Too Costly & Too Scarce

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Chapter 3

Constraints and challenges in access to insulin: a global perspective

ABSTRACT

Considerable attention has been paid to the issue of access to medicines for communicable diseases; however, access to essential medicines for diabetes, especially insulin, has had insufficient focus. Although insulin was discovered in 1921, the drug is unattainable to many globally, and this Review aims to highlight the range and complexity of factors that contribute to this unattainability. Manufacturers' selling prices of various insulin formulations and presentations, duties, taxes, mark-ups, and other supply chain costs affect the price of insulin and hence the drug's affordability to health systems and individuals. Unlike drugs for HIV and AIDS, the production of generic or biosimilar insulin has not had an effect on the overall market. Other factors contributing to poor availability of insulin include its quantification at the national level, in-country distribution, and determination of needs at lower levels of the health system. Although insulin is essential for the survival of people with type 1 diabetes and is needed for improved management of diabetes for some people with type 2 diabetes, very little has been done globally to address the issue of access, despite the UN's political commitment to address non-communicable diseases and ensure universal access to drugs for these disorders.

KEY MESSAGES

Background

- Sustainable Development Goals and other key global policy documents now include non-communicable diseases as a priority within the larger context of universal health coverage and health system strengthening.
- The insulin market is dominated by three multinational companies, which might restrict price competition and enable these companies to shape the market with, for example, the substantial increase in higher priced analogue insulin.
- Regulatory aspects around biosimilars in addition to the cost of production are also barriers to entry.
- Intellectual property is not a barrier on the actual insulin molecule but shifts to use of insulin from pen devices, which are patented, might act as a barrier to access.
- Prices of insulin are affected by an increase in use of analogues and pen devices as well as mark-ups and taxes within the supply chain.
- Affordability of insulin to individuals and health systems must be scrutinized in the context of universal health coverage.

Call to Action

- Diabetes funders to allocate 5% of funds for innovation in the delivery of care and insulin.
- Include insulin in universal health coverage benefit packages.
- WHO to investigate prequalification of insulin, develop a regulatory framework for biosimilars and insulin, and promote existing guidelines and methods for effective purchasing of quality assured, safe, efficacious and cost-effectiveness drugs for insulin therapy.
- Development of a global compact with the insulin industry to guarantee that human insulin and insulin in vial form will not be removed from the market.
- Ensure that organisations and academics speak with a united voice when calling for better diabetes care.

INTRODUCTION

Before the discovery of insulin, children with type 1 diabetes needed to count calories, weigh their food, sometimes fast, and use starvation diets in order to stay alive (1). These harsh measures prevented these children from dying of diabetic ketoacidosis and extended their life expectancy by some years before they unfortunately died of starvation (2). This situation changed in 1921 when Frederick Banting and Charles Best at the University of Toronto discovered insulin (3). In January, 1922, Leonard Thompson became the first person to be treated with insulin for type 1 diabetes, saving him from near certain death. Today, more than 90 years later, poor access to insulin translates into a life expectancy for a child with type 1 diabetes in sub-Saharan Africa as low as one year (4). This figure contrasts recent data showing that people diagnosed with type 1 diabetes in the 1960s and 1970s in the USA have only a 4–6 year difference in life expectancy compared with that of the general population (5). Access to insulin and poor health outcomes are not issues only for low-income and middle-income countries. In the USA, discontinuation of insulin use because of the drug's cost was the leading cause of diabetic ketoacidosis in people in an inner city setting (6). Access to insulin has also become a problem in Europe, due to the financial crisis (eg. in Greece) and insulin's increasing burden on health budgets (eg. in the UK) (7,8). This situation exists despite human insulin being included on WHO's Model Essential Medicines List, emphasizing this drug's importance, since 1977 and being off patent (9).

Substantial attention has been given to the issue of access to medicines for HIV and AIDS, tuberculosis, and malaria (10-14) but there has been little consideration of questions regarding access to essential medicines for non-communicable diseases. In September, 2011, the UN held a General Assembly on non-communicable diseases, the UN's second ever health related assembly, after its 2001 meeting on HIV and AIDS. Cardiovascular diseases, cancer, chronic respiratory diseases, and diabetes were the four non-communicable diseases prioritised because these diseases contribute the largest amount to morbidity and mortality worldwide (15). The resulting political declaration from the 2011 UN declaration includes commitments by member states to address access to drugs, in parallel to strengthening health systems and providing universal health coverage (16). Until the 2015 Sustainable Development Goals (17) non-communicable diseases had not been firmly placed on the development agenda (18,19).

One of the six key responsibilities of a health system is to ensure equitable access to essential medicines of assured quality, safety, efficacy and cost-effectiveness, and to ensure

that medicines are used in a scientifically sound and cost-effective way (20). The target established by the global action plan for the prevention and control of non-communicable diseases 2013–20 is "an 80% availability of the affordable basic technologies and essential medicines, including generics, required to treat major non-communicable diseases in both public and private facilities"(15). This target has already been reached in many settings for drugs to treat HIV and AIDS, malaria, tuberculosis, as well as for contraceptives and vaccines, but data in the 2014 global status report on non-communicable diseases show that this target is far from being achieved for drugs for non-communicable diseases (21).

