ACCESS TO INSULIN

Current Challenges & Constraints

October 2015

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Addressing the Challenge and Constraints of Insulin Sources and Supply

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DIABETES CENTRE / KITUO CHA KISUKARI


Dia Mundial da Diabetes
Moçambique Unidos pela Diabetes

ACCESS TO INSULIN

Current Challenges & Constraints

October 2015

David Beran
Geneva University Hospitals and University of Geneva

Margaret Ewen
Health Action International

Richard Laing
Boston University

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Overtoom 60 (2) | 1054 HK Amsterdam
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Acronyms

ARV	Antiretroviral
CRD	Chronic respiratory disease
CVD	Cardiovascular disease
DKA	Diabetic ketoacidosis
DNA	Deoxyribonucleic acid
EML	Essential medicines list
GAP	Global Action Plan for the Prevention and Control of Non-communicable Diseases 2013-2020
GDP	Gross domestic product
HAI	Health Action International
HIV/AIDS	Human immunodeficiency virus / Acquired immune deficiency syndrome
IDF	International Diabetes Federation
IIF	International Insulin Foundation
LMIC	Low- and middle-income countries
MSH	Management Sciences for Health
NCD	Non-communicable disease
UHC	Universal health coverage
UN	United Nations
WHO	World Health Organization

EXECUTIVE SUMMARY

One in three people around the world do not have guaranteed access to essential medicines. While access to essential medicines for infectious diseases, like HIV/AIDS, tuberculosis and malaria, has received considerable attention, little has been done to address access to essential medicines for non-communicable diseases (NCDs). This is particularly the case for insulin, which is essential for the survival of people with type 1 diabetes and required for better management of some type 2 diabetes cases. Although this life-saving medicine was discovered in 1921 and first used for treatment in 1922, numerous barriers continue to make it unattainable for many people in 2015.

The consequences of poor insulin access are devastating. In Sub-Saharan Africa, for example, lack of insulin access results in a life expectancy of less than a year for a child with type 1 diabetes, compared to almost normal life expectancy in high-income settings. In addition to increasing life expectancies for children with type 1 diabetes, improved insulin access would decrease blindness, amputations, kidney failure and premature mortality in people with type 1 and 2 diabetes around the world.

Although little is known about the global demand for insulin, approximately 381 million people worldwide between the ages of 20 and 79 had diabetes in 2013. By 2035, it is estimated that 592 million people will have diabetes—an increase of 55 percent over the 2013-2035 period. Whereas most of this data relates to type 2 diabetes, data on the global disease burden for type 1 diabetes is lacking. It is estimated that 497,100 children between zero and 14 years of age have type 1 diabetes and its prevalence is increasing by three percent per year. In high-income countries, between 10 and 15 percent of all diabetes is attributable to type 1 diabetes, while in low- and middle-income countries (LMICs), the figure is probably lower.

Research shows various barriers to insulin access, one of which is its overall price in comparison to other NCD medicines. In different countries, the average price of insulin in the public sector varied from US$4.10 in Mozambique in 2003 to US$8.40 in Kyrgyzstan in 2009. Some countries had access to a differential pricing scheme developed by a leading insulin manufacturer. Different duties, taxes and mark-ups increase the price of insulin and impact affordability to the health system and individuals. The financial burden of insulin to the health system is of concern not only in low-income countries, but also in middle- and high-income countries. Affordability to the individual is dependent upon the types of insulin purchased, mark-ups within the system, whether insulin is available in the public sector and other factors. Most importantly, though, is whether people with diabetes must pay for their insulin out-of-pocket, or the cost is covered by the health system.

Little is known about why the price of insulin has remained consistently high over the years; however, it is thought to be the result of market domination by three multi-national companies. This domination has led to withdrawals of certain insulin formulations, as well as shifts in the insulin market. This has meant that individuals with diabetes have had to change types of insulin and, in the past decade, the entire market has seen a dramatic increase in the use of higher-priced analogue insulins despite a lack of evidence to demonstrate significant benefits.

Another aspect specific to insulin is that, unlike medicines for HIV/AIDS or other medicines, the production of generic or biosimilar insulin is a more complex issue, especially from a regulatory perspective. Part of the issue is that, unlike chemical entities, it is difficult to produce an exact "copy" of a biological product. Patent protection is also linked to the issue of biosimilar products. Given the complexity of these molecules, patent holders tend to file many patents to protect a biological product.

The price of insulin is only one part of the equation. Insulin not only needs to be at a price an individual can afford, but also be present when this person needs to buy it. Poor availability is due to a variety of factors, such as problems with quantification at a national level, in-country distribution, and determination of needs at lower levels of the health system.

Availability and affordability of medicines have been addressed in many ways in different contexts and by different organisations; however, very little has been done to address the problem of insulin access. The response, to date, from the diabetes community has focused on unsustainable models of donation, initiatives led by the pharmaceutical industry, or activities more focused on health system strengthening, advocacy or research.

To improve access, it is therefore important to understand the path of insulin from "production" to "administration". In a 2012 paper published in *The Lancet* for World Diabetes Day, leading academics

BACKGROUND

and advocates specialising in access to medicines issues, type 1 diabetes, and access to insulin stated the need to "map the global insulin market and develop models to improve access to quality-assured insulin." Inequities and inefficiencies in the global insulin market demonstrate the need to develop a scientific approach to address the challenges and constraints described above. This was done with the launch of an innovative global study, Addressing the Challenge and Constraints of Insulin Sources and Supply (ACCISS), managed by Health Action International and funded by a grant from The Leona M. and Harry B. Helmsley Charitable Trust.

This report is the first step of the ACCISS Study. It highlights where we currently stand with access to insulin in 2015. Although there are multiple challenges that the ACCISS Study must address, it is hoped that this work will enable the 100 Campaign to achieve its goal of ensuring that 100 percent of people living with type 1 diabetes have access to insulin by 2022.

> "Research into the inequities and inefficiencies in the global insulin market is long overdue. The ACCISS Study is a unique opportunity for action to improve access to insulin."
>
> Margaret Ewen, Health Action International and ACCISS Co-investigator

The Global Context

Globally, it is estimated that one in three people do not have guaranteed access to essential medicines.(1-3) In the poorest parts of Africa and Asia, this proportion increases to one-half.(4) Considerable attention has been paid to the issue of access to medicines for HIV/AIDS, tuberculosis and malaria(5-12); however, little attention has been paid to questions of access to essential medicines for non-communicable diseases (NCDs). In September 2011, the United Nations (UN) held a General Assembly on NCDs, its second-ever health-related Assembly, after its 2001 meeting on HIV/AIDS. Despite being the main cause of mortality worldwide with 63 percent of total deaths,(13) NCDs have not been firmly placed on the development agenda.(14, 15) Although often thought of as "diseases of the rich", close to 80 percent of NCD deaths occur in low- and middle-income countries (LMICs). Four NCDs were prioritised by the World Health Organization (WHO), namely, cardiovascular disease (CVD), cancer, chronic respiratory diseases (CRDs) and diabetes, because they contribute the largest morbidity and mortality.(16) The political declaration from the UN includes commitments by Member States to address the issue of access to medicines in parallel to health system strengthening and universal health coverage (UHC).(17) The priority placed on the issue of NCDs and access to medicines was also reaffirmed following the Rio20+ Summit.(18)

One of the six key elements of a health system is to ensure equitable access to essential medicines of assured quality, safety, efficacy and cost-effectiveness, and that they are used in a scientifically sound and cost-effective way.(19) The target established by the Global Action Plan for the Prevention and Control of Non-communicable Diseases 2013-2020 (GAP) is of "80 percent availability of the affordable basic technologies and essential medicines, including generics, required to treat major NCDs in both public and private facilities."(16) This target has already been reached in many settings for medicines to treat HIV/AIDS, malaria and tuberculosis and also for vaccines(20), but data presented in the 2014 global status report on NCDs shows that the target for NCD medicines is far from being achieved.(21)

Lessons from HIV/AIDS show that it is possible to deliver care and medicines for a complex chronic disease in LMICs.(22) The difference between antiretrovirals (ARVs) and medicines for NCDs is that the medicines needed to treat CVD, cancer, CRDs

and diabetes present four distinct categories of challenges in terms of access:(23)

1. Oral medicines, marketed in generic form, are available at lower prices on the international market, but are still not available in countries and are often of uneven quality.
2. Asthma inhalers and insulin are available at higher costs and, to a certain extent, are more complicated to manufacture. It is important to note, however, that these medicines cost less than most ARV regimens.
3. Some NCD medicines, especially those for cancer, are still under patent and priced at such a level that they are accessible only via expanded access programmes of individual companies, which leads to varied accessibility.
4. Effective and affordable pain management and opioid analgesics, such as morphine, which are essential for palliative care, are of limited access in many countries due to regulatory limitations.

A combination of an active and dedicated civil society, substantial funding, and innovative approaches enabled the dramatic increase in access to medicines for HIV/AIDS.(8, 24-26) To date, funding for NCDs has been non-commensurate with the burden of disease(15) and progress has been weak(21).

> "The concept of essential medicines is one of the major public health achievements in the history of WHO. It is as relevant for the world of today as it was at its inception 30 years ago."
>
> Dr. Margaret Chan, Director-General of the WHO(27)

Why Focus on Insulin?

Before the discovery of insulin, children with type 1 diabetes needed to count calories, weigh their food, sometimes fast and use "starvation diets".(28) This method of treatment was the only way to keep children with this condition alive. These harsh measures prevented children from dying of diabetic ketoacidosis (DKA) and extended their life expectancy by some years before they unfortunately died of starvation.(29) This situation changed when, in 1921, work carried out by Frederick Banting and Charles Best at the University of Toronto led to the discovery of insulin.(30, 31) Leonard Thompson received his first injection of insulin on 11 January, 1922, in Canada, and became the first person to be treated with insulin for type 1 diabetes. Access to insulin saved Leonard from near certain death.

Elliott Joslin, who spent most of his career seeing patients with type 1 diabetes die, remarked in 1922 that, with access to insulin, "a new race of diabetics has come upon the scene".(32) Joslin's vision has fallen short in that, globally, the most common cause of death for a child with type 1 diabetes today is the lack of access to insulin.(33) Although highlighted as an issue by many academics and organisations, there has been a global failure in addressing this issue.(34-38) This situation exists despite insulin[1] being included on the WHO's Model Essential Medicines List (EML)(39) and off patent.

As a result of poor access to insulin, the life expectancy for a child with type 1 diabetes in Sub-Saharan Africa is as low as a year.(40) This is contrasted by recent data by Miller et al.(41), which shows that people diagnosed with type 1 diabetes in the United States of America (USA) in the 1960s and 1970s have only a four- to six-year difference in life expectancy from that of the general population.

Research in Kyrgyzstan, Mali, Mozambique, Nicaragua, the Philippines, Vietnam and Zambia, led by the International Insulin Foundation (IIF), found a variety of barriers to insulin access, including its overall price, in comparison to other medicines.(42-51) Access to insulin and poor health outcomes are not just problems for LMICs. In the USA, insulin discontinuation was the leading cause of DKA in 68 percent of people in an inner-city setting.(52) Amongst those who stopped taking insulin, 27 percent reported a lack of money to buy insulin and five percent were eking out their insulin supplies. Access to insulin has also become problematic in some European countries, like Greece, as a result of the global financial crisis. The growing need for insulin has also increased the burden on many countries' health budgets, such as that of the United Kingdom (UK).(53, 54)

Global estimates do not exist for the number of people who require insulin. It is essential for the survival of people with type 1 diabetes worldwide. Without insulin, these individuals face death in a matter of weeks. In addition, insulin is required for better management of some cases of type 2 diabetes. Improving access to insulin would lead to longer life expectancies for children with type 1 diabetes, as well as decreased blindness, amputations, kidney failure and premature mortality in people with type 1 and 2 diabetes.

1 Soluble and intermediate acting: as compound insulin zinc suspension or isophane insulin in vial form

"Nearly 100 years after insulin was first used to save the life of a diabetic patient, people around the world still die because they cannot access this same hormone."

Ban Ki-moon, UN Secretary-General, speaking on World Diabetes Day in 2013(55)

What is Insulin?

