efforts are needed to diagnose people with T2D early and connect link them to effective treatment.

The WHO Expert Committee's assessment highlighted the clinical benefits of the SGLT2 inhibitors but recommended that additional data were needed to confirm their effects in decreasing cardiovascular mortality. These data are likely to become available soon, through a number of ongoing trials and observational data from real-world cohorts.[56–62] If data were to confirm the findings, concerns around availability and affordability in LMICs would likely arise, and licensing through the MPP could contribute to making these medicines more widely available at affordable prices through a collaborative accesss mechsnism.

4.12 References

1 WHO EML Expert Committee. Report of the WHO Expert Committee on Selection and Use of Essential Medicines. WHO Tech. Rep. Ser. 2017. http://www.who.int/medicines/publications/essentialmedicines/EML_2017_EC21_Unedited_Full_Report.pdf?ua=1 (accessed Sept 14, 2017).

2 International Diabetes Federation. IDF diabetes atlas 8th edition. http://www.diabetesatlas.org/ (accessed Sept 10, 2017).

3 World Health Organization. Global report on diabetes. 2016. http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf?ua=1 (accessed Oct 3, 2017).

4 Abajobir AA, Abate KH, Abbafati C, *et al.* Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; 390: 1260–344.

5 Beagley J, Guariguata L, Weil C, Motala A. Global estimates of undiagnosed diabetes in adults. *Diabetes Res Clin …* 2014. http://www.sciencedirect.com/science/article/pii/S0168822713003847.

6 Atun R, Davies JI, Gale EAM, *et al.* Diabetes in sub-Saharan Africa: from clinical care to health policy. *Lancet Diabetes Endocrinol* 2017; 5: 622–67.

7 DeFronzo RA, Ferrannini E, Groop L, *et al.* Type 2 diabetes mellitus. *Nat Rev Dis Prim* 2015; : 15019.

8 Bommer C, Sagalova V, Heesemann E, *et al.* Global Economic Burden of Diabetes in Adults: Projections From 2015 to 2030. *Diabetes Care* 2018; : dc171962.

9 Narayan KMV. Type 2 Diabetes: Why We Are Winning the Battle but Losing the War? 2015 Kelly West Award Lecture. *Diabetes Care* 2016; 39: 653–63.

10 Mbanya JCN, Motala AA, Sobngwi E, Assah FK, Enoru ST. Diabetes in sub-Saharan Africa. *Lancet (London, England)* 2010; 375: 2254–66.

11 Kengne AP, Echouffo-Tcheugui J-B, Sobngwi E, Mbanya J-C. New insights on diabetes mellitus and obesity in Africa-part 1: prevalence, pathogenesis and comorbidities. *Heart* 2013; 99: 979–83.

12 O'Hara EG, Nuche-Berenguer B, Kirui NK, *et al.* Diabetes in rural Africa: what can Kenya show us? *Lancet Diabetes Endocrinol* 2016; 4: 807–9.

13 Hu FB. Globalization of diabetes: The role of diet, lifestyle, and genes. *Diabetes Care* 2011; 34: 1249–57.

14 Yau JWY, Rogers SL, Kawasaki R, *et al.* Global Prevalence and Major Risk Factors of Diabetic Retinopathy. *Diabetes Care* 2012; 35: 556–64.

15 The Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010; 375: 2215–22.

16 Laakso M. Cardiovascular Disease in Type 2 Diabetes from Population to Man to Mechanisms. *Diabetes Care* 2010; : 442–9.

17 Levitt NS. Diabetes in Africa: epidemiology, management and healthcare challenges. *Heart* 2008; 94: 1376–82.

18 Ramachandran A, Wan Ma RC, Snehalatha C. Diabetes in Asia. *Lancet* 2010; 375: 408–18.

19 World Health Organization. Global Report on Diabetes. 2016.

20 Beran D, Yudkin JS. Looking beyond the issue of access to insulin: What is needed for proper diabetes care in resource poor settings. *Diabetes Res Clin Pract* 2010; 88: 217–21.