As few data are available, we combine medical literature from different settings and used specific country examples to highlight certain issues. We focused on type 1 and type 2 diabetes, recognising that the need for insulin is different for these two disorders. For type 1 diabetes an absolute need for the drug exists, because without insulin people will die in a matter of weeks. By contrast, use of insulin in the management of type 2 diabetes is needed for improved disease control, and its use varies from country to country depending on resources, guidelines, health-care worker training, and the level of the health system where the diabetes is managed. The proportion of type 2 diabetes patients using insulin varies across countries and has been increasing (22-27). We discuss present challenges and existing solutions and propose a way forward to address the factors impeding access to insulin.

Factors affecting affordability

Little is known about why insulin has remained consistently expensive over the years. One possible explanation is the market domination by three multinational companies, which control 99% of the global insulin market in terms of value and 96% in terms of volume (28). These same companies control 100% of the US market (29). In parallel to this market domination, the rate of insulin use has increased. For people in the USA with type 2 diabetes and private insurance, the use of insulin increased from 10% in 2000 to 15% in 2010 (30). The number of people using insulin in the UK from 1991 to 2010 increased three times, mainly driven by the use of insulin in people with type 2 diabetes (27). Over this 20 year period, a shift was noted from the majority of insulin being used in people with type 1 diabetes to people with type 2 diabetes.

The USA and UK have also seen dramatic growth in the use of analogue insulin over the past decade, leading to a rise in cost (8,31). Data for changing patterns of global insulin use from 1999 to 2009 show three clear trends, despite the limitations in terms of countries represented (Figure 1) (32-34). First, animal insulin has disappeared from the market during

the period 1999–2009. Second, human insulin has gone from being virtually the only formulation used in high-income and middle-income countries to representing only about a third of insulin used in high-income countries and two-thirds in middle-income countries by 2009. Finally, the decreased use of human insulin is mirrored by rising consumption of analogue insulin, which represents two-thirds of all insulin in high-income countries by 2009, with trends in middle-income and lower middle-income countries following the same pattern. In low-income countries, however, analogue insulin still represented a median of only 4% of insulin used in 2009.

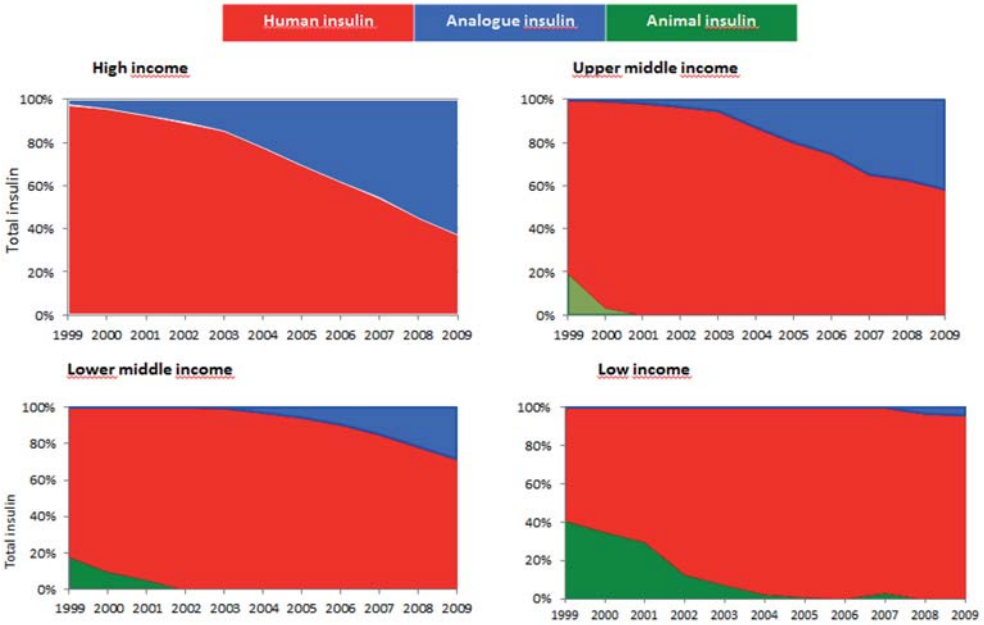

Figure 1: Transition from human to analogue insulin by insulin type and country-income groupings, (1999–2009) (33).
Authors obtained the data with permission from IMS

The trend toward increasing use of insulin analogues is occurring despite a 2011 report of the WHO's 17th Expert Committee on the Selection and Use of Essential Medicines (35) which compared the efficacy and cost-effectiveness of analogue insulin (insulin glargine, insulin detemir, insulin aspart, insulin lispro, and insulin glulisine) with human insulin,

stating “while many of the comparative trials find a statistically significant difference between analogue insulins and standard recombinant human insulin for some blood glucose measurements, there is no evidence of a clinically significant difference in most outcomes. The Committee concluded that insulin analogues currently offer no significant clinical advantage over recombinant human insulin and there is still concern about possible long-term adverse effects” (35).