Insulin is a hormone, normally made by the pancreas, which regulates glucose metabolism. It is necessary to allow for normal carbohydrate, protein and fat metabolism for glucose to enter muscle and fat cells.(56) Insulin helps regulate the transformation of glucose into glycogen for storage of glucose. It also inhibits the release of stored glucose. Normally after eating, blood glucose levels rise to a peak and return to normal levels after two to three hours.(57)

Insulin is a treatment for diabetes—not a cure—and is administered by daily injections. In some settings, insulin can be administered through special insulin pumps. The dosage of insulin injected by the individual varies from person to person based on age, nutritional status and activity. In the past, insulin was obtained from pork or beef pancreases. Today, it is more commonly obtained through recombinant DNA technology.(57) Insulin analogues now exist where the amino acid sequence of the insulin molecule has been modified, impacting its chemical properties. Although analogue insulins have gained market share in recent years, evidence about their effectiveness remains weak.(58-61)

"Insulin is survival."

34-year-old Swiss female with type 1 diabetes

Box 1: More about insulin.

Insulin is available in rapid-, short-, intermediate-, and long-acting formulations.(62) Details about different insulin formulations can be found below.(63-65)

TYPES OF INSULIN	ACTION CHARACTERISTICS ONSET[2]	PEAK[3]	DURATION[4]
Rapid-acting analogues • Lispro (Humalog®) • Aspart (Novorapid®) • Glulisine (Apidra®)	5-10 minutes	0.5-2 hours	3-4 hours
Fast-acting	0.5-1 hour	2-5 hours	6-8 hours
Intermediate-acting	0.5-1 hour	2-5 hours	6-8 hours
Long-acting	3-4 hours	8-15 hours	22-26 hours
Very long-acting analogues • Glargine (Lantus®, Toujeo®) • Detemir (Levemir®) • Degludec (Tresiba®)	0.5-1.5 hours	None	20-40 hours

Worldwide, there were 180 branded insulin preparations available in 2001.(57) The WHO Model EML(66) contains two insulin formulations: soluble and intermediate-acting. These are the two most-commonly available formulations in the public sector in developing countries.

Insulin mostly comes in 10 ml vials with a concentration of 100 IU, meaning each vial has 1,000 units of insulin. This quantity is sufficient for approximately one month of treatment, with the yearly consumption of insulin estimated at 35 units per day, which is equivalent to 13 vials a year.(67)

2 Onset is how fast the insulin starts to work.
3 Peak period is how long the insulin administered is at its most effective level.
4 Duration is how long the insulin is working in the person's system to lower blood glucose.

WHAT IS KNOWN ABOUT INSULIN AVAILABILITY & AFFORDABILITY

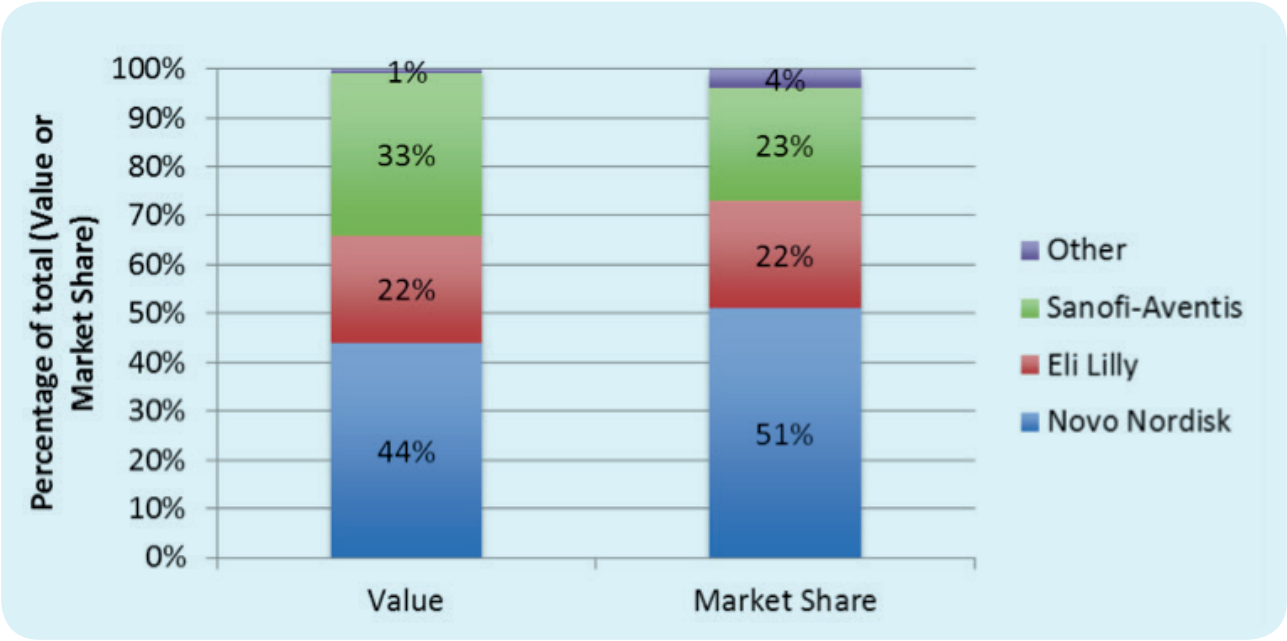
Work by the IIF in Kyrgyzstan, Mali, Mozambique, Nicaragua, the Philippines, Vietnam and Zambia found a variety of barriers to insulin access, one of which was its overall price in comparison to other medicines. Insulin prices were, on average, US$4.20 per month for treatment, which is up to 74 times higher than other treatment courses for NCDs. (42-51, 68) In addition, in Mali and Mozambique, for example, insulin was present in only 20 percent of facilities that should have stocked it. This means that availability was an issue in addition to affordability. (69) Because insulin must ideally be maintained between two and eight degrees Centigrade, the cold chain is sometimes seen as a hurdle to access. This, however, was not a significant barrier in these studies. The factors causing poor insulin availability exist at both global and national levels and cannot be addressed in isolation. Therefore, to improve insulin access, it is important to understand its path from "production" to "administration".(70)

Affordability of Insulin: Global Market Dynamics

A snapshot survey carried out by Health Action International (HAI) in 2010 found the average prices for insulin manufactured by two companies were similar within most regions, except in Europe and Southeast Asia where one company's insulin was priced 60 percent higher than its competitors in Europe, but 40 percent less in Southeast Asia. (71) The survey noted the dominance of two manufacturers with little competition identified. Across WHO Regions, the average price of insulin from one company doubled from US$15 per vial in Southeast Asia to US$32 in Europe. The variation for the other main manufacturer was found to be slightly less with an average of US$15 in the Eastern Mediterranean Region to US$25 in the Americas. Insulin vials from other manufacturers had an average price of US$3 in Southeast Asia to US$23 in the Americas.

Little is known about why the price of insulin has remained consistently high over the years. It is thought, however, to be the result of market domination by three multi-national companies controlling 99 percent of the insulin market value and 96 percent of its volume.(72) (Figure 1)

Figure 1: Worldwide insulin market by value and market share by volume in 2011.(72)

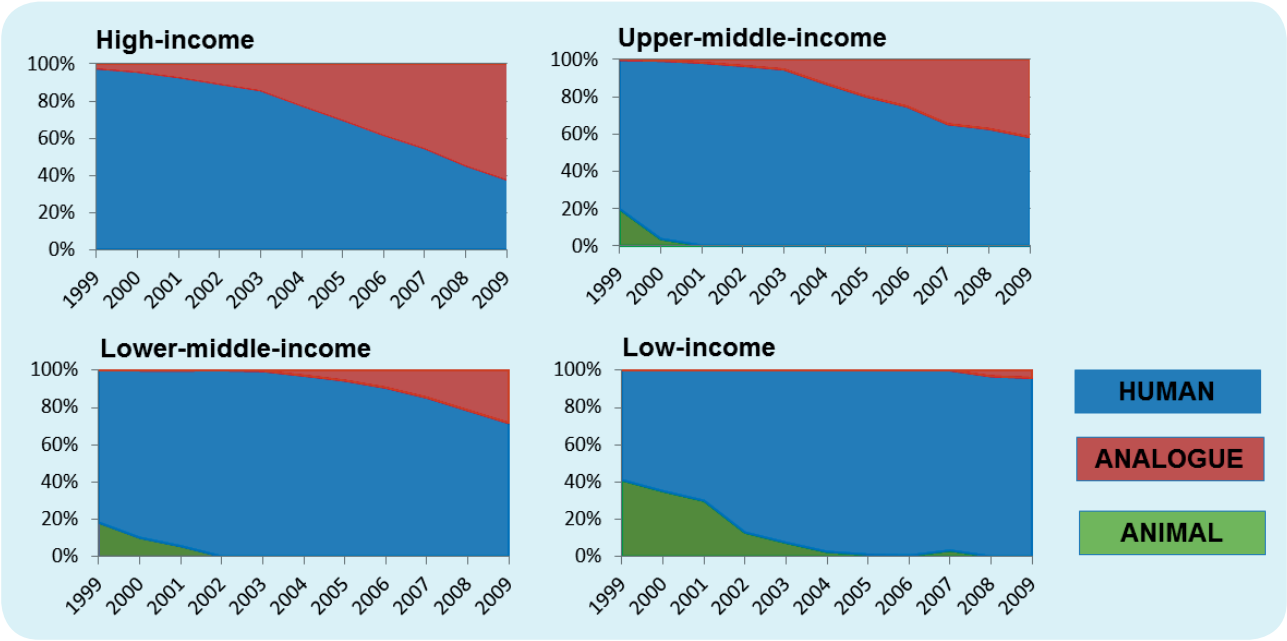


This domination has also meant that individuals with diabetes have had to change types of insulin because these companies have the ability to withdraw formulations on the market.(73, 74)

This control of the market has resulted in a dramatic increase in the use of analogue insulin over the past decade despite a lack of evidence showing significant benefits commensurate with its higher price.(75) A 2006 Cochrane Review and other studies on short-acting analogues found that they were identical in effectiveness compared to regular human insulin in terms of long-term blood glucose control and episodes of low blood glucose (hypoglycaemia).(58) The main advantage found with long-acting analogues was that their nocturnal effect resulted in lower levels of fasting glucose, but, nevertheless, fewer events of nocturnal hypoglycaemia. Again, as with short-acting analogues, the authors call for caution in the use of these newer products.(59) In a 2006 observational report from South Africa, no improvements in blood glucose levels were found in people with type 1 diabetes who were switched from isophane to long-acting analogue insulin; however, people with frequent hypoglycaemia reported a reduced number of these episodes.(60) Guidance for the use of analogue insulin in people with type 2 diabetes have been promoted, for example, in the UK.(76) In addition, the WHO's report on its 18th Expert Committee on the Selection and Use of Essential Medicines assessed the comparative effectiveness and cost-effectiveness of analogue insulin (insulin glargine, insulin detemir, insulin aspart, insulin lispro, and insulin glulisine) compared to human insulin. It found that: "While many of the comparative trials find a statistically significant difference between analogue insulins and standard recombinant human insulin for some effects on 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."(61)

Data on changing patterns of global insulin use over the first decade of the century, despite the limited number of countries represented and lack of an overall representation of the insulin market, show three clear trends as presented in Figure 2.(75, 77, 78)

Figure 2: Transition from human to analogue insulin by percentage of total insulin by type and by country income groupings, 1999-2009.(77)



The trends presented in Figure 2 are:

1. A global decline in the use of animal insulin in all regions of the world, with less than 25 percent of countries in all regions using any animal insulin at all in 2009.
2. A decline in the use of human insulin. It has gone from being the only formulation of insulin used to only about one-third of insulin used in high-income countries and two-thirds in middle-income countries by 2009. In low-income countries, this decline started later, with human insulin still comprising over 94 percent of all insulin in 2009 in countries where data is available.
3. A proportional decrease in the use of human insulin, which is mirrored by rising proportions of analogue insulin, representing two-thirds of all insulin in high-income countries by 2009, with trends in middle- and lower-middle-income countries following suit. In low-income countries, however, analogue insulin still represented a median of only four percent of insulin use in 2009.

Similar trends are described in work by Currie et al.(54) who found that, in the UK, from 2000 to 2008, the use of animal and human insulin decreased from 2.9 to 0.7 percent and 86.3 to 23.2 percent, respectively, while the use of analogue insulin increased from 10.7 to 76.1 percent. This evolution is at different stages within different income groups. Although not immediately visible from the data presented in Figure 2 (possibly because data from low-income countries is poor), IIF's research results in Kyrgyzstan(51) show a clear trend in the international insulin market with animal insulin being replaced by human insulin and then human insulin being replaced by analogue.(75)

In the USA, the value of insulin sales in 2011 totalled US$8.3 billion, a 14.9 percent increase compared to 2010.(79) Information on volume is not available, but this growth cannot be explained by increasing prevalence or the progression of diabetes, meaning that more people need insulin.(80) Therefore, the factors leading to this are that the price of insulin is increasing and/or more people are being put on insulin. Lipska et al.(81) found that insulin use increased from 10 percent in 2000 to 15 percent in 2010 amongst people in the USA who had both type 2 diabetes and private health insurance.

