ACCESS TO INSULIN: CURRENT CHALLENGES AND CONSTRAINTS

Update March 2017

acciss
Addressing the Challenge and Constraints of Insulin Sources and Supply

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Contents

Acronyms

ACCISS	Addressing the Challenge and Constraints of Insulin Sources and Supply
ADF	Asthma Drug Facility
AFRO	WHO Regional Office for Africa
AMRO	WHO Regional Office for the Americas
ARV	Antiretroviral
Canada Drug Product Database	Canadian Online Drug Product Database Online Query and its Patent Register
COMTRADE	United Nations Commodity Trade Statistics
Eli Lilly	Eli Lilly and Company
EMRO	WHO Regional Office for the Eastern Mediterranean
EURO	WHO Regional Office for Europe
GCC	Gulf Cooperation Council
HAI	Health Action International
HIC	High income country
HIV/AIDS	Human Immunodeficiency Virus / Acquired Immune Deficiency Syndrome
LIC	Low income country
LMIC	Lower- and middle-income countries
MSH	Management Sciences for Health
NCD	Non-communicable disease
NEML	National Essential Medicines List
NMRA	National Medicine Regulatory Agencies
Orange Book	US Food and Drug Administration's Orange Book
SEARO	WHO Regional Office for South-East Asia
UMIC	Upper- middle income country
UNRWA	United National Relief and Works Agency for Palestine Refugees
US	United States
UK	United Kingdom
VAT	Value Added Tax
WHO	World Health Organization
WPRO	WHO Regional Office for the Western Pacific

Note: All prices for insulin if not otherwise stated are standardised to 10ml of 100IU/ml insulin in US dollars.

Executive Summary

The Addressing the Challenge and Constraints of Insulin Sources and Supply (ACCISS) Study has completed its first phase of work, which aimed to gain an overall understanding of the insulin market through different profiles. These included profiles on the insulin market, intellectual property, insulin trade, prices, and taxes and tariffs. The main lessons from this work are presented in this report. The full profiles are referenced and available on the Health Action International website[a].

From the insulin market profile 40 independent insulin manufacturers were identified in 17 countries, however following additional discussions and reviews it would seem that there are probably only 10 independent insulin manufacturers globally. A total of 55 countries had 1,985 insulin products registered. Of these, 58 percent were human insulin, 38 percent were analogue insulin, three percent were animal insulin, and one percent was unknown. Novo Nordisk had the highest number of registered products (719) followed by Eli Lilly and Company (470) and Sanofi (369). Together, these companies represent 88 percent of total product registrations globally. Only two countries did not list any insulin on their National Essential Medicines List. In looking at insulin use in people with type 2 diabetes, the literature showed a range from 2.4 percent in Taiwan to 23.5 percent in the United States.

Regarding intellectual property, no patents were found for human insulin. For analogue insulins, 61 patents were found in the United States Food and Drug Administration's Orange Book and eight patents were listed in the Canadian Online Drug Product Database Online Query and its Patent Register. For products already marketed in the United States and Canada, Eli Lilly and Company, Novo Nordisk, and Pfizer will have their patents expire by 2023. Sanofi has an additional 10 years of protection for these products.

The trade profile gives a unique insight into the overall insulin market. In looking at exports between 2003 and 2013, 10 countries made up 98 percent to 99 percent of the global value of retail insulin exports. Over this period, Denmark, France, and Germany collectively exported between 85 percent to 96 percent of global retail insulin by value. Fifty percent of global imports were to the United States, United Kingdom, Germany, and Japan. Around 60 countries (mostly low- and middle income countries with no local insulin manufacturing) imported insulin from only one country for at least one year, making then vulnerable to disruptions in supply.