From an innovation perspective, Greene and Riggs (36) state that each new insulin formulation has been marginally more effective than its predecessor, but these authors question the cost of this innovation in a context in which people are still unable to afford any insulin. Also, instead of generic products being developed and replacing the branded older products, these earlier products have disappeared from the market. Luo and Kesselheim (29) reported that 53% of patents on insulin were linked to the delivery devices and not the insulin itself, and therefore intellectual property is not a barrier for earlier versions of insulin entering the market. Luo and Kesselheim note, however, that the cost of entering the market is high in terms of processes such as production and distribution.

Another challenge specific to insulin is that, unlike antiretrovirals or other drugs, the production of generic or biosimilar insulin is a more complex undertaking, especially from a regulatory perspective. Unlike chemical entities, the production of an exact copy of a biological product is difficult (37). The process in the production of these molecules is as important as the final product. Each step in the manufacturing process could affect the end molecule and its equivalence to the original protein. Issues about interchangeability also exist, further complicating the uptake of biosimilars (38). Although innovations in the types of insulin available may not be necessary, improvements in different health system factors for diabetes drug delivery and care are necessary. 11 health system factors are needed to ensure a positive diabetes environment (4) and two of these, accessibility and affordability of drugs and drug procurement and supply, focus specifically on access to drugs. Other aspects such as the health-care workforce and prevention measures are also of vital importance.

AFFORDABILITY TO THE HEALTH SYSTEM

Factors affecting the affordability of insulin to the health-care system include manufacturers’ selling prices, duties, taxes, mark-ups, and other supply chain costs.

To estimate the per person cost of insulin, we used the average buyer price for insulin from the Management Sciences for Health's International Drug Price Indicator Guide (39) (US$6.56 from 1996 to 2013) and assumed that a person with type 1 diabetes would need 13 vials of insulin per year, resulting in a cost of $85.28 per person per annum. This equates to a health expenditure per capita of 120% in Mozambique, 13% in Thailand, and 3% in the UK (39-41). Affordability is not linked only to a country's available finances but also to how resources are used. For example, 71% of insulin purchased in 2009 in Kyrgyzstan met WHO's suggested guidelines (9) and accounted for 43% of total insulin expenditure. This finding implies that the remaining 29%, comprising analogue insulin in vials or pen fills, accounts for 57% of the insulin budget. Following WHO's guidelines would have reduced costs by $740,000, equivalent to the health-care expenditure for about 5000 people. High financial burdens for health systems are not only an issue in low-income and middle-income countries, but also in high-income countries such as the UK (8). From 2000 to 2010 the UK National Health Service spent the equivalent of $4145 million on insulin (42). One of the drivers of this cost was expenditure on analogue insulins, which represented 12% of total insulin costs in 2000 and 85% in 2010.

Data from the International Insulin Foundation showed that the average government procurement price of human insulin in a 10mL 100IU/mL vial ranged from $4.10 in Mozambique (2003) to $8.40 in Kyrgyzstan (2009) (43). By comparison, in 2013 the UK National Health Service purchases 10mL 100IU/mL of human insulin at $9.71 (44). Mozambique and Zambia access a differential pricing scheme developed by one of the leading insulin manufacturers which offers insulin to governments of least developed countries at a price not exceeding 20% of the average price in North America, Europe, and Japan (45). By contrast, WHO and Health Action International surveys noted that some governments purchased insulin at higher prices than those available on the international market (46). The range reported in ten studies for a range of insulin formulations was 0.33 to 5.87 times the Management Sciences for Health's international reference price or $2.55–48.25 per vial.

Duties and taxes for insulin also apply in some countries. Based on data from the World Trade Organization in 2008, 92 out of 132 countries had no tariffs on insulin, 22 countries charged 0%–5%, 11 countries charged between 5% and 10%, six countries charged between 10% and 20% and one country charged 52% (34). Insulin was exempt from any taxes and duties in Kyrgyzstan, Mozambique and Zambia. In Mali, all drugs, including insulin, are subject to 2.5% duty (47,48). In Nicaragua, no taxes or duties exist in the public sector but a 6% customs duty exists for all imported drugs destined for the private sector

(49). In Vietnam, 5% import duties and 5% value added tax are applied to drugs no matter the sector (50).