21 Gomez-Perez FJ, Aguilar-Salinas CA, Almeda-Valdes P, Cuevas-Ramos D, Lerman Garber I, Rull JA. HbA1c for the Diagnosis of Diabetes Mellitus in a Developing Country. A Position Article. *Arch Med Res* 2010; 41: 302–8.

22 World Health Organization. Global Report on Diabetes. Geneva, Switzerland: World Health Organization, 2016 DOI:ISBN 978 92 4 156525 7.

23 World Health Organization. Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013-2020. 2013. http://apps.who.int/iris/bitstream/10665/94384/1/9789241506236_eng.pdf (accessed March 4, 2018).

24 American Diabetes Association. Standards of Medical Care in Diabetes. *Diabetes Care* 2018; 41.

25 Inzucchi SE, Bergenstal RM, Buse JB, *et al.* Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia* 2015; 58: 429–42.

26 International Diabetes Federation. IDF Clinical Practice Recommendations for managing Type 2 Diabetes in Primary Care. 2017. https://www.idf.org/component/attachments/attachments.html?id=1270&task=download (accessed Sept 28, 2017).

27 DiabetesInControl.com. New Oral GLP-1 Promising for Type 2 Diabetes. 2016. http://www.diabetesincontrol.com/new-oral-semaglutide-promising-for-type-2-diabetes/ (accessed Oct 16, 2017).

28 Consoli A, Formoso G. Do thiazolidinediones still have a role in treatment of type 2 diabetes mellitus? *Diabetes Obes Metab* 2013; 15: 967–77.

29 Tuccori M, Filion KB, Yin H, Yu OH, Platt RW, Azoulay L. Pioglitazone use and risk of bladder cancer: population based cohort study. *BMJ* 2016; : i1541.

30 Soccio RE, Chen ER, Lazar MA. Thiazolidinediones and the Promise of Insulin Sensitization in Type 2 Diabetes. *Cell Metab* 2014; 20: 573–91.