Data from different sources were used to develop an overall understanding of the varying price of insulin. Data from Management Sciences for Health for 1996 to 2013 shows that median supplier and buyer prices for human insulin were, on average, US$5.30 and US$4.31, respectively, for 10ml 100IU/ml of human insulin. A difference between the price of insulin versus other non-communicable disease medicines was seen when looking at the overall range of prices for defined daily doses. Insulin had the smallest range over the period of analysis. Over the time period, all antiretrovirals and simvastatin were at one point higher priced than insulin. At the end of the analysis only zidovudine remained higher priced than insulin. Looking at government procurement prices for 10ml 100IU/ml insulin, human insulin was more often procured and were lower priced (median US$5.99) than analogue insulin (US$34.20). Procurement prices varied across countries e.g. regular/isophane (premixed) 30/70 insulin ranged from US$2.24 in Pakistan to US$32.00 in the Kyrgyzstan. Presentation of insulin also had an impact on price. Across the five insulin types with the most price points (aspart, glargine, isophane, regular, and premixed 30/70), vials (US$5.84) were lower priced than cartridges (US$17.93) and pens (US$27.31).

[a] http://haiweb.org/what-we-do/acciss/

For insulin users, the median price in the public sector was US$7.64 for human insulin and US$45.03 for analogue. A similar picture was seen in the private sector with analogue insulin higher priced (US$39.35) than human insulin (US$16.65). Overall, insulins were unaffordable for those on low incomes. Mean affordability in the public sector was 2.5 days' wages for human insulin, and 7.5 day's wages for analogue insulin. In the private sector, it was 3.5 and 9.5 days' wages for human and analogues insulin, respectively. Reimbursement price for human and analogue insulin was also high at US$19.14 and US$27.90, respectively.

Different mark-ups along the supply chain, including tariffs and taxes, impact the final price of insulin to individuals. The proportion of countries without tariffs on insulin has increased since 2004 from 52 percent to 77 percent. Global weighted average import tariffs have decreased from slightly less than 3.5 percent (2004) to about 1.9 percent (2013). Value added tax on insulin ranged from 0-24 percent.

The profiles and other data within this report provide a unique addition to the information presented previously by the ACCISS Study. Although this data needs to be complemented by on-going work, it already highlights some areas of possible intervention. It also confirms from different data perspectives the dominance of Eli Lilly and Company, Novo Nordisk, and Sanofi with regards to the global insulin market. Although other insulin manufacturers have been identified based on data available, their size and market penetration seems to be low. Another factor that has again been highlighted by this work is the high price of insulin–both for governments when purchasing insulin and for insulin users when forced to pay out-of-pocket. The price of human insulin based on Management Sciences for Health data has remained stable over time in comparison to other non-communicable disease medicines and those used in the treatment of HIV/AIDS. Insulin affordability is poor in both the public and private sectors in many countries. Unlike for many other medicines, intellectual property is not an issue for insulin itself.

With the completion of this phase of its work, the ACCISS Study has further contributed to a better understanding of the insulin market. And as it progresses into its final year, the information collected to date, as well as additional research, will assist in developing interventions to address the challenge of access to insulin.

"People with diabetes who depend on life-saving insulin pay the ultimate price when access to affordable insulin is lacking."
Margaret Chan Director General of the World Health Organization (1)

1. Background

Insulin for type 1 diabetes is a rare example where there is an absolute need for a given medicine. According to the International Diabetes Foundation, approximately 542,000 children aged 0-14 have type 1 diabetes and the prevalence is increasing by three percent per year.(2) Although global disease burden data is lacking and there are no statistics on the total amount of people living with type 1 diabetes, it is estimated they represent five percent of the total diabetes burden, of 514 million, or 20.8 million people.(3) In contrast, use of insulin in the management of type 2 diabetes is required for better control and its use is dependent on capabilities existing within different health systems.

Previous work by the Addressing the Challenge and Constraints of Insulin Sources and Supply (ACCISS) Study highlighted the poor availability and affordability of insulin.(4, 5) The factors leading to this included a variety of barriers at global and national level. 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, Eli Lilly and Company (Eli Lilly), Novo Nordisk, and Sanofi.(6) This domination has also meant that individuals with diabetes have had to change types of insulin as these companies have the ability to withdraw formulations from the market.(7, 8)

The ACCISS Study has completed its first phase of work, which aimed to gain an overall understanding of the insulin market. This was achieved by profiling the insulin market, intellectual property issues, insulin trade, prices at different levels of the health system, and tariffs and taxes on insulin. Key findings from the profiles are presented in this report.