Another challenge specific to insulin and other biological molecules is that, unlike ARVs, or other medicines, the production of generic or biosimilar insulin is a more complex issue, especially from a regulatory perspective. Part of the issue is that, unlike chemical entities, it is difficult to produce an exact "copy" of a biological product.(82) Wang(83) defines a biosimilar as "a biological product which is similar to the referenced product 'approved before' and 'on market', and is expected to have substantially similar clinical results (in terms of safety profile and efficacy) of the referenced product."

The process in the production of these molecules is as important as the final product. Each step in the manufacturing process may impact the end molecule and its "equivalence" to the original protein. Because of this, the clinical and regulatory requirements are more complex than for generic small molecule medicines. Issues around inter-changeability also exist and further complicate the uptake of these products.(84) The biosimilar market is significantly increasing with many biological products coming off patent.(83) It is estimated that biosimilars in Europe could offer savings of 20 to 30 percent in comparison with the originator medicines and decreases in prices from 12 to 51 percent have been seen on the originator product once a biosimilar is introduced.(82, 85)

Although some regulatory authorities have established guidelines for the approval of biosimilar products, this is still a relatively new area. Despite the impact on cost, many authorities have not kept pace with regulatory developments.(83) Regulatory authorities in LMICs have yet to grapple with this challenge.

Patent protection is also linked to the issue of biosimilar products. Given the complexity of these molecules, patent holders file many patents to protect the biological product.(83) Not only are the patents on the product important, but also on the production processes and associated technologies (e.g., insulin pens).

> "The global insulin market was valued at US$19.99 billion in 2012 and is expected to grow at a CAGR [Compound Annual Growth Rate] of 6.1 percent from 2013 to 2019 to reach US$32.24 billion in 2019."(86)

Affordability to the Health System

In countries such as Mali, Mozambique and Zambia, government healthcare expenditure is equivalent to US$28, US$14 and US$36 per person per year, respectively, at average exchange rates.(87) With an average buyer price for insulin of US$6.17 on Management Sciences for Health's (MSH) International Drug Price Indicator Guide, and assuming that a

person with type 1 diabetes would need 13 vials of insulin per year, this is equivalent to 2.9, 5.7 and 2.2 times what Mali, Mozambique and Zambia spend per person per year on healthcare.(88, 89) Affordability is not only linked to the funding available for health, but also to how money is used. Kyrgyzstan is a country with a gross domestic product (GDP) of US$2,070 per capita and spends US$140 per capita on healthcare.(90) Analogue insulin is purchased, although it is not included on the WHO Model EML. (51, 91) (Table 1)

Table 1: Irrational choices and their financial implications – The example of Kyrgyzstan. (51)

INSULIN	TOTAL UNITS (10ML 100IU VIAL EQUIVALENT)	PERCENTAGE OF TOTAL VOLUME	COST PER 100IU 10ML VIAL EQUIVALENT (US$)	TOTAL COST (US$)	PERCENTAGE OF TOTAL COST
Non-analogue, non-cartridge insulin	160,000	71%	$5.10	$819,200	43%
Analogue or cartridge insulin	64,150	29%	$16.70	$1,068,098	57%
Total	**224,150**			**$1,887,298**	
Cost purchasing non-analogue insulin in vial presentation	224,150		$5.10	$1,147,648	
Potential saving				**$739,650**	

Although 71 percent of insulin purchased in 2009 in Kyrgyzstan met WHO guidelines, this accounted for only 43 percent of total expenditure; therefore, the remaining 29 percent, comprising analogue insulin in vials or penfills, consumed 57 percent of the insulin budget. Following WHO guidance would have reduced the annual expenditure by US$740,000, or around 40 percent of the total in 2009.(51) This represents healthcare expenditure for about 5,000 people in this country.

Overall, in countries where studies have used a standardised rapid assessment protocol, the average price of insulin purchased by the public sector varied from US$4.10 in Mozambique in 2003 to US$8.40 in Kyrgyzstan in 2009.(69) (Figure 3) Both Mozambique and Zambia accessed a differential pricing scheme developed by a leading insulin manufacturer, which supplies insulin to governments of least-developed countries at a price not exceeding 20 percent of the average price in North America, Europe, and Japan.(45) Through this scheme, the price of insulin purchased by both national health systems was between US$4.30 and US$4.60 per 10 ml IU 100 vial, including freight costs.

Data from HAI also found that some governments purchase insulin at higher prices than those available on the international market.(92) The range found in 10 studies for a variety of insulin formulations was 0.33 to 5.87 times the international reference price (price per vial from US$2.55 to US$48.25).(93)

Insulin was exempt from any taxes and duties in Kyrgyzstan, Mozambique and Zambia. Insulin and all other medicines in Mali are subject to 2.5 percent duty.(42, 94) In Nicaragua's public sector, there are no taxes or duties on medicines but there is a six percent customs duty on all imported medical material and medicines destined for the private sector. (43) In Vietnam, medicines have an import duty and value added tax of five percent no matter the sector to which they are destined.(44)

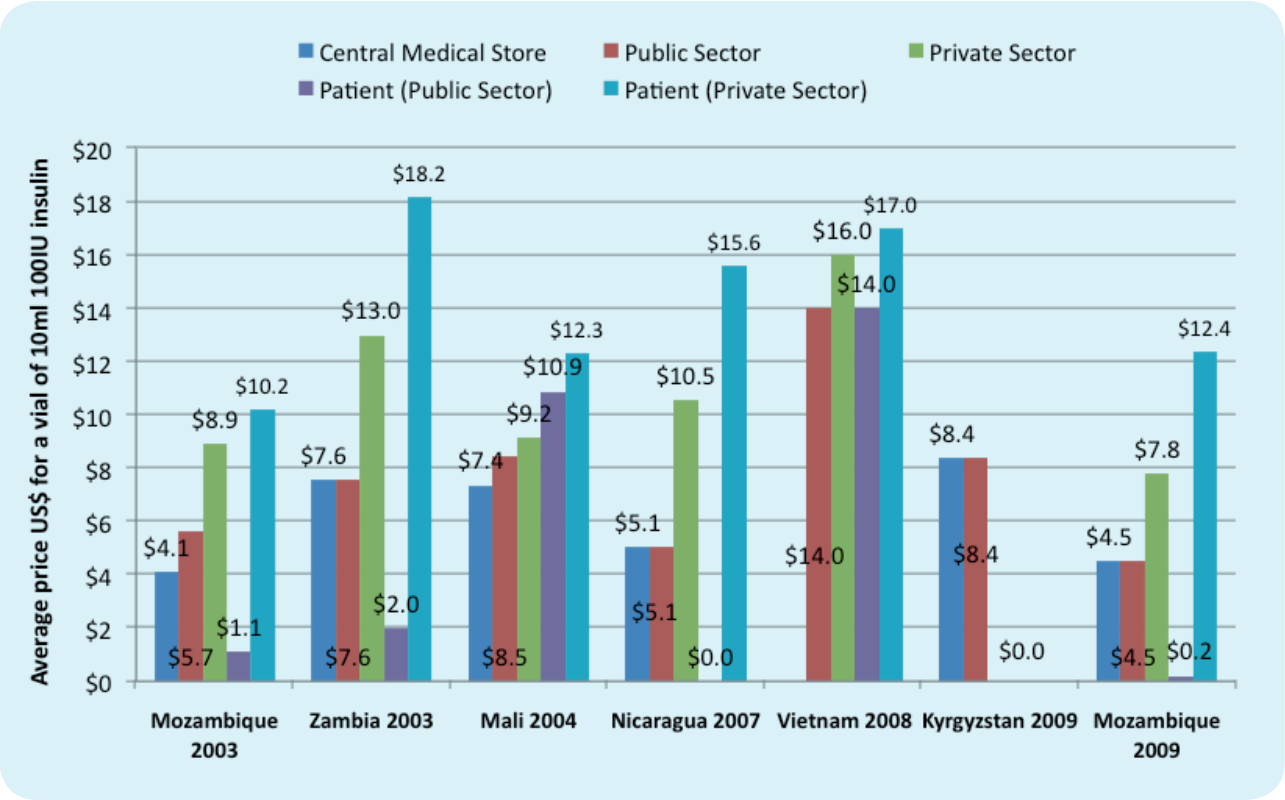
In 2006, the International Diabetes Federation (IDF) Insulin Task Force carried out a global survey of diabetes associations on access to insulin and other diabetes-related supplies.(95) Fifty-five percent of countries reported that taxes were charged on insulin. On imported insulin, the average tax of all surveyed countries was 13 percent with the highest in Mongolia at 30 percent. The average tax on locally produced insulin was 20.5 percent with the highest reaching 35 percent in Brazil. Data from the World Trade Organization in 2008 showed that 22 countries (17 percent) had tariff rates between zero and five percent.(78) Eight percent of the countries had tariff rates between 5.1 and 10 percent of the price of the finished products containing insulin; five percent of the 132 countries charged a tariff of between 10.1 and 20 percent and only one country

charged an import tariff of more than 20 percent of the price of the product.

In Mozambique, insulin purchased locally from wholesalers, rather than through international tenders, was between 25 and 125 percent more costly ($5.47–$9.91 per 10ml IU100 vial).(45) In Zambia, insulin from private wholesalers was 85 to 125 percent higher priced, depending on the manufacturer. These local purchases were due to the quantity purchased through tenders being insufficient for need, which required additional costly purchases to be made from the private sector. As these countries carry out one annual purchase of insulin, any errors in estimates mean that more insulin may need to be purchased locally.

Ten percent of government expenditure on medicines in 2003 in Mozambique was spent on insulin.(45) High financial burdens for health systems is not only an issue in LMICs, but also in high-income countries, including the UK.(54) Currie et al. (96) report that, from 2000 to 2010, the UK National Health Service spent the equivalent of US$4,145 million on insulin.(97) A driver was expenditure on analogue insulin, which represented 12 percent of total insulin cost in 2000 and 85 percent of total insulin cost in 2010.

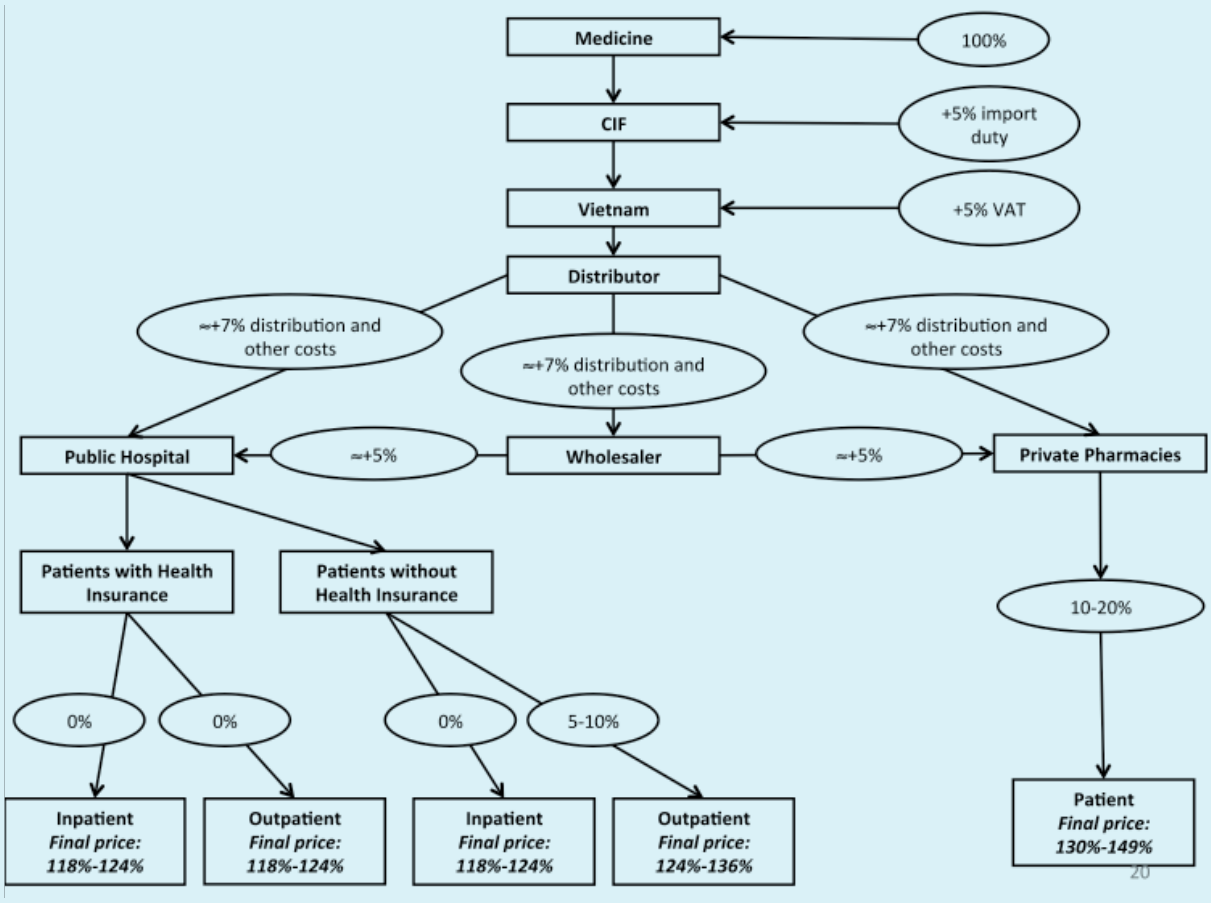
Figure 3: Average prices of insulin (per 100IU 10ml vial) in six countries at different levels of the health system.(69)