31 Zhu Z-N, Jiang Y-F, Ding T. Risk of fracture with thiazolidinediones: An updated meta-analysis of randomized clinical trials. *Bone* 2014; 68: 115–23.
32 Hernandez A V., Usmani A, Rajamanickam A, Moheet A. Thiazolidinediones and Risk of Heart Failure in Patients with or at High Risk of Type 2 Diabetes Mellitus. *Am J Cardiovasc Drugs* 2011; 11: 115–28.
33 Clemens KK, Shariff S, Liu K, *et al.* Trends in Antihyperglycemic Medication Prescriptions and Hypoglycemia in Older Adults: 2002-2013. *PLoS One* 2015; 10: e0137596.
34 Hampp C, Borders-Hemphill V, Moeny DG, Wysowski DK. Use of Antidiabetic Drugs in the U.S., 2003–2012. *Diabetes Care* 2014; 37: 1367–74.
35 Sharma M, Nazareth I, Petersen I. Trends in incidence , prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care : a retrospective cohort study. 2016. DOI:10.1136/bmjopen-2015-010210.
36 Christensen DH, Rungby J, Thomsen RW. Nationwide trends in glucose-lowering drug use, Denmark, 1999–2014. *Clin Epidemiol* 2016; Volume 8: 381–7.
37 Castilla-Guerra L, Fernandez-Moreno M del C, Leon-Jimenez D, Carmona-Nimo E. Antidiabetic drugs and stroke risk. Current evidence. *Eur J Intern Med* 2017; published online Sept. DOI:10.1016/j.ejim.2017.09.019.
38 Liu R, Wang H, Xu B, *et al.* Cerebrovascular Safety of Sulfonylureas: The Role of K ATP Channels in Neuroprotection and the Risk of Stroke in Patients With Type 2 Diabetes. *Diabetes* 2016; 65: 2795–809.
39 Methods and Applications Group for Indirect Treatment Comparisons. Application for the revision of second line treatments of type II diabetes. 2017. http://www.who.int/selection_medicines/committees/expert/21/applications/s18_T2D_antidiabetics_rev.pdf?ua=1 (accessed Sept 14, 2017).
40 Polonsky W, Henry R. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. *Patient Prefer Adherence* 2016; Volume 10: 1299–307.
41 Hanefeld M, Frier BM, Pistrosch F. Hypoglycemia and Cardiovascular Risk: Is There a Major Link? *Diabetes Care* 2016; 39: S205–9.
42 Canadian Agency for Drugs and Technologies in Health. New Drugs for Type 2 Diabetes: Second-Line Therapy — Recommendations Report. 2017. https://www.cadth.ca/sites/default/files/pdf/TR0012_T2DM_Final_Recommendations.pdf (accessed Sept 14, 2017).
43 Zinman B, Wanner C, Lachin JM, *et al.* Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 2015; 373: 2117–28.
44 Neal B, Perkovic V, Mahaffey KW, *et al.* Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med* 2017; 377: 644–57.
45 Liu J, Li L, Li S, *et al.* Effects of SGLT2 inhibitors on UTIs and genital infections in type 2 diabetes mellitus: a systematic review and meta-analysis. *Sci Rep* 2017; 7: 2824.
46 Fadini GP, Avogaro A. SGTL2 inhibitors and amputations in the US FDA Adverse Event Reporting System. *Lancet Diabetes Endocrinol* 2017; 5: 680–1.
47 Shyangdan D, Jacob RP, Connock M, Johnston R, Cummins E, Waugh N. Empagliflozin for the treatment of type 2 diabetes: a single technology assessment. 2014. https://www.nice.org.uk/guidance/ta336/documents/diabetes-type-2-empagliflozin-id641-evaluation-report2.
48 Copley V, Pickett K, Shepherd J, Loveman E, Jones J. Canagliflozin in combination therapy for treating type 2 diabetes. https://www.nice.org.uk/guidance/ta315/evidence.
49 Dapagliflozin STA: ERG comments on economics of manufacturer ACD submission. https://www.nice.org.uk/guidance/ta288/documents/diabetes-type-2-dapagliflozin-evaluation-report2 (accessed June 9, 2017).
50 World Health Organization. Assessing national capacity for the prevention and control of noncommunicable diseases. 2016. http://apps.who.int/iris/bitstream/10665/246223/1/9789241565363-eng.pdf (accessed Oct 5, 2017).
51 International Diabetes Federation. Access to Medicines and Supplies for People with Diabetes: a global survey on patients' and health professionals' perspective. 2016.
52 Ewen M, Zweekhorst M, Regeer B, Laing R. Baseline assessment of WHO's target for both availability and affordability of essential medicines to treat non-communicable diseases. *PLoS One* 2017; 12: e0171284.
53 Management Sciences for Health. International Medical Products Price Guide. 2015. http://mshpriceguide.org/ (accessed Oct 6, 2017).
54 van Doorslaer E, O'Donnell O, Rannan-Eliya RP, *et al.* Effect of payments for health care on poverty estimates in 11 countries in Asia: an analysis of household survey data. *Lancet* 2006; 368: 1357–64.
55 MSD price catalogue 2017-2018. http://www.msd.go.tz/index.php/msd-price-catalogue (accessed Jan 22, 2018).
56 ClinicalTrials.gov. Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58). https://www.clinicaltrials.gov/ct2/show/NCT01730534?term=TIMI+declare&rank=1 (accessed Sept 10, 2017).
57 ClinicalTrials.gov. Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure (Dapa-HF). https://clinicaltrials.gov/ct2/show/NCT03036124?term=dapa-hf&rank=1 (accessed Jan 5, 2018).
58 ClinicalTrials.gov. A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease (Dapa-CKD). https://clinicaltrials.gov/ct2/show/NCT03036150?term=dapa-ckd&rank=1 (accessed Jan 5, 2018).