AFFORDABILITY TO THE INDIVIDUAL

Insulin needs to be purchased by individuals in many contexts, placing a large financial burden on people with diabetes and their families, especially in low-income and middle-income countries. Affordability to the individual depends on many factors, including the types of insulin purchased, mark-ups within the system, and whether insulin is available in the public sector. In Mali (2004) and Mozambique (2003), the price for insulin increased within the health system between the central levels and the periphery (43). Price increases were used to cover some of the costs linked to transportation and storage. Mark-ups in private pharmacies between the purchasing and selling price were noted to range from 13% in Mali to 49% in Nicaragua (43). In a range of countries, the proportion of the individuals' total diabetes costs spent on insulin varies from 0% to 68% (Table 1) (51-56). In some countries, people have to pay the full cost for their insulin, whereas in others the cost (in part or in whole) is covered by the health system.

We compared the cost of insulin to individuals in various countries on the basis of studies with data from a standardized rapid assessment protocol carried out by the International Insulin Foundation or data from Health Action International, which uses the price and availability of originator brands. If the price of originator brands was not available, we used the lowest-priced biosimilar. Median prices across the facilities sampled per sector were used. In terms of cost for a year's supply of insulin (13 vials), eight countries provided insulin free-of-charge in the public sector, including Kuwait, Kyrgyzstan, Laos, Lebanon, Mauritius, Mexico, Nicaragua, and Vietnam (for people with health insurance and benefiting from donated insulin; Figure 2).

In countries where patients have to pay, the average annual cost was $35.40 ($2.60–$141.44) in the public sector and $95.71 ($6.89–$218.40) in the private sector. Many countries partially subsidise the cost of insulin. For example, in Mozambique in 2003 a chronic disease law existed in which people with non-communicable diseases, including diabetes, could access drugs at an 80% subsidy, with similar subsidies also present in Zambia. In Mali, cost recovery was in place and Vietnam had insurance schemes, which covered all or a portion of costs related to drugs but not everyone benefited from this health insurance. Mendis and colleagues reported that the cost of insulin treatment in terms of the number

of days that the lowest paid unskilled government worker would have to work to pay for a month's supply of insulin was 2.8 days in Brazil, 19.6 days in Malawi, 7.3 days in Nepal, 4.7 days in Pakistan and 6.1 days in Sri Lanka (57).

Table 1: Costs of diabetes care to individuals

	Aspect of diabetes care	Population studied	Cost* (percentage of total cost spent on insulin)
Brazil (2008-10)[51]	Total cost per capita for a person with type 1 diabetes	Children and adults with type 1 diabetes	$1319.15 (26%;second overall cost after testing equipment)
Italy (2006)[52]	Total expenditure for an adult with type 1 diabetes	Adults (18-55 years) with type 1 diabetes	$3254.83 (36%)
Lithuania (2011)[53]	Direct cost of covered drugs for an adult only using insulin	Adults with type 2 diabetes	$543.02 (-%)
Mali (2004)[47]	Average annual cost for a person with diabetes requiring insulin	Children and adults with type 1 and type 2 diabetes	$339.40 (38%)
Mexico (2002-03)[54]	Average annual direct cost of treatment and monitoring for a child with type 1 diabetes	Children with type 1 diabetes	$1690.00 (15%)
Mozambique (2004)[45]	Average annual cost for a person with diabetes requiring insulin	Children and adults with type 1 and type 2 diabetes	$273.60 (5%)
Nicaragua (2007)[49]	Average annual cost for a person with diabetes requiring insulin	Children and adults with type 1 and type 2 diabetes	$74.40 (0%)
Sudan (2005)[55]	Median annual expenditure per child with type 1 diabetes	Children with type 1 diabetes	$283.00 (36%)
Tanzania (1997)[56]	Average annual direct outpatient cost for a person with diabetes requiring insulin	Children and adults with type 1 and type 2 diabetes	$229.00 (68.2%)
Vietnam (2009)[50]	Average annual cost for a child with type 1 diabetes	Children with type 1 diabetes	$660.00 (21%)
Zambia (2003)[45]	Average annual cost for a person with diabetes needing insulin	Children and adults with type 1 and type 2 diabetes	$199.10 (12%)

*All figures are shown in US$

Affordability to the individual is complex in many low-income and middle-income countries because of the high poverty levels. For example in Zambia, the annual price of insulin to the individual is $23.89 (3% of per capita gross domestic product) in the public sector and $218.40 per year in the private sector. The question is whether $23.89 per annum would be deemed to be affordable in a country where 69% of the population live below the international poverty line of $1.25 per day and where the lowest paid government worker in 2013 made $163.79 per month (58,59).

Insulin affordability is also a problem in the USA with uninsured people with type 1 diabetes being unable to access the care they need (60). Discontinuation of insulin use was the leading cause of diabetic ketoacidosis in 68% of people in a US inner city setting (6). Among those who stopped use of insulin, 27% reported no money to buy insulin and 5% were being sparing with their insulin supplies. For insured individuals with type 2 diabetes in the USA, out of pocket expenditure per prescription increased from a median of $19 to $36, mainly because of increased use of analogues (30).