2.The Global Insulin Market

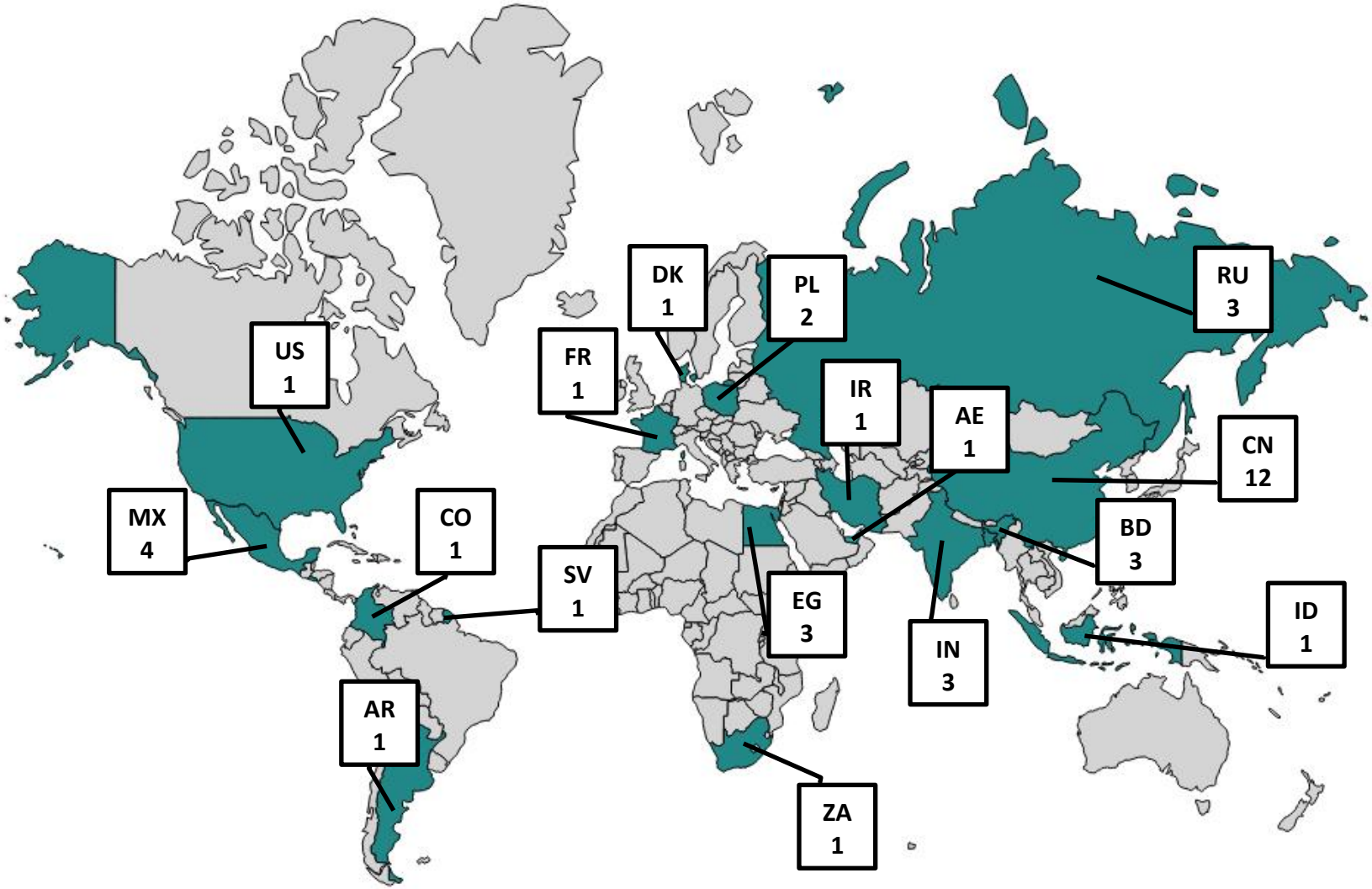
The aim of this research was to describe key aspects of the insulin market in order to better understand the supply and demand of insulin globally. The *Insulin Market Profile* researched and analysed data on the following topics, amongst others: identification of insulin manufacturers; insulin formulations registered in different countries; of the inclusion of insulin in National Essential Medicines Lists (NEML); and two systematic reviews looking at the use of insulin in type 2 diabetes.(9)

2.1. Who Makes Insulin

Each company's role as manufacturer, licensed manufacturer, subsidiary, distributor, or other (e.g. no involvement in the insulin market) was determined from product listings, other summary information, and references to insulin production on the company websites. Data was collected from business market and industry reports, academic databases, and search engines (such as Google©).