59 ClinicalTrials.gov. Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy (CREDENCE). https://clinicaltrials.gov/ct2/show/NCT02065791?term=credence&rank=2 (accessed Jan 5, 2018).
60 ClinicalTrials.gov. EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction (EMPEROR-Preserved). https://clinicaltrials.gov/ct2/show/NCT03057951?term=emperor&rank=2 (accessed Jan 5, 2018).
61 ClinicalTrials.gov. EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction (EMPEROR-Reduced). https://clinicaltrials.gov/ct2/show/NCT03057977?term=emperor&rank=1 (accessed Jan 5, 2018).
62 Udell JA, Yuan Z, Rush T, Sicignano NM, Galitz M, Rosenthal N. Cardiovascular Outcomes and Risks After Initiation of a Sodium Glucose Co-Transporter 2 Inhibitor: Results From the EASEL Population-Based Cohort Study. *Circulation* 2017; : CIRCULATIONAHA.117.031227.
63 Bazargani YT, de Boer A, Leufkens HGM, Mantel-Teeuwisse AK. Selection of Essential Medicines for Diabetes in Low and Middle Income Countries: A Survey of 32 National Essential Medicines Lists. *PLoS One* 2014; 9: e106072.
64 SpicyIP. Compulsory Licence Application filed over AstraZeneca's Saxagliptin. https://spicyip.com/2015/07/compulsory-licence-application-filed-over-astrazenecas-saxagliptin.html (accessed Jan 28, 2018).
65 SpicyIP. Novartis sues Biocon over anti-diabetes drug vildagliptin: Bitter pill? https://spicyip.com/2014/04/novartis-sues-biocon-over-anti-diabetes-drug-vildagliptin-bitter-pill-2.html (accessed Jan 28, 2018).
66 SpicyIP. Questionable Witnesses and Unquestionable Reasoning: Observations on Merck v. Glenmark. https://spicyip.com/2015/10/questionable-witnesses-and-unquestionable-reasoning-observations-on-merck-v-glenmark.html (accessed Jan 28, 2018).
67 Press release. Sun Pharma and AstraZeneca India enter partnership in Type 2 diabetes. 2016. https://www.astrazeneca.com/content/dam/az/Country-Sites/India/AstraZeneca_Press release 23 March 2016.pdf (accessed Sept 14, 2017).
68 Press release. Type 2 Diabetes: Boehringer Ingelheim India and Lupin Announce Strategic Co-marketing Agreement. 2016. http://www.lupin.com/boehringer-ingelheim-india-and-lupin-announce-strategic-co-marketing-agreement.php (accessed Sept 13, 2017).
69 Aurobindo. Product list. http://www.aurobindo.com/our-business-units/api/product-list (accessed March 21, 2018).
70 Lupin. Product catalogue. http://lupin.com/product-catalogue.php (accessed March 21, 2018).
71 Global Type 2 Diabetes Market Set to Almost Double to $58.7 Billion. *Drug Dev Deliv* 2016; published online Aug. http://www.drug-dev.com/Main/Back-Issues/Global-Type-2-Diabetes-Market-Set-to-Almost-Double-1140.aspx (accessed Oct 9, 2017).
72 Strategy&. Pharma emerging markets 2.0: How emerging markets are driving the transformation of the pharmaceutical industry. 2013. https://www.strategyand.pwc.com/media/file/Strategyand_Pharma-Emerging-Markets-2.0.pdf (accessed Oct 9, 2017).
73 1mg. http://www.1mg.com/ (accessed May 7, 2017).
74 Ramachandran A, Snehalatha C, Shetty AS, Nanditha A. Trends in prevalence of diabetes in Asian countries. *World J Diabetes* 2012; 3: 110.
75 Beran D, Ewen M, Laing R. Constraints and challenges in access to insulin: a global perspective. *Lancet Diabetes Endocrinol* 2016; 4: 275–85.
76 World Health Organization. Global action plan for the prevention and control of non-communicable diseases 2013–2020. 2013 http://apps.who.int/iris/bitstream/10665/94384/1/9789241506236_eng.pdf?ua=1.