Although four of the six countries in Figure 3 provide insulin for free or at subsidised prices, assuming a daily insulin dose of 35 units, the mean annual cost of purchasing insulin for the health service in these countries would be US$56.03. This represents an average of 40 times the annual public sector pharmaceutical expenditure per person.(45)

As seen in Figure 3, at different levels of the health system, different prices for insulin exist. As previously mentioned, some of this price increase might be due to taxes and import duties, but additional mark-ups along the supply chain can influence the final price to the health system, facility or individual. For example, in Mali and Mozambique in 2003, there was a price increase for insulin within the health system between the central levels and periphery. This is common in health systems where cost-recovery occurs between different levels of the health system. Price increases are used to cover some of the costs linked to transportation and storage. Centralised tendering was not used in Vietnam; therefore, each facility conducted separate tenders. In Vietnam, different mark-ups along the supply chain mean that individuals pay a minimum 18 to 49 percent more for their medicines than when they arrive in Vietnam, as presented in Figure 4.(44)

Figure 4: Mark-ups within the health system in Vietnam.(44)



Affordability to the Individual

In many developing countries, diabetes and the price of insulin have been found to place a large financial burden on individuals and their families. (98, 99) Table 2, below, details some of these costs.

Table 2: Costs of diabetes care in low- and middle-income countries.

COUNTRY	ASPECT OF DIABETES CARE	COSTS IN USD
Tanzania 1997 (100)	Average annual direct outpatient cost for a person with diabetes requiring insulin	$229 (68.2% on insulin)
Sudan 2005 (101)	Median annual expenditure per child with type 1 diabetes	$283 (36% on insulin)
Mexico 2008 (102)	Average annual direct cost of treatment and monitoring for type 1 diabetes	$1,690 (15% on insulin)
Vietnam 2009 (44)	Average annual cost for a child with type 1 diabetes	$660 (21% on insulin)

Affordability to the individual is dependent upon various elements described above, including the types of insulin purchased, mark-ups within the system, whether insulin was available in the public sector, and other factors. The most important factor, however, as presented in Figure 3, is whether people with diabetes must pay for their insulin, or if the cost (in part or in whole) is covered by the health system. In Mozambique, in 2003, there was a "chronic disease law", which stated that people with chronic diseases, including diabetes, were able to access medicines at an 80 percent subsidy. Similar subsidies were in place in Zambia. The Nicaraguan health system provided insulin for free, whereas in Mali, cost-recovery was in place. Vietnam had insurance schemes, which covered all or a portion of costs related to medicines, but not everyone benefited from this health insurance. This results in different financial burdens for individuals for the purchase of a year's supply of insulin in these countries, as presented in Table 3, ranging from US$0 in Nicaragua to US$168 in Vietnam.

Table 3: Cost of insulin as part of diabetes care.(51, 103, 104)

COUNTRY	TOTAL COST OF INSULIN PER YEAR (US$)	PERCENTAGE OF TOTAL COST FOR PURCHASE OF INSULIN	TOTAL COST OF DIABETES MANAGEMENT PER YEAR (US$)	PERCENTAGE OF GDP PER CAPITA (NOMINAL RATE)
Kyrgyzstan (2009)	$0.00	0.0%	$80.40	9%
Mali (2004)	$130.60	38.5%	$339.36	87%
Mozambique (2003)	$13.20	4.8%	$273.60	116%
Mozambique (2009)	$2.40	0.8%	$305.28	71%
Nicaragua (2007)	$0.00	0.0%	$74.40	6%
Zambia (2003)	$24.00	12.1%	$199.08	44%
Vietnam (2008)	$168.00	39.3%	$426.96	37%

The total cost of diabetes as a percentage of GDP per capita represents a substantial burden on individuals. Mendis et al.(105) found that the affordability of insulin treatment in terms of the number of days that the lowest-paid government worker would have to pay 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.

The prices in the private sector presented in Figure 3 (price range from US$10.20 to US$18.20) are out of reach for the majority of individuals in these countries. HAI's snapshot survey found the price an individual with diabetes would pay for a 10ml vial of soluble human insulin in the private sector ranged from US$1.55 in Iran to US$76.69 in Austria, a difference of almost 5,000 percent.(71) For insulin formulations from specific manufacturers, significant price variations were seen for insulin from Eli Lilly, ranging from US$2.57 in Egypt to US$76.99 in Austria (a 30-fold price variation). Novo Nordisk insulin was seen to have a 21-fold price differential between a vial priced at US$2.97 in Senegal and US$61.32 in the USA.

Affordability of insulin is also a problem in the USA where uninsured people with type 1 diabetes are unable to access the care they need.(106) There, insulin discontinuation was the leading cause of DKA in 68 percent of people in an inner-city setting.(52) Amongst those who stopped taking insulin, 27 percent reported a lack of money to buy insulin and five percent were eking out their insulin supplies. With the increased use of analogues, out-of-pocket expenditure for insured people with type 2 diabetes increased from a median of US$19 to US$36.(81)

> "I think it does help to have everything free on the National Health Service. I spoke to this Australian girl I met and she was telling me all these ways around saving insulin because it cost her so much."

28-year-old female from the UK with type 1 diabetes

Availability of Insulin

The price of insulin is only one side of the equation. Insulin must not only be at a price the individual can afford, but also be present when a person needs to buy it. In both Mozambique and Zambia, the EMLs included both short- and prolonged-acting insulin in 100 IU/ml formulations.(45) In addition, Mozambique had intermediate-acting and mixed insulin preparations in its formulary. Guidance stated that insulin should be available at hospitals and referral health centres; however it was found that in Mozambique, insulin was always only present at some hospitals and not at health centres (overall availability of 20 percent). In Zambia, insulin was present at all hospitals, but only at some referral health centres (overall availability of 42 percent). In Vietnam, insulin was also readily available in the public and private sectors, but this was not the case in the public sector in the Philippines.(107) Insulin availability in six countries is shown in Table 4 (below).(105)

Table 4: Percentage availability of at least one type (generic and innovator brands) of different insulin formulations in six countries in 2007.(105)

INSULIN FORMULATION	TYPE	BANGLADESH	BRAZIL	MALAWI	NEPAL	PAKISTAN	SRI LANKA
Soluble	Generic	60%	10%	6%	23%	53%	8%
	Innovator	5%	40%	25%	8%	0%	40%
Isophane	Generic	20%	35%	0%	18%	55%	12%
	Innovator	5%	50%	0%	3%	0%	48%
Zinc suspension	Generic	0%	0%	25%	9%	NA	NA
	Innovator	0%	0%	30%	3%	NA	NA

Studies carried out by HAI found similar low availability in a variety of countries.(92) Availability in the public sector ranged from 3.3 to 100 percent and 4.8 to 56.7 percent in the private sector.

Poor availability was due to a variety of factors, such as problems with quantification at the national level, in-country distribution, and determination of needs at lower levels of the health system. In Mozambique, for example, Maputo Province represented only 11.3 percent of the total population, yet it received 77.3 percent of the total amount of insulin ordered by Mozambique. This problem with distribution of overall supplies of insulin was also seen in Kyrgyzstan.(51) Orders from facilities for specific formulations of insulin were not met, resulting in the facilities receiving what was available rather than what they ordered.

Another reason for poor availability can be highlighted by the example of findings from the IIF's work in Mali.(70) The Central Medical Store in Mali in August 2004 bought insulin for the first time in two to three years. The quantity purchased was extremely small and not sufficient to cover all needs. The reasons given for why insulin had not been ordered were because Mali promotes the use of generics and it was unable to find a generic supplier of insulin. In addition, when preparing a tender, the Central Medical Store needed to get quotes from three potential suppliers. Because there are few suppliers, it was unable to do this. The last factor was that insulin is a high-priced medicine and the limited budget available needed to be prioritised.

Availability was also variable in different countries in the private sector. Private sector availability was poor in Kyrgyzstan and Nicaragua, but wider mainly in capital cities, in Mali, Mozambique and Zambia, and large urban areas in Vietnam.

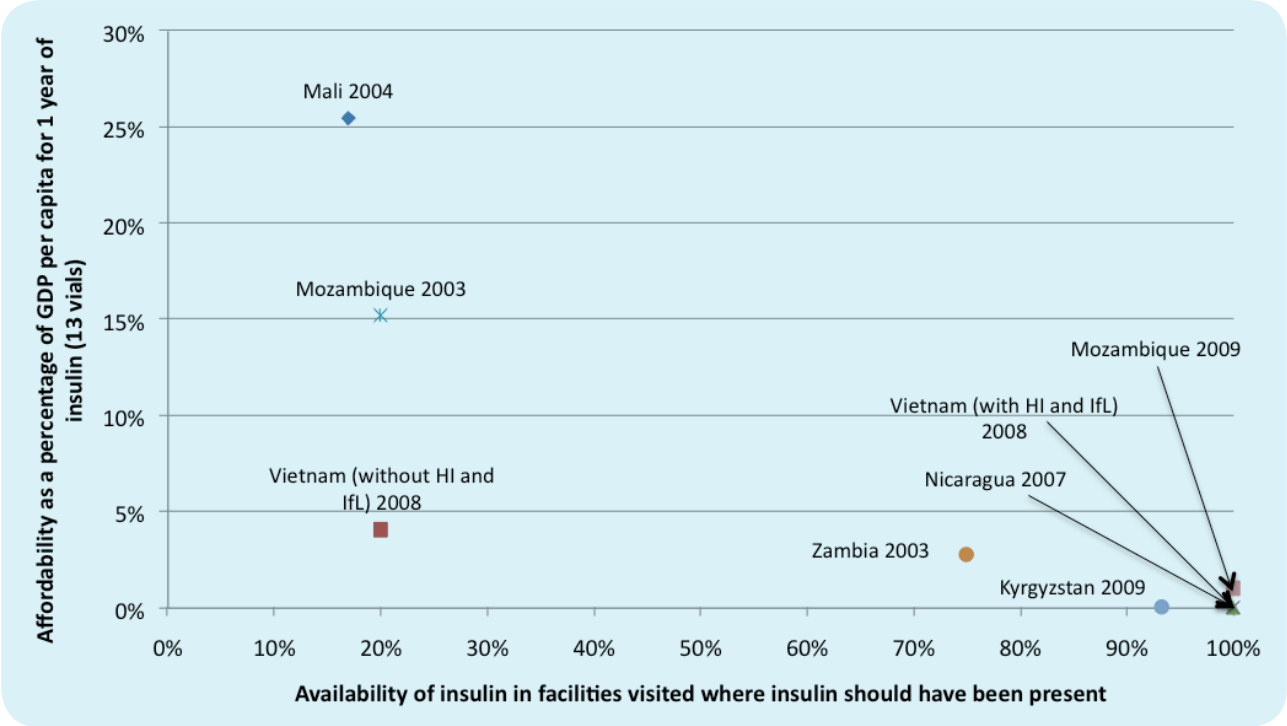
> "My biggest concern is the unstable supply of insulin in the market."
>
> Father of 15-year-old boy with type 1 diabetes in Vietnam

Bringing Availability & Affordability Together

The target established by the GAP is "80 percent availability of the affordable basic technologies and essential medicines, including generics, required to treat major NCDs in both public and private facilities."(16) Based on the data presented in Figure 5, one could argue that 4 countries—Mali, Vietnam (for people without health insurance and not benefitting from an insulin donation programme, like Insulin for Life), Mozambique in 2003, and Zambia—would fail the 80 percent availability target proposed by the GAP. In Mali, this was due to an overall shortage of insulin in the health system. In Mozambique in 2003, however, and in Zambia, this was likely linked to improper distribution from the central level to facilities. In Vietnam, for children without health insurance and unable to benefit from an insulin donation programme, insulin was not available in the public sector and had to be purchased in the private sector. It is important to note that this lack of public access leads to the need to purchase medicines in the private sector where they are priced out of reach for the majority of these countries' populations. For example, at US$18.20 per vial in the private sector in Zambia, this would be equivalent to US$218.40 per year or almost 10 times the cost of insulin in the public sector.