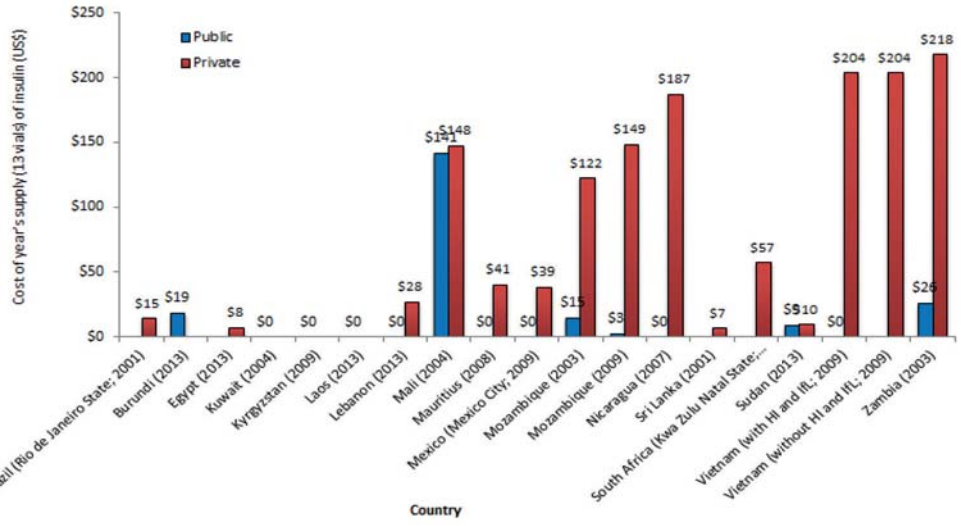

Figure 2: Cost of insulin in different countries in public and private sectors for individuals (45-50).
Where data are not given, data are not available. HI=health insurance, IfL=donated human insulin from the charity Insulin for Life

WHAT ABOUT INSULIN AVAILABILITY?

Insulin not only needs to be affordable to the individual, but also obtainable when the individual needs it. Availability is affected by national and global factors. At a national level, availability can be assessed by the presence of insulin on national essential medicines lists and guidance as to where insulin should be present eg. health centres versus hospitals. The global control of the market means that countries have a small number of suppliers to choose from, and this factor has resulted in people having to change the type of insulin they take as companies have withdrawn formulations from the market (61,62).

Global control of the insulin market affects the drug's availability in many low-income and middle-income countries. For example in 2004 in Mali, the Central Medical Store purchased insulin for the first time in 2–3 years (63). This lapse in insulin purchasing was attributed to an inability to find a generic supplier of insulin (Mali promotes the use of generics) and the requirement for tender quotes from three potential suppliers, which was not possible because of the small number of suppliers. Another factor was the high cost of insulin in view of the government's small budget and the need for prioritisation, resulting in the purchase of an insufficient amount of insulin to cover needs.

Insulin availability was noted to be low in a study of six countries (Bangladesh, Brazil, Malawi, Nepal, Pakistan, and Sri Lanka), with most insulin formulations available in less than 60% of facilities sampled (57). Overall availability of soluble and isophane insulin was 19% and availability of zinc suspension insulin was 7%. In Malawi, soluble insulin was available in 25% of facilities surveyed, isophane in 0%, and zinc suspension in 30%, in contrast to Brazil where 40% of facilities had soluble insulin, 50% had isophane, and 0% had zinc suspension. Poor availability can be due to various factors, such as issues of quantification at national level, in-country distribution and determination of needs at lower levels of the health system. For example, Maputo Province represented only 11.3% of the total population of Mozambique in 2003, yet it received 77.3% of the total amount of insulin purchased by the government. Distribution of supplies was also problematic in Kyrgyzstan with facilities receiving only what was available rather than what they ordered because of poor distribution systems and requests for specific types if insulin that might not have been available at a central level (48).

Insulin availability in the private sector was also variable. Although availability was poor in Kyrgyzstan and Nicaragua, it was wider in the capital in Mali, Mozambique and Zambia and large urban areas in Vietnam. On the basis of available data, only four of 15 countries had 100% availability of insulin in the public sector, and six countries had more than 80%

availability (Figure 3). Private sector availability was less than 80% in all but two countries. The average availability was 56% in the public sector (17%–100%) and 39% in the private sector (0%–95%).