In total, 40 independent insulin manufacturers were identified in 17 countries. (Figure 1) Twelve companies were located in China, four in Mexico and three in Bangladesh, Egypt, India and Russia. (Annex 1) During 2016, a number of the companies were found to be distributors or not independent insulin manufacturers due to links with other companies (for example through licensing agreements). Based on additional discussions and reviews it would seem that there are probably only 10 independent insulin manufacturers globally.

Figure 1. Number of identified insulin manufacturers within each of 17 countries (country names abbreviated).



2.2. Which Insulin Products are Registered and Where?

Using the list of National Medicine Regulatory Agencies (NMRA) websites available from the World Health Organization (WHO), each NMRA website was searched for information on current marketing authorisations for insulin products (i.e. registration status). A total of 55 countries had 1,988 insulin products registered. Of these, 58 percent were human insulin, 38 percent were analogues, three percent were animal insulin and one percent were not stated. (Annex)

On average, there were 36 products registered per country. Looking at numbers of registered products per WHO region, on average the WHO Regional Office for Africa (AFRO) countries and WHO Regional Office for the Americas (AMRO) countries had 28 products; WHO Regional Office for the Eastern Mediterranean (EMRO) countries had 35, WHO Regional Office for Europe (EURO) countries 39, WHO Regional Office for the South-East Asia (SEARO) countries 29, and WHO Regional Office for the Western Pacific (WPRO) countries 52. (Figure 2) Proportions of different insulin formulations also varied across country income groups. (Figure 3) The percentage of registered human insulin products decreased with increasing national wealth based on World Bank income groups (68 percent in low- income countries (LICs); 62 percent: upper- middle income countries (UMICs) and 50 percent: high-income countries (HICs)). In contrast, the percentage registration of analogues increased with increasing national wealth (29 percent: LIC; 47 percent: UMICs, and 43 percent: HICs).

Figure 2. Number of insulin products registered by type and WHO Region.