In Mali, with 25 percent of per capita GDP needing to be spent on insulin, this is clearly unaffordable. In Zambia, where expenditure on insulin was three percent of per capita GDP (representing US$23.89 per year), 69 percent of the population lives on less than the international poverty line of US$1.25 (108) per day, and the lowest-paid government worker made US$163.79 per month until recently (109), would insulin be viewed as affordable? In linking both the availability and affordability elements of the 80 percent target, Kyrgyzstan, Mozambique (assuming that US$2.30 per annum is viewed as affordable), Nicaragua and Vietnam (for people with health insurance and benefitting from donated insulin) would meet the target focusing only on the public sector.

Figure 5: Availability and affordability of insulin in six countries. (HI: health insurance; IfL: Insulin for Life donation scheme)



Data from HAI identified seven studies where insulin was provided for free in the public sector(92); however, only two countries, Mauritius and Kuwait, could be said to have substantial availability with 96.7 percent and 100 percent, respectively, of this free insulin. Other studies showed availabilities of 30.8 percent and less.

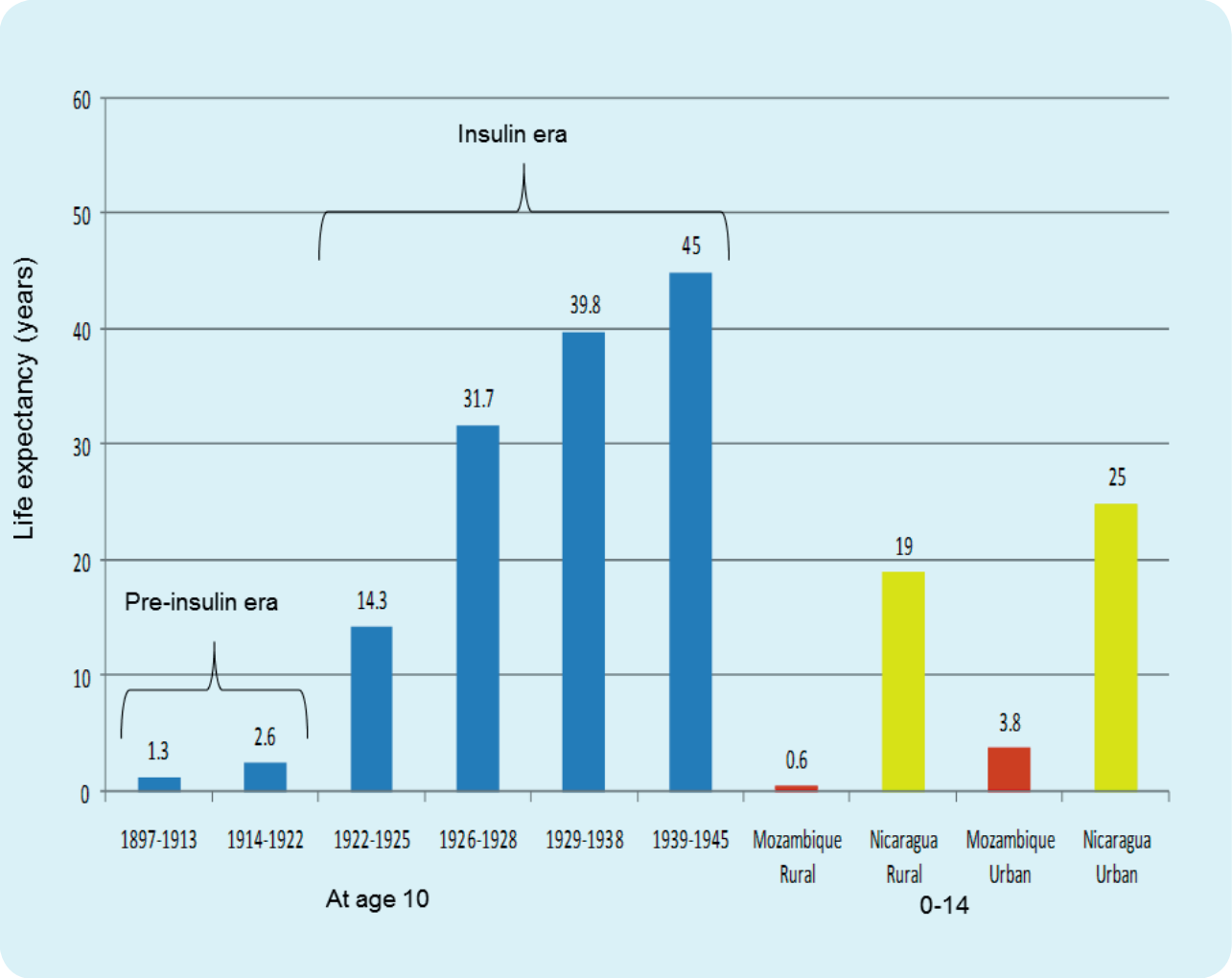
> "Insulin with the ratio 30/70 is very difficult to find. Sometimes I need to go all around the city just to get one vial."
>
> Father with an 11-year-old daughter with type 1 diabetes in Vietnam

The Impact of these Barriers

The impact of these barriers to insulin access and care is decreased life expectancy. In rural Mozambique, life expectancy after onset was seven months compared to 3.8 years in the capital city(45). This statistic is all the more striking in that the life expectancy for a child in rural Mozambique in 2003 is less than that of a child in Boston before the discovery of insulin(110), as shown in Figure 6. In the Democratic Republic of Congo, one-sixth of people with type 1 diabetes died within five years of diagnosis(111).

> "What is the commonest cause of death in a child with diabetes? The answer—from a global perspective—is lack of access to insulin"
>
> Professor Edwin Gale(33)

Figure 6: Comparison between life expectancy Boston (1897-1945), Mozambique (2003) and Nicaragua (2007). (43, 45, 110)



ESTIMATING THE GLOBAL NEED

Globally, it is estimated that 381 million people between the ages of 20 and 79 had diabetes in 2013 and that an additional 175 million people were living with the disease, but had not been diagnosed.(112) Estimates for 2035 show that there will be 592 million people with diabetes, a 55 percent increase over the 2013 to 2035 period. Eighty percent of these people live in LMICs and diabetes was responsible for 5.1 million deaths in 2013. Whereas most of this data relates to the type 2 diabetes, global disease burden data for type 1 diabetes is lacking. It is estimated that 497,100 children between zero and 14 years of age have type 1 diabetes and that its prevalence is increasing by three percent every year.(112)

The incidence rate of type 1 diabetes is not uniform throughout the world. A wide range of incidence rates exist within different continents.(113) There is a 10-fold variation of incidence rates for type 1 diabetes in Europe.(114) Even within countries, there is significant variation. For example, a study in Stockholm found a 3.4-fold variation between high-incidence and low-incidence areas(115). In Latin America, the incidence of type 1 diabetes increases proportionally with the size of the population that is of European origin as incidence rates in indigenous populations are much lower.(116) Yang et al.(117) found that the incidence of type 1 diabetes in China was 0.51 per 100,000, but that there was a 12-fold variation in this rate based on geography.

Incidence not only varies from one region to another, but also in age of onset. In Africa, the age of onset of type 1 diabetes is later than in Western countries, with peak age of onset occurring 10 years later.(118) In a South African study, the peak age of onset was 23.5 years in males and 22 years in females. In Tanzania, the peak age of onset was 29.4 years and, in Ethiopia, 21.4 years in males and 18.1 years in females.(118) This is compared with a median of 12 years in a matched group of white individuals of European origin.(118) Such analyses are problematic because the single source of global comparative data from the IDF only examines type 1 diabetes in populations aged zero to 14. Data for the different IDF/WHO Regions is presented in Table 5.

Table 5: IDF data on type 1 diabetes (zero to 14 years of age) by region.(112)

REGION	NUMBER OF CHILDREN WITH DIABETES	NUMBER OF NEWLY DIAGNOSED CASES PER YEAR
Africa	39,100	6,400
Europe	129,400	20,000
Middle-East and North Africa	64,000	10,700
North America and Caribbean	108,600	16,700
South and Central America	45,600	7,300
Southeast Asia	77,900	12,500
Western Pacific	32,500	5,300

In high-income countries, it is estimated that between 10 and 15 percent of all diabetes is attributable to type 1 diabetes, while it is probably lower in LMICs.(119) In the USA, it is estimated that there are up to 3 million people with type 1 diabetes.(120) Eighty-five percent of these individuals are adults and 15 percent are children.(121) This would represent about 12 percent of the total population with diabetes in the USA. Although global numbers do not exist for the total population of people with type 1 diabetes, estimates show that they may represent five percent of the total diabetes burden (estimated at 386 million) or 19.3 million people.(112)

The Different Needs for Insulin

Insulin is essential for people with type 1 diabetes to survive. Without it, these individuals face death in a matter of weeks. Insulin use in type 2 diabetes can be initiated when required to manage blood glucose.(122) Insulin initiation in type 2 diabetes should be done for people with poor blood glucose control and already using the maximum dosage of oral medicines.(123, 124)

The number of people with type 2 diabetes who require insulin depends on a variety of factors, including:

1. The actual number of people diagnosed (plus the issue of undiagnosed individuals with diabetes).
2. Clinical practice and how insulin is used as part of the treatment of type 2 diabetes.
3. Guidelines and quality measures of healthcare systems and health insurers.

In Nicaragua, it was found that, in comparison to global estimates, the number of people with diabetes who were actually cared for by the health system was half of what one would expect for type 1 diabetes and one-fifth for type 2 diabetes.(43) This is an issue not only in LMICs, but also in high-income countries, such as the UK, where approximately 750,000 adults with type 2 diabetes are not diagnosed. This is equal to 16.5 percent of the total number estimated to have diabetes in 2013.(125)

Clinical practice and use of insulin in the management of type 2 diabetes is, of course, dependent upon training, where diabetes is managed in the health system, resource levels of the country, and guidelines. In looking at different countries and treatment options for type 2 diabetes data in Table 6, it is clear that the use of insulin in type 2 diabetes is variable.

Table 6: Different treatment regimens for type 2 diabetes (percentage of total).

COUNTRY	PERCENTAGE OF ALL PEOPLE WITH TYPE 2 DIABETES USING DIFFERENT TREATMENT OPTIONS		
	ORAL TABLETS	TABLETS AND INSULIN	ONLY INSULIN
Algeria (126)	53.8%	26.3%	19.6%
Indonesia (127)	61.9%	19.4%	17.3%
Thailand (128)	81.9%		2.8%
USA (129)	56.9%	14.7%	14%

In France, 16.5 percent of people with type 2 diabetes in 2002 were treated with insulin, either alone or in combination with oral tablets.(130) This was an increase from 12.3 percent in 1998. The use of insulin is also increasing in the UK. There, the prevalence rate of insulin use increased from 2.43 per 1,000 population in 1991 to 6.71 per 1,000 in 2010. The use of insulin in type 2 diabetes increased by a factor of 6.5.(131) This study found that in 1991, most insulin was used by people with type 1 diabetes, but by 2010, the majority of insulin was being used by people with type 2 diabetes.

"Through previous work by the International Insulin Foundation, we have a good understanding of the barriers to insulin access at a country level. We now need to understand the global picture to develop responses in order to make access to insulin a reality globally."

David Beran, Geneva University Hospitals and University of Geneva and ACCISS Co-investigator

5 Data for the USA is for treatment of diabetes amongst people aged 18 years or older, so combines both type 1 and 2 diabetes; however, the source does not disaggregate between the two types of diabetes.