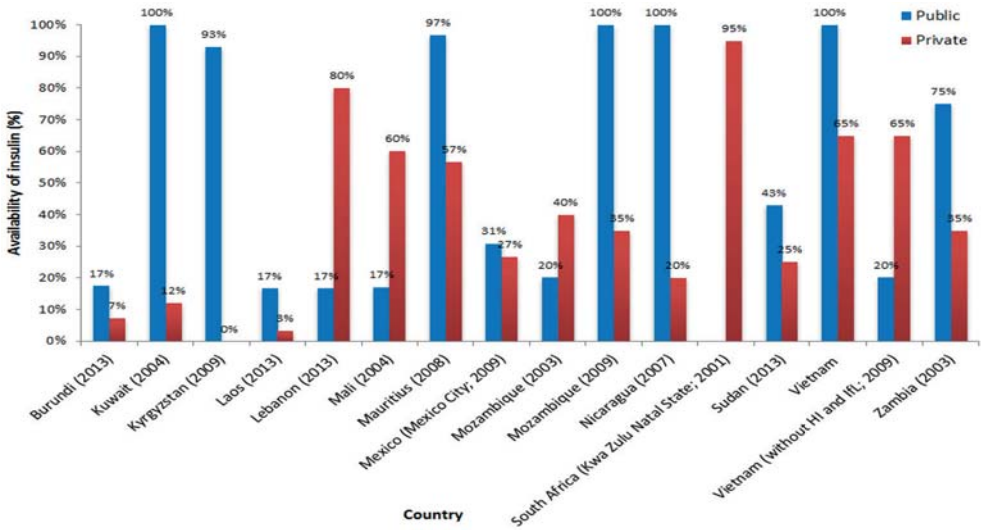

Figure 3: Availability of insulin in different countries in public and private sectors (45-50)
Where data are not given, data are not available. HI=health insurance, IfL=donated human insulin from the charity Insulin for Life

In linking both the availability and affordability elements (Figures 2 and 3), only six of the countries surveyed would meet the WHO's 80% availability target of affordable insulin in the public sector. These countries include Kuwait, Kyrgyzstan, Mauritius, Mozambique (assuming that $2.30 per annum is viewed as affordable), Nicaragua, and Vietnam (for people with health insurance and benefiting from donated insulin). In the private sector, only Lebanon and South Africa (KwaZulu-Natal province) had more than 80% availability of insulin. In terms of affordability in these countries, a year's supply of the drug would represent 0.3% of Lebanon's per capita GDP and 0.9% of South Africa's per capita GDP, or the equivalent wages for the lowest paid government worker of 13.2 days in Lebanon or 5.2 days in South Africa. Therefore many of the barriers described previously need to be addressed to achieve the global action plan's target for access to insulin.

Past experience in addressing access to drugs

Different means of addressing the availability and affordability of safe, effective and quality assured drugs have been implemented in various contexts and by a range of organisations. Notable approaches include pooled procurement, differential pricing, and promotion of the use of generics.

Pooled procurement allows groups of countries to benefit from increased bargaining power because large quantities of drugs are purchased. This strategy was used by a small group of eastern Caribbean countries, resulting in a decrease in the cost of pharmaceuticals (64). The Asthma Drug Facility also used pooled procurement, combined with negotiations with companies and quality assurance mechanisms, to get asthma drugs at prices lower than those available on the international market (65,66). This approach was also used by the Global Fund to Fight AIDS, Tuberculosis and Malaria (67).

Many organizations have promoted differential pricing, which is the adaptation of drug prices to the purchasing power in different geographical or socio-economic regions. The Clinton Foundation HIV/AIDS Initiative negotiated prices with suppliers and also provided technical support to help them lower costs (67). Differential pricing was also used by the now defunct Accelerating Access Initiative, a private sector collaboration that some viewed as being unsuccessful in truly lowering prices (67). Other initiatives, such as UNITAID and Global Alliance for Vaccines and Immunizations (GAVI), use market-shaping approaches to bring down the price of existing medicines and vaccines, and to promote research in new technologies (68,69). Both UNITAID and GAVI have been well funded and have taken a vertical approach to addressing specific health problems.

One of the lessons from HIV and AIDS has been a focus on drugs from generic producers, which allowed for savings of more than 50% (67,70). An issue for generics is whether the quality of these products meets national and international standards. To address this, WHO developed a prequalification scheme for drugs for HIV and AIDS, malaria, and tuberculosis and has since expanded this programme to other diseases (67,68). This scheme allows countries to know whether manufacturers meet the required standards for good manufacturing practices and provides assurances on the quality and efficacy of the products. To date, insulin is not included.

THE RESPONSE TO DATE FOR DIABETES

In 2007, the UN passed a resolution declaring diabetes to be a major global health threat (73). More recently, the UN declaration, which served as a basis for the development of the WHO's global action plan, included efforts "… to improve access to and affordability of medicines and technologies in the prevention and control of non-communicable diseases" (74). Specifically for diabetes, the St. Vincent Declaration (1989) brought together the European branches of WHO and International Diabetes Federation (IDF) to address diabetes in the scope of WHO's Health for All programme (75). The International Society for Pediatric and Adolescent Diabetes developed the Kos Declaration (1993), which stated that they would work towards ensuring access to insulin (76). The African Diabetes Declaration (2006) stated that African Governments should ensure adequate, appropriate, and affordable drugs and supplies for people with diabetes (77). In 2013, the IDF published the Melbourne Declaration stating that "affordable access to health-care providers and treatments including insulin, other oral and injectable medicines, self-management supports and technologies can help prevent most of the complications of diabetes." (78).

These statements have not yielded a definitive response to adequately address the complexity of the challenges with respect to access to insulin (Table 2). To date, solutions include the IDF's Life for a Child programme, which is a donation scheme in which funds and in-kind donations are used to provide selected countries with insulin to support 17000 children in 46 countries (79). The programme also supports blood glucose monitoring equipment, appropriate clinical care, HbA1c testing, diabetes education, and technical support for health professionals. The IDF also collaborates with Insulin for Life, which distributes emergency diabetes supplies in situations of acute need (80). Operating within the IDF, the Insulin Task Force aims to address the issue of access to insulin and other diabetes related supplies. Novo Nordisk (Bagsværd, Denmark) has its Changing Diabetes in Children programme, which takes a similar approach to Life for a Child and is active in nine countries with 13000 children supported (81). This company also operates a differential pricing mechanism for insulin in 35 of 49 least developed countries and a pricing programme in Kenya in which the retail price of insulin has been set at 500 Kenyan shillings (approximately $5.70) (82).

Eli Lilly (Indianapolis, USA) has the Lilly NCD Partnership that works in Brazil, India, Mexico, and South Africa to develop models of care focusing on primary care, efficiency of health systems, use of drugs and adherence (83). The company also donates insulin

Table 2: Barriers, responses and gaps and remaining questions with regards to access to insulin

	Present response	Gaps and questions remaining
Domination of insulin market by three multinational companies	None	What about biosimilar competition?
High and increasing prices of insulin	Donation programmes Differential pricing Pricing mechanisms	Sustainability Effect of these programmes as they work in isolation of the health system
Increased use of insulin in type 2 diabetes; overall increased demand	None	Will this barrier affect insulin availability for type 1 diabetes? Can supply keep up with demand?
Increase in use of analogue insulin despite not being included on WHO Model List of Essential Medicines	None	Will human insulin disappear the same way animal insulin did? Will insulin in vial form remain on the market?
Challenging regulatory landscape for biosimilars and the link to intellectual property	None	What mechanisms can be put in place to promote biosimilar insulin? What barriers exist from an intellectual property perspective (production processes and technologies) and regulatory perspective that might be a barrier to biosimilar insulin?
Health expenditure in countries versus cost of diabetes care	Donation programmes Global push for UHC SDGs	Absence of true civil society mobilization for diabetes What specific measures can be taken to ensure that insulin is included in benefit packages? Designated funding allocated to improve diabetes care
Irrational use of scarce resources	Health system assessments provide information on resource use	Development of guidelines Use of the WHO's Model List of Essential Medicines as a guide for purchases
Poor procurement and supply systems for insulin	Differential pricing Donation programmes Health system assessments and strengthening	Use of existing price information; use of existing WHO guidance

to the Life for a Child programme, supports diabetes related projects run by Project Hope, and for the least developed countries, explores differential pricing and does not enforce intellectual property rights (84). Although Sanofi (Paris, France) has an Access to Medicines Department, access to diabetes drugs is not included (85). However, the company has specific projects addressing diabetes in schools in Algeria, India, and Turkey,

as well as other diabetes projects in north and sub-Saharan Africa (86,87). In Egypt in 2012, Sanofi designed a programme to improve access to certain drugs for the most common acute and chronic diseases, including diabetes (86).

The International Insulin Foundation, a UK based charity, has worked in a variety of low-income and middle-income countries to implement a rapid assessment protocol to understand the barriers to access to diabetes care and insulin and to propose definitive recommendations for local stakeholders. In Mozambique, the International Insulin Foundation has helped to improve access to insulin also to implement other health system changes, including a national strategy for non-communicable diseases (88). The International Insulin Foundation has also launched the 100 Campaign, which aims to reach 100% availability of insulin by the 100th anniversary of the first person receiving insulin in 2022 (89).

DISCUSSION

Many people have emphasised that non-communicable diseases could learn from the HIV and AIDS response in general (90,91) as well as for improvements in access to drugs (92). Although solutions for improvements in access to drugs and care for HIV and AIDS can be criticised for their vertical approach (93-96), there are three lessons about how the prices for antiretrovirals were lowered. The first element was substantial funding. Next, the market was reshaped by promotion of generic competition and funder negotiations with companies, and centralized financing and procurement mechanisms, including prequalification with transparency in reporting procurement pricing and quality testing. Finally, civil society, governments, donors and the UN there had a uniting message and a unified front.

The situation for the access to insulin is more complex than for antiretrovirals, and the way to improve access is clearly different. By contrast with antiretrovirals, which were paid for by donors such as the Global Fund, insulin is not purchased by donors but rather directly from country budgets. A global diabetes or non-communicable diseases fund is unimaginable and might even be unwelcome as the Sustainable Development Goals are implemented with a focus on universal health coverage and an integrated approach to health.