CURRENT RESPONSE

Different means of addressing availability and affordability of medicines have been implemented in different contexts and by different organisations. One such example is bulk procurement, which has been implemented by a small group of Eastern Caribbean countries that joined together to purchase their medicines.(132) This allows these countries to benefit from increased bargaining power because larger quantities are purchased through this mechanism than if each country bought their medicines individually. The Asthma Drug Facility (ADF), which was established by the International Union Against Tuberculosis and Lung Disease, also used pooled procurement and purchasing mechanisms in order to get the lowest possible price for asthma medicines for multiple countries.(133, 134)

A lesson from HIV/AIDS has been the procurement of medicines from generic producers, which has allowed for savings of over 50 percent.(135, 136) An issue with generic manufacturers is concern about whether the quality of the medicines they produce meets national and international standards. To address this, the WHO has developed a prequalification scheme for medicines for HIV/AIDS, malaria and tuberculosis.(137) This scheme allows countries to know that the producer they are buying their medicines from meets the required standards with regards to good manufacturing practices, as well as giving assurance on the quality and efficacy of the products.

For ARVs, Waning et al.(136) describe how different approaches have been taken to decrease prices of medicines. For example, the Global Fund to Fight AIDS, TB and Malaria used pooled procurement of medicines for these three conditions, while the Clinton Foundation HIV/AIDS Initiative negotiates prices with suppliers and provides technical support to suppliers to help them lower costs. Differential pricing was also used through the Accelerating Access Initiative (a private sector collaboration). Other initiatives such as UNITAID and GAVI play the role of market shapers in both bringing down the price of existing medicines and vaccines and promoting research in new technologies.(138, 139) These initiatives are all similar in that they have been extremely well-funded and have taken a vertical approach to addressing specific health problems.

Current Response for Diabetes

In 1989, the St. Vincent Declaration brought together the European branches of the WHO and IDF in a call to address diabetes in the scope of the WHO's programme, Health for All.(140) On 4 September, 1993, the newly formed International Society for Paediatric and Adolescent Diabetes (ISPAD) developed the Kos Declaration, which stated that it would work towards ensuring access to insulin.(141) The African Diabetes Declaration also stated that African governments should ensure adequate, appropriate and affordable medicines and supplies for people with diabetes.(142) In 2007, the UN passed a resolution declaring diabetes to be a major global health threat.(143) Most recently, the IDF launched the Melbourne Declaration in 2013. It stated that "affordable access to healthcare providers and treatments, including insulin, other oral and injectable medicines, self-management supports and technologies can help prevent most of the complications of diabetes."(144) The UN declaration, which served as a basis for the development of the WHO's GAP, included the following resolution: "Efforts to improve access to and affordability of medicines and technologies in the prevention and control of NCDs."(145)

Despite the existence of such statements about improving access to diabetes care throughout the world, many challenges remain with respect to access to optimal care for people with diabetes, especially those who require insulin.

The response, to date, from the diabetes community has focused on models of donation, such as IDF's Life for a Child programme(146), Insulin for Life(147), initiatives led by the pharmaceutical industry(148, 149) or activities focussing on health systems, advocacy and research led by the IIF(150, 151).

IDF's Life for a Child programme is a donation scheme that uses funds and in-kind donations to provide selected countries with insulin for children in need.(146) In addition, the programme supports blood glucose monitoring equipment, appropriate clinical care, HbA1c testing, diabetes education and technical support for health professionals.

IDF also collaborates with Insulin for Life, which distributes emergency diabetes supplies in situations of acute need. Insulin for Life collects and distributes insulin and other diabetes supplies that would otherwise be wasted.(147) IDF also has an Insulin Task Force, which aims to address the issue of access to insulin and other diabetes-related supplies.

Novo Nordisk, one of the leading insulin manufacturers, runs a programme, Changing Diabetes in Children, which is very similar to the activities of Life for a Child.(148) This company also runs two

other projects aimed at lowering the price of insulin to individuals and countries. A differential pricing mechanism for insulin has been established in 35 out of 49 least-developed countries(152), as well as a pricing programme in Kenya where the price of insulin has been set at 500 Kenyan shillings (approximately US$5.70).

The two other leading insulin manufacturers also have initiatives focused on diabetes and NCDs, although not on access to insulin. Lilly has the Lilly NCD Partnership which is working in Brazil, India, Mexico and South Africa to develop models of care focusing on primary care, efficiency of health systems, use of medicines and adherence.(153) The company also donates insulin to the Life for a Child programme, supports diabetes-related projects run by Project Hope, and states that, for least-developed countries, it explores differential pricing and does not enforce intellectual property rights.(154) Although Sanofi has an Access to Medicines Department, this programme does not include access to diabetes medicines.(155) The company has specific projects to address diabetes in schools in Algeria, India and Turkey, as well as other diabetes projects both in North and Sub-Saharan Africa.(156, 157) One such project looked specifically at diabetes foot complications and another used mHealth to inform the public about diabetes and hypertension. In Egypt, the company designed a programme in 2012 to improve access to certain medicines for the most common acute and chronic diseases, including diabetes.(156)

The IIF, a UK-registered charity, was established to understand the general barriers to insulin and diabetes care in LMICs. It has successfully implemented a rapid assessment protocol to understand the barriers to access to diabetes care and proposed concrete recommendations to local stakeholders in Kyrgyzstan, Mali, Mozambique, Nicaragua, Vietnam and Zambia. It also launched the 100 Campaign, which aims to reach 100 percent availability of insulin by the 100th anniversary of the first person to receive insulin in 2022.(158)

Work in Mozambique by the IIF, supported through the Diabetes UK Twinning programme and World Diabetes Foundation, from 2003 to 2009, resulted in improved access to insulin and diagnostic tools. It also helped train health workers in a variety of projects targeted at different areas of the health system and in the development of diabetes associations and a national NCD strategy.(104) The success of this project demonstrated the need to understand the local context, which was achieved using an initial rapid assessment.

> "Perhaps it is time for the diabetes community to embrace the idea of collective impact, which other movements have used to affect change in complex problems."
>
> Professor Mark Atkinson and Dr Graham Ogle(159)

THE WAY FORWARD

In a Lancet paper for World Diabetes Day in 2012, leading academics and advocates working in the area of access to medicines, type 1 diabetes and access to insulin stated the need "to map the global insulin market and develop models to improve access to quality-assured insulin."(158)

A wide set of needs exist for people with type 1 diabetes for proper disease management, including syringes or other methods of insulin administration, blood glucose meters, education and information and family support.(160) Because insulin for the management of type 1 diabetes equals survival, it provides a rare case for a medicine where such an absolute need exists. Given the inequities and inefficiencies in the global insulin market, there is a clear need to develop a scientific approach to addressing the challenges and constraints described above. This was addressed with the launch of an innovative global study, Addressing the Challenge and Constraints of Insulin Sources and Supply (ACCISS), managed by

HAI and funded by a grant from The Leona M. and Harry B. Helmsley Charitable Trust. The objectives of the ACCISS Study are three-fold:

1. To develop and provide a comprehensive, first-of-its-kind evidence base on the global insulin market, including the type, extent and impact of barriers to global insulin access.
2. To develop innovative models of supply, policies and interventions, in collaboration with multiple stakeholders, to overcome barriers to global insulin access by learning from other pioneering access programmes.
3. To develop a network, along with a toolbox of materials, in collaboration with multiple stakeholders, to reduce or eliminate the barriers to global insulin access.

The ACCISS Study comprises multiple phases over a 36-month period. The first phase will establish an overall understanding of the insulin market in terms of volumes, prices, intellectual property, market, trade and other issues. Interviews and site visits to selected manufacturers identified during the first phase will set the stage for work in the second phase. Results from Phase 2 may highlight additional possible manufacturers that could expand the global supply of insulin, as well as act as a first step towards prequalification. In addition, the distribution chain in selected countries will be assessed to measure the 'add-on' costs in the supply chain. The results of the work will be presented at a multi-stakeholder meeting to determine the best way forward to address the issue of access to insulin (Phase 3). This multi-stakeholder meeting will include people living with diabetes, representatives from LMICs (governments and diabetes associations), multi- and bi-lateral donors, WHO Regional Offices and Headquarters, third-party payers, the pharmaceutical industry (originator and generic), regulators, diabetes-related organisations and other parties.

Lessons learned in Phases 1 and 2 of the ACCISS Study will enable project members to present data, discuss issues and offer solutions.(158) Communications work will focus on mapping individuals, organisations, networks, initiatives, media and events that may serve as channels for ACCISS Study materials.

This mapping will help develop a global network of individuals and groups from different sectors (including policymakers, groups representing people living with diabetes, civil society organisations, healthcare professionals, academia and others). This global network will be the main conduit for materials generated from the ACCISS Study. Fact sheets and journal articles will be prepared for sharing with network members, the media, WHO and others. Another benefit of the mapping exercise will be to identify international, regional and national opportunities to present the findings of the ACCISS Study.

As the first step in the ACCISS Study, this report highlights where we currently stand in regard to access to insulin in 2015. There are multiple challenges that the ACCISS Study must address, but given the scientific approach developed and individuals involved, this work will enable the 100 Campaign to achieve its goal of ensuring 100 percent of people living with type 1 diabetes have access to insulin by 2022.

> "Lessons from HIV/AIDS show us that improving access to medicines for a chronic disease in low-income settings is possible. The ACCISS Study has the potential to do the same for insulin."

Richard Laing, Boston School of Public Health and ACCISS Co-investigator

REFERENCES

1. Hardon A. New WHO leader should aim for equity and confront undue commercial influences. Lancet. 2003 Jan 4;361(9351):6. PubMed PMID: 12521037. Epub 2003/01/11. eng.
2. Health Action International. Drug Policy at the 54th World Health Assembly: Increasing and Sustaining Access to Essential Medicines. Amsterdam: Health Action International, 2001.
3. Cameron A, Ewen M, Ross-Degnan D, Ball D, Laing R. Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis. Lancet. 2009 Jan 17;373(9659):240-9. PubMed PMID: 19042012.
4. World Health Organization. WHO to address trade and pharmaceuticals. Geneva: World Health Organization, 1999.
5. Kessel E. Access to essential drugs in poor countries. JAMA. 1999;282(7):630-1; author reply 1.
6. Pecoul B, Chirac P, Trouiller P, Pinel J. Access to essential drugs in poor countries: a lost battle? JAMA. 1999;281(4):361-7.
7. Berman D. AIDS, essential medicines, and compulsory licensing. J Int Assoc Physicians AIDS Care. 1999;5(4):24-5.
8. Chirac P, von Schoen-Angerer T, Kasper T, Ford N. AIDS: patent rights versus patient's rights. Lancet. 2000;356(9228):502.
9. Nicol D. Balancing access to pharmaceuticals with patent rights. Monash Bioeth Rev. 2003;22(2):50-62.
10. Hagmann M. Deadlock on access to cheap drugs at global trade negotiations. Bull World Health Organ. 2003;81(2):150-1. Epub 2003 Mar 25.
11. Attaran A, Gillespie-White L. Do patents for antiretroviral drugs constrain access to AIDS treatment in Africa? JAMA. 2001;286(15):1886-92.
12. Quick J. Essential medicines twenty-five years on: closing the access gap. Health Policy Plan. 2003;18(1):1-3.
13. WHO. Global status report on non-communicable diseases. Geneva: World Health Organization, 2010.
14. Nugent R, Feigl A. Where Have All the Donors Gone? Scarce Donor Funding for Non-Communicable Diseases. Washington D.C.: Center for Global Development, 2011.
15. Stuckler D, King L, Robinson H, McKee M. WHO's budgetary allocations and burden of disease: a comparative analysis. Lancet. 2008 Nov 1;372(9649):1563-9. PubMed PMID: 18984189. Epub 2008/11/06. eng.
16. WHO. Global Action Plan for the Prevention and Control of Non-communicable Diseases 2013-2020 - Revised draft (Version dated 11 February 2013). Geneva: World Health Organization, 2013.
17. UN. Prevention and control of non-communicable diseases: Report of the Secretary-General. New York: United Nations, 2011.
18. UN. The Future We Want. New York: United Nations, 2012.
19. WHO. Monitoring the building blocks of health systems: a handbook of indicators and their easurement strategies. Geneva: World Health Organization, 2010.
20. WHO. A Comprehensive Global Monitoring Framework, Including Indicators, and a Set of Voluntary Global Targets for the Prevention and Control of Noncommunicabale Diseases - Revised WHO Discussion Paper (Version dated 25 July 2012). Geneva: World Health Organization, 2012.
21. WHO. Global status report on non-communicable diseases. Geneva: World Health Organization, 2014.
22. Hogerzeil HV, Liberman J, Wirtz VJ, Kishore SP, Selvaraj S, Kiddell-Monroe R, et al. Promotion of access to essential medicines for non-communicable diseases: practical implications of the UN political declaration. Lancet. 2013 Feb 11. PubMed PMID: 23410612.
23. Beran D, Perrin C, Billo N, Yudkin JS. Improving global access to medicines for non-communicable diseases. The Lancet Global health. 2014 Oct;2(10):e561-2. PubMed PMID: 25304626.
24. Baleta A. AIDS activists force attention to fluconazole in South Africa. Lancet. 2000;356(9241):1584.
25. Brandt AM. How AIDS invented global health. N Engl J Med. 2013 Jun 6;368(23):2149-52. PubMed PMID: 23738542.
26. Clinton W. Turning the tide on the AIDS pandemic. N Engl J Med. 2003;348(18):1800-2.
27. WHO. The pharmaceutical scene 2008-2009. Geneva: World Health Organization, 2010.
28. Lawrence RD. The Diabetic Life 17th ed. London: J. & A. Churchill Ltd; 1965.
29. Madeb R, Koniaris LG, Schwartz SI. The discovery of insulin: the Rochester, New York, connection. Ann Intern Med. 2005;143(12):907-12.
30. Bliss M. The discovery of insulin. Chicago: University of Chicago Press; 1984.
31. Bliss M. The history of insulin. Diabetes Care. 1993;16(Suppl. 3):4-7.
32. Gale EA. Type 1 diabetes in the young: the harvest of sorrow goes on. Diabetologia. 2005;48(8):1435-8.
33. Gale EA. Dying of diabetes. Lancet. 2006;368(9548):1626-8.
34. McLarty D, Swai, ABM and Alberti, KGMM. Insulin availability in Africa: an insoluble problem? International Diabetes Digest. 1994;5:15-7.
35. Alberti K. Insulin: availability and cost. World Health Forum. 1994;15:6.
36. Alberti K. Insulin dependent diabetes mellitus: a lethal disease in the developing world. Bmj. 1994;309(6957):754-5.
37. Deeb L, Tan, MH and Alberti, KGMM. Insulin availability among International Diabetes Federation member associations. Diabetes Care. 1994;17:220-3.
38. Savage A. The Insulin dilemma: a survey of Insulin treatment in the tropics. International Diabetes Digest. 1994;5:19-20.
39. WHO. 18th Model List of Essential Medicines. Geneva: World Health Organization, 2013.
40. Beran D, Yudkin J. Diabetes Care in Sub-Saharan Africa. The Lancet. 2006;368(9548):1689-95.

41. Miller RG, Secrest AM, Sharma RK, Songer TJ, Orchard TJ. Improvements in the life expectancy of type 1 diabetes: the Pittsburgh Epidemiology of Diabetes Complications study cohort. Diabetes. 2012 Nov;61(11):2987-92. PubMed PMID: 22851572. PMCID: 3478551.
42. Abdraimova A, Beran D. Report on the Rapid Assessment Protocol for Insulin Access in Kyrgyzstan. London: International Insulin Foundation, 2009.
43. Beran D, Atlan-Corea C, Tapia B, Martinez AJ. Report on the Rapid Assessment Protocol for Insulin Access in Nicaragua. Managua: International Insulin Foundation and Handicap International, 2007.
44. Beran D, Binh TV, Khue NT, Uoc HK, Toan LQ, Phuong NB, et al. Report on the Rapid Assessment Protocol for Insulin Access in Vietnam. London: International Insulin Foundation, 2009.
45. Beran D, Yudkin J, de Courten M. Access to care for patients with insulin-requiring diabetes in developing countries: case studies of Mozambique and Zambia. Diabetes Care. 2005;28(9):2136-40.
46. Higuchi M. Costs, availability and affordability of diabetes care in the Philippines. Tokyo: Foundation for Advanced Studies on International Development, 2009.
47. IIF. Final Report of the International Insulin Foundation on the Rapid Assessment Protocol for Insulin Access in Mali. London: International Insulin Foundation, 2004.
48. IIF. Report of the International Insulin Foundation on the Rapid Assessment Protocol for Insulin Access in Mozambique. London: International Insulin Foundation, 2004.
49. IIF. Report of the International Insulin Foundation on the Rapid Assessment Protocol for Insulin Access in Zambia. London: International Insulin Foundation, 2004.
50. Beran D, Higuchi M. Delivering Diabetes Care in the Philippines and Vietnam: Policy and Practice Issues. Asia Pac J Public Health. 2011;Epub ahead of print. Epub 3 July 2011.
51. Beran D, Abdraimova A, Akkazieva B, McKee M, Balabanova D, Yudkin JS. Diabetes in Kyrgyzstan: changes between 2002 and 2009. Int J Health Plann Manage. 2013 Apr-Jun;28(2):e121-37. PubMed PMID: 23125073. Epub 2012/11/06. Eng.
52. Randall L, Begovic J, Hudson M, Smiley D, Peng L, Pitre N, et al. Recurrent diabetic ketoacidosis in inner-city minority patients: behavioral, socioeconomic, and psychosocial factors. Diabetes Care. 2011 Sep;34(9):1891-6. PubMed PMID: 21775761. PMCID: 3161256. Epub 2011/07/22. eng.
53. Daley S. Fiscal Crisis Takes Toll on Health of Greeks. New York Times. 2011 26 December.
54. Currie CJ, Peters JR, Evans M. Dispensing patterns and financial costs of glucose-lowering therapies in the UK from 2000 to 2008. Diabet Med. 2010 Jul;27(7):744-52. PubMed PMID: 20636954. Epub 2010/07/20. eng.
55. UN. On World Diabetes Day, Ban urges greater access to health foods, physical activity. UN News Centre. 2013 14 November.
56. Lawson GR, Jefferson I. The Diagnosis (Practical Issues). In: Court S, Lamb B, editors. Childhood and Adolescent Diabetes. Chichester: John Wiley and Sons; 1997.
57. Owens DR, Zinman B, Bolli GB. Insulins today and beyond. Lancet. 2001;358(9283):739-46.
58. Siebenhofer A, Plank J, Berghold A, Jeitler K, Horvath K, Narath M, et al. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. Cochrane Database Syst Rev. 2006 (2):CD003287. PubMed PMID: 16625575.
59. Vardi M, Jacobson E, Nini A, Bitterman H. Intermediate acting versus long acting insulin for type 1 diabetes mellitus. Cochrane Database Syst Rev. 2008 (3):CD006297. PubMed PMID: 18646147.
60. Distiller LA, Joffe BI. From the coalface: does glargine insulin improve hypoglycaemic episodes, glycaemic control or affect body mass in type 1 diabetic subjects who are attending a 'routine' diabetes clinic? Diabetologia. 2006 Nov;49(11):2793-4. PubMed PMID: 17047914. Epub 2006/10/19. eng.
61. WHO. The selection and use of essential medicines: report of the WHO Expert Committee, March 2011 (including the 17th WHO model list of essential medicines and the 3rd WHO model list of essential medicines for children). Geneva: World Health Organization, 2011.
62. ADA. American Diabetes Association: Insulin administration. Diabetes Care. 2001;24(11):1984-7.
63. Daneman D. Type 1 diabetes. Lancet. 2006;367(9513):847-58.
64. Crasto W, Jarvis J, Khunti K, Davies MJ. New insulins and new insulin regimens: a review of their role in improving glycaemic control in patients with diabetes. Postgrad Med J. 2009;85(1003):257-67.
65. Haahr H, Heise T. A review of the pharmacological properties of insulin degludec and their clinical relevance. Clin Pharmacokinet. 2014 Sep;53(9):787-800. PubMed PMID: 25179915. PMCID: 4156782.
66. WHO. WHO Model List of Essential Medicines. Geneva: World Health Organization, 2007.
67. Yudkin JS. Insulin for the world's poorest countries. Lancet. 2000;355(9207):919-21.
68. NCD Alliance. Access to Essential Medicines and Technologies for NCDs. Geneva: NCD Alliance, 2011.
69. 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.
70. Beran D. Improving access to insulin: what can be done? Diabetes Management. 2011;1(1):67-76.
71. Health Action International. Life-saving insulin largely unaffordable - A one day snapshot of the price of insulin across 60 countries 2010 [cited 2010 17 August]. Available from: http://www.haiweb.org/medicineprices/07072010/Global_briefing_note_FINAL.pdf.
72. Schultz K. The global diabetes care market. Novo Nordisk, 2011.
73. Hunter M. Doctors worried about threat to supplies of animal insulin. BMJ. 2002 Jan 19;324(7330):130. PubMed PMID: 11799021. PMCID: 1122063.
74. Mixtard 30 - going, going, gone? Drug and therapeutics bulletin. 2010 Aug;48(8):85. PubMed

PMID: 20685897.
75. Gill GV, Yudkin JS, Keen H, Beran D. The insulin dilemma in resource-limited countries. A way forward? Diabetologia. 2011 Jan;54(1):19-24. PubMed PMID: 20835860. Epub 2010/09/14. eng.
76. National Collaborating Centre for Chronic Conditions. Type 2 Diabetes: National Clinical Guideline for Management in Primary and Secondary Care (Update). London: Royal College of Physicians, 2008.
77. IMS Health. IMS Health MIDAS. London: 2010.
78. Volman B. Direct costs and Availability of Diabetes Medicines in Low-income and Middle-income Countries. Geneva: World Health Organization, Health Action International, 2008.
79. Rotenstein LS, Ran N, Shivers JP, Yarchoan M, Close KL. Opportunities and Challenges for Biosimilars: What's on the Horizon in the Global Insulin Market? Clinical Diabetes. 2012;30(4):138-50.
80. Beran D, Yudkin JS. The double scandal of insulin. J R Coll Physicians Edinb. 2013;43(3):194-6. PubMed PMID: 24087795.
81. Lipska KJ, Ross JS, Van Houten HK, Beran D, Yudkin JS, Shah ND. Use and out-of-pocket costs of insulin for type 2 diabetes mellitus from 2000 through 2010. JAMA. 2014 Jun 11;311(22):2331-3. PubMed PMID: 24915266. PMCID: 4133975.
82. Muller R, Renner C, Gabay C, Cassata G, Lohri A, Hasler P. The advent of biosimilars: challenges and risks. Swiss Med Wkly. 2014;144:w13980. PubMed PMID: 24984255.
83. Wang S. Patent search on biologics as potential biosimilar candidates. World Patent Information. 2011;33:67-71.
84. Minghetti P, Rocco P, Cilurzo F, Vecchio LD, Locatelli F. The regulatory framework of biosimilars in the European Union. Drug Discov Today. 2012 Jan;17(1-2):63-70. PubMed PMID: 21856438.
85. Mulcahy AW, Predmore Z, Matke S. The Cost Savings Potential of Biosimilar Drugs in the United States. RAND Corporation, 2014.
86. Market Watch. Global Insulin Market Expected to Reach USD 32.24 Billion Globally in 2019: Transparency Market Research Albany, N.Y.2014 [cited 2015 6 January]. Available from: http://www.marketwatch.com/story/global-insulin-market-expected-to-reach-usd-3224-billion-globally-in-2019-transparency-market-research-2014-07-25.
87. World Health Oragnization. Core Health Indicators Geneva: World Health Organization; 2005 [cited 2010 27 April]. Available from: http://www.who.int/countries/en/.
88. MSH. International Drug Price Indicator Guide. Medford, MA: Management Sciences for Health, 2013.
89. Yudkin JS. Insulin for the world's poorest countries. Lancet. 2000;355:919-21.
90. WHO. Kyrgyzstan Country Health Profile 2013 [cited 2014 4 février]. Available from: http://www.who.int/countries/kgz/en/.
91. Gill GV, Yudkin JS, Keen H, Beran D. The insulin dilemma in resource-limited countries. A way forward? Diabetologia. 2010 Sep 12. PubMed PMID: 20835860. Epub 2010/09/14. Eng.
92. HAI. Database of medicine prices, availability, affordability and price components 2012 [cited 2015 9 July]. Available from: http://www.haiweb.org/MedPriceDatabase/
93. Management Sciences for Health. International Drug Price Indicator Guide West Hartford, CT: Management Sciences for Health; 2008 [cited 2010 27 April]. Available from: http://erc.msh.org/dmpguide/searchresult.cfm?module=dmp&language=english&year=2008&type=byname.
94. IIF. Diabetes Foundation Report on insulin-requiring diabetes in Sub-Saharan Africa. London: International Insulin Foundation, 2005.
95. IDF Insulin Task Force. Report on the International Insulin and Diabetes Supplies Survey on Cost and Availability. Brussels: International Diabetes Federation, 2006.
96. Currie CJ, Gale EA, Poole CD. Estimation of primary care treatment costs and treatment efficacy for people with Type 1 and Type 2 diabetes in the United Kingdom from 1997 to 2007*. Diabet Med. 2010 Aug;27(8):938-48. PubMed PMID: 20653753. Epub 2010/07/27. eng.
97. Holden SE, Poole CD, Morgan CL, Currie CJ. Evaluation of the incremental cost to the National Health Service of prescribing analogue insulin. BMJ Open. 2011 Jan 1;1(2):e000258. PubMed PMID: 22021891. PMCID: 3191605.
98. Kirigia JM, Sambo HB, Sambo LG, Barry SP. Economic burden of diabetes mellitus in the WHO African region. BMC Int Health Hum Rights. 2009;9:6. PubMed PMID: 19335903. PMCID: 2674592. Epub 2009/04/02. eng.
99. Barcelo A, Aedo C, Rajpathak S, Robles S. The cost of diabetes in Latin America and the Caribbean. Bull World Health Organ. 2003;81(1):19-27. Epub 2003 Mar 11.
100. Chale S, McLarty D. The Economics of Diabetes Care: Africa. In: Alberti K, Zimmet P, DeFronzo R, Keen H, editors. International Textbook of Diabetes Mellitus, Second Edition. London: Wiley & Sons Ltd; 1997.
101. Elrayah H, Eltom M, Bedri A, Belal A, Rosling H, Ostenson CG. Economic burden on families of childhood type 1 diabetes in urban Sudan. Diabetes Res Clin Pract. 2005;70(2):159-65.
102. Altamirano-Bustamante N, Islas-Ortega L, Robles-Valdes C, Garduno-Espinosa J, Morales-Cisneros G, Valderrama A, et al. Economic family burden of metabolic control in children and adolescents with type 1 diabetes mellitus. J Pediatr Endocrinol Metab. 2008;21(12):1163-8.
103. 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 Jun;88(3):217-21. PubMed PMID: 20447710. Epub 2010/05/08. eng.
104. Beran D, Silva Matos C, Yudkin JS. The Diabetes UK Mozambique Twinning Programme. Results of improvements in diabetes care in Mozambique: a reassessment 6 years later using the Rapid Assessment Protocol for Insulin Access. Diabet Med. 2010 Aug;27(8):855-61. PubMed PMID: 20653740. Epub 2010/07/27. eng.
105. Mendis S, Fukino K, Cameron A, Laing R, Filipe A, Jr., Khatib O, et al. The availability and affordability of selected essential medicines