Yudkin (41) estimated in 2000 that for highly indebted poor countries, $3–5 million would be sufficient to provide insulin for all those needing the drug. Diabetes attracts substantial

funding with the US National Institute for Health, in 2015 more than a billion dollars was designated for diabetes research, making this research area the 41st of 244 research areas by spending (97). The Juvenile Diabetes Research Foundation has $98 million allocated to different areas of improving lives and finding a cure for type 1 diabetes (98). Other foundations, governments, and the private sector allocate additional funds to different aspects of diabetes prevention and care. Governments, whether in the UK or Mozambique, spend substantial amounts of money on insulin and other aspects of diabetes care. If a small portion of this diabetes funding could be allocated to finding ways to improve access to insulin and improve existing health systems, this effort could have a substantial impact. Generics have not affected the insulin market as they did for antiretrovirals. Although the reasons behind this are not entirely clear, one distinction is that insulin is a biological product whereas antiretrovirals are chemical entities. The proof of similarity and the production process are more complicated for biologics. Antiretrovirals were also under patent, whereas this is not the case for human insulin. This situation made the argument of a barrier to antiretrovirals much simpler because intellectual property was blocking access to a life-saving product.

Whereas HIV and AIDS was a global issue, the main need for antiretrovirals was in the southern hemisphere, including mostly low-income and middle-income countries. By contrast, the diabetes market is still concentrated mainly in high-income countries and emerging markets despite the global increase in prevalence. For both type 1 diabetes and HIV and AIDS, an absolute need for treatment is arguable. Insulin is essential for the management of type 1 diabetes and provides a rare case of a drug in which such absolute need exists. An absolute need also exits for antiretrovirals, although the urgency is not necessarily the same as with type 1 diabetes. For type 2 diabetes, the need is variable and depends largely on clinical practice. The level of action noted after the 2001 UN meeting on HIV and AIDS has not been replicated after a similar meeting on non-communicable diseases a decade later (99). Arguably, this scarcity of action is mainly because of the lack of global diabetes voices defending the interests of those with diabetes in less fortunate situations.

In view of this lack of global leadership, the response to diabetes might be a unique chance for individual countries to take the lead and identify ways to address the challenge of access to insulin specifically for their context. To help with this situation, in January, 2015, Health Action International launched the Addressing the Challenge and Constraints of Insulin Sources and Supply (ACCISS) Study (see Panel) (100,101). This global study aims

to provide a greater understanding of the complexity and causes of poor access to insulin and to develop interventions tailored to the different challenges countries might face.

Insulin alone is not enough for proper diabetes management, which also requires syringes, blood glucose meters, education, information, and family support (102). An opportunity is available to capitalize on the newly announced Sustainable Development Goals that include statements on universal health coverage, access to drugs, non-communicable diseases, and human resources for health (17). Opportunities exist to raise awareness about this issue in 2016 because the theme for World Health Day in April, 2016, is diabetes, and the work of the *Lancet Diabetes & Endocrinology* Commission on diabetes in sub-Saharan Africa will be published (103).

We live in a world of globalized markets and information and therefore scientific advances can have a global impact, such as the progress noted with antiretrovirals and vaccines. Innovation, a dedicated civil society, and funding will be necessary to achieve the goal of the 100 Campaign of "100% of people living with type 1 diabetes having access to insulin by 2022" (89). With the beginning of the Sustainable Development Goals and their aim to ensure "healthy lives and promote well-being for all ages" (17) as the overarching goal for health, the diabetes community owes those with diabetes struggling to access insulin a more equitable future.

Search strategy and selection criteria

To identify barriers for insulin access, the medical literature was reviewed in a systematic way from published studies and other data sources available looking at factors affecting availability and affordability of insulin. We searched PubMed in January and February, 2015, with regular updates until June, 2015, with the search terms "Insulin" in combination with the terms: "Price", "Affordability", "Availability", "Cost", "Developing Countries" and "Insulin/economics" with no restrictions on language and date of publication. Additionally, we used highly referenced papers on the topic, reports from WHO and other sources as primary sources of information, and the bibliographies of these sources to identify additional material. Information on initiatives was identified in these secondary sources with additional information obtained from searching the websites of the respective organisations.

***Panel*: The Addressing the Challenges and Constraints of Insulin Sources and Supply Study**

Overview

In January, 2015, Health Action International in collaboration with Boston University School of Public Health, the Geneva University Hospitals, and University of Geneva Division of Tropical and Humanitarian Medicine launched an innovative global study, the Addressing the Challenge and Constraints of Insulin Sources and Supply (ACCISS) Study. ACCISS is funded by a 3 year grant from The Leona M. and Harry B. Helmsley Charitable Trust.

Objectives

A comprehensive, pioneering evidence base on the global insulin market, including the type, extent and effect of barriers to global insulin access.

Innovative models of supply and interventions, in collaboration with multiple stakeholders, to overcome the barriers to global insulin access learning from other pioneering access programmes.

An advocacy network, along with various advocacy materials, in collaboration with multiple stakeholders, to reduce or eliminate the barriers to global insulin access.

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