for chronic diseases in six low- and middle-income countries. Bulletin of the World Health Organization. 2007 Apr;85(4):279-88. PubMed PMID: 17546309. eng.
106. Boddiger D. Lack of insurance hinders Americans' diabetes care. Lancet. 2006;368(9529):15-6.
107. Beran D, Higuchi M. Delivering diabetes care in the Philippines and Vietnam: policy and practice issues. Asia Pac J Public Health. 2013 Jan;25(1):92-101. PubMed PMID: 21727084.
108. UNICEF. Zambia 2014 [cited 2014 25 February]. Available from: http://www.unicef.org/infobycountry/zambia_statistics.html.
109. Chimpinde K. Lowest-paid govt worker to get K2.9m net Lusaka: The Post Online; 2013 [cited 2014 25 February]. Available from: http://www.postzambia.com/Joomla/post-read_article.php?articleId=30703.
110. Gale EA. Is there really an epidemic of type 2 diabetes? Lancet. 2003;362(9383):503-4.
111. Muyer MT, Buntinx F, Mapatano MA, De Clerck M, Truyers C, Muls E. Mortality of young patients with diabetes in Kinshasa, DR Congo. Diabet Med. 2010 Apr;27(4):405-11. PubMed PMID: 20536511. Epub 2010/06/12. eng.
112. IDF. International Diabetes Federation Diabetes Atlas 6th Edition. Brussels: International Diabetes Federation, 2013.
113. Green A, Patterson CC. Trends in the incidence of childhood-onset diabetes in Europe 1989-1998. Diabetologia. 2001;44(Suppl 3):B3-8.
114. EURODIAB ACE Study Group. Variation and trends in incidence of childhood diabetes in Europe. EURODIAB ACE Study Group. Lancet. 2000;355(9207):873-6.
115. Gopinath S, Ortqvist E, Norgren S, Green A, Sanjeevi CB. Variations in incidence of type 1 diabetes in different municipalities of Stockholm. Ann N Y Acad Sci. 2008;1150:200-7.
116. Aschner P. Diabetes trends in Latin America. Diabetes Metab Res Rev. 2002;18(Suppl 3):S27-31.
117. Yang Z, Wang K, Li T, Sun W, Li Y, Chang YF, et al. Childhood diabetes in China. Enormous variation by place and ethnic group. Diabetes Care. 1998;21(4):525-9.
118. Motala A. Diabetes trends in Africa. Diabetes Metab Res Rev. 2002;18(Suppl 3):S14-20.
119. Guariguata L. Estimating the worldwide burden of type 1 diabetes. Diabetes Voice. 2011;56(2):6-8.
120. Chiang JL, Kirkman MS, Laffel LM, Peters AL, Type 1 Diabetes Sourcebook A. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. Diabetes Care. 2014 Jul;37(7):2034-54. PubMed PMID: 24935775.
121. JDRF. Statistics: JDRF and Diabetes New York2015 [cited 2015 4 February]. Available from: http://jdrf.org/about-jdrf/fact-sheets/jdrf-and-diabetes-statistics/.
122. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: pathogenesis and treatment. Lancet. 2008 Jun 28;371(9631):2153-6. PubMed PMID: 18586159.
123. Dale J, Martin S, Gadsby R. Insulin initiation in primary care for patients with type 2 diabetes: 3-year follow-up study. Prim Care Diabetes. 2010 Jul;4(2):85-9. PubMed PMID: 20392683.
124. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):854-65. PubMed PMID: 9742977.
125. Holman N, Young B, Gadsby R. What is the current prevalence of diagnosed and yet to be diagnosed diabetes in the UK. Diabet Med. 2014 May;31(5):510-1. PubMed PMID: 24460635.
126. Belhadj M, Malek R, Boudiba A, Lezzar E, Roula D, Sekkal F, et al. DiabCare Algérie. Médecine Mal Métaboliques. 2011;5(4):24-8.
127. Soewondo P, Soegondo S, Suastika K, Pranoto A, Soeatmadji D, Tjokroprawiro A. The DiabCare Asia 2008 study – outcomes on control and complications of type 2 diabetic patients in Indonesia. Med J Indones. 2010;19(4):235–44.
128. Aekplakorn W, Stolk RP, Neal B, Suriyawongpaisal P, Chongsuvivatwong V, Cheepudomwit S, et al. The prevalence and management of diabetes in Thai adults: the international collaborative study of cardiovascular disease in Asia. Diabetes Care. 2003 Oct;26(10):2758-63. PubMed PMID: 14514576.
129. CDC. National Diabetes Statistics Report 2014. Atlanta: Centers for Disease Control, 2014.
130. Detournay B, Raccah D, Cadilhac M, Eschwege E. Epidemiology and costs of diabetes treated with insulin in France. Diabetes Metab. 2005 Jun;31(3 Pt 2):3-18. PubMed PMID: 16142041.
131. Holden SE, Gale EA, Jenkins-Jones S, Currie CJ. How many people inject insulin? UK estimates from 1991 to 2010. Diabetes Obes Metab. 2014 Jan 10. PubMed PMID: 24410846.
132. Huff-Rousselle M, Burnett F. Cost containment through pharmaceutical procurement: a Caribbean case study. Int J Health Plann Manage. 1996;11(2):135-57.
133. Ait-Khaled N, Enarson DA, Bissell K, Billo NE. Access to inhaled corticosteroids is key to improving quality of care for asthma in developing countries. Allergy. 2007;62(3):230-6.
134. Billo N. Asthma drug facility: from concept to reality. Int J Tuberc Lung Dis. 2006;10(7):709.
135. Chien CV. HIV/AIDS drugs for Sub-Saharan Africa: how do brand and generic supply compare? PLoS One. 2007;2(3):e278. PubMed PMID: 17372625. PMCID: 1805689. Epub 2007/03/21. eng.
136. Waning B, Kaplan W, King AC, Lawrence DA, Leufkens HG, Fox MP. Global strategies to reduce the price of antiretroviral medicines: evidence from transactional databases. Bulletin of the World Health Organization. 2009 Jul;87(7):520-8. PubMed PMID: 19649366. PMCID: 2704041.
137. World Health Oragnization. Prequalification Programme Geneva2010 [cited 2010 4 May]. Available from: http://apps.who.int/prequal/default.htm.
138. WHO. About UNITAID 2013 [cited 2013 11 November]. Available from: http://www.unitaid.eu/en/who/about-unitaid.
139. GAVI Alliance. GAVI's strategy 2013 [cited 2013 11 November]. Available from: http://www.gavialliance.org/about/strategy/.
140. Diabetes care and research in Europe: the Saint Vincent declaration. Diabet Med. 1990 May;7(4):360. PubMed PMID: 2140091.

141. ISPAD. International Society for Pediatric and Adolescent Diabetes: Declaration of Kos. Pediatric Diabetes. 2007;8:7.
142. IDF, WHO AFRO, AU. African Diabetes Declaration. International Diabetes Federation, World Health Organization AFRO Region and African Union, 2006.
143. United Nations General Assembly. World Diabetes Day. New York: United Nations, 2007 Contract No.: 61/225.
144. IDF. Melbourne Declaration Melbourne: International Diabetes Federation; 2013 [cited 2015 6 February]. Available from: https://www.idf.org/sites/default/files/Melbourne_Declaration.pdf
145. UN General Assembly. Political Declaration of the High-level Meeting of the General Assembly on the Prevention and Control of Non-communicable Diseases. New York: United Nations General Assembly, 2012 Contract No.: 66/2.
146. Life for a Child. Life for a Child 2013 [cited 2014 11 March]. Available from: http://www.lifeforachild.idf.org/.
147. Insulin for Life. Insulin for Life 2011 [cited 2014 11 March]. Available from: http://www.insulinforlife.org/navigate-to/about-us.html.
148. Novo Nordisk. Changing Diabetes in Children 2010 [cited 2014 11 March]. Available from: http://www.changingdiabetesaccess.com/programmes_and_partnerships/diabetes_in_children.asp.
149. Novo Nordisk. Access to Health: Our approach. Novo Nordisk, 2011.
150. IIF. The International Insulin Foundation: International Insulin Foundation; 2015 [cited 2015 6 February]. Available from: http://www.access2insulin.org.
151. IIF. 100 Campaign: International Insulin Foundation; 2015 [cited 2015 6 February]. Available from: http://www.100campaign.org.
152. Novo Nordisk. Novo Nordisk Annual Report 2013. Novo Nordisk, 2013.
153. Lilly. The Lilly NCD Partnership: Eli Lilly and Company; 2015 [cited 2015 18 February]. Available from: http://www.lilly.com/Responsibility/access-to-medicines/Pages/the-lilly-ncd-partnership.aspx.
154. Lilly. Access to Medicines: Eli Lilly and Company; 2015 [cited 2015 18 February]. Available from: http://www.lilly.com/Responsibility/access-to-medicines/Pages/access-to-medicines.aspx - 6.
155. Sanofi. Caring for the most disadvataged patients: Sanofi; 2014 [cited 2015 18 February]. Available from: http://en.sanofi.com/csr/patient/priorities/access_to_care/access_to_medicines/access_to_medicines.aspx.
156. Sanofi. Sanofi and Africa: A sustained commitment to serving patients. Paris: Sanofi, 2014.
157. Sanofi. Access to care: Addressing diabetes in schools in Turkey and India: Sanofi; 2014 [cited 2015 18 February]. Available from: http://en.sanofi.com/csr/patient/in_action/access_to_care/access_to_care.aspx.
158. Beran D, Basey M, Wirtz V, Kaplan W, Atkinson M, Yudkin JS. On the road to the insulin centenary. Lancet. 2012;380(9854):1648.
159. Atkinson MA, Ogle GD. Improving diabetes care in resource-poor countries: challenges and opportunities. The lancet Diabetes & endocrinology. 2013 Dec;1(4):268-70. PubMed PMID: 24622408.
160. Beran D. Developing a hierarchy of needs for Type 1 diabetes. Diabet Med. 2014 Jan;31(1):61-7. PubMed PMID: 23869848.

Health Action International
Overtoom 60 (2)
1054 HK Amsterdam
The Netherlands
+31 20 412 4523
www.haiweb.org

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