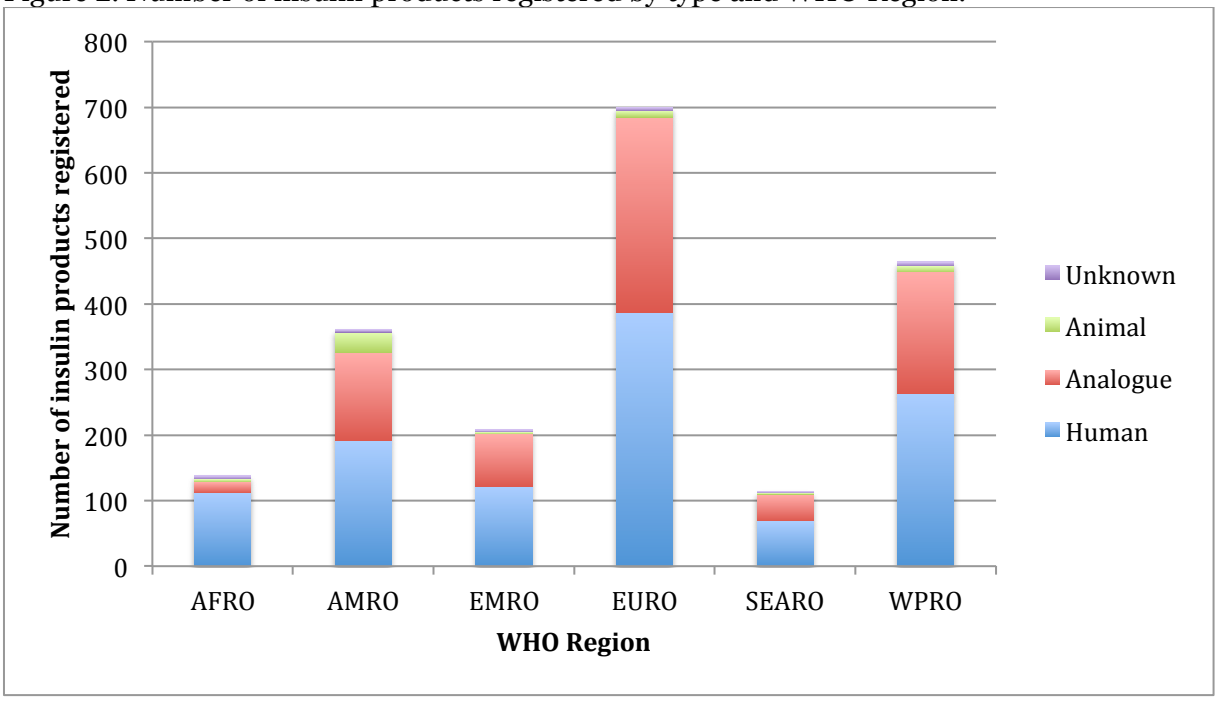
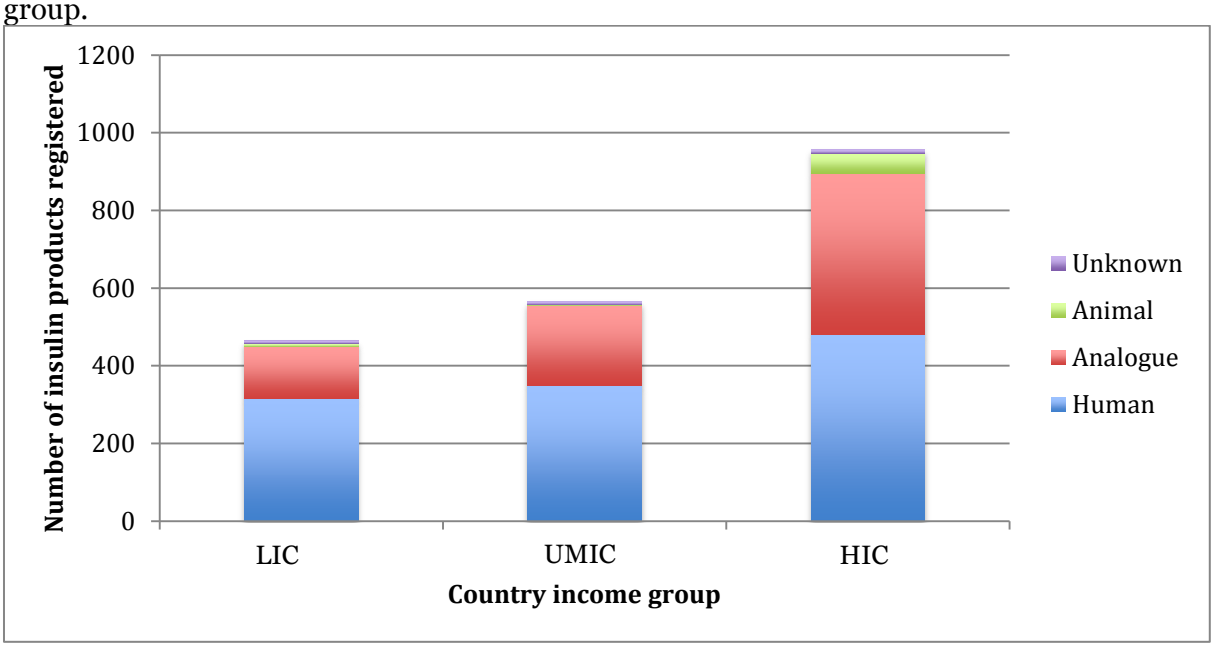
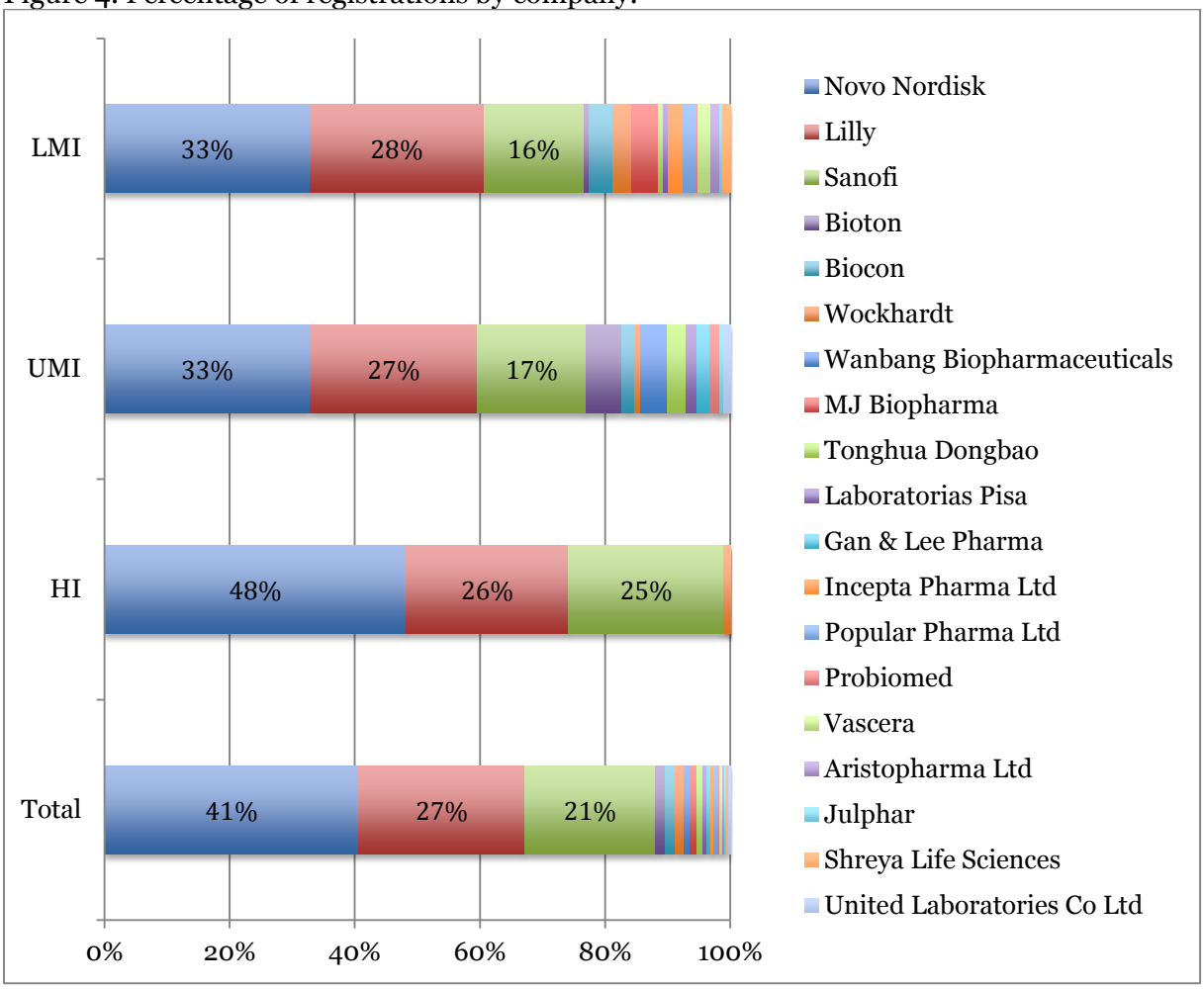


Figure 3. Number of insulin products registered by type and World Bank country income group.



In looking at manufacturers, Novo Nordisk had the highest number of registered products (719), followed by Eli Lilly (470) and Sanofi (369). Together, these three companies represent 88 percent of total product registrations. (Figure 4)

Figure 4. Percentage of registrations by company.



In LICs and UMICs, Eli Lilly, Novo Nordisk, and Sanofi represented a combined total of 76 percent and 77 percent of total products registered, respectively. Twelve other companies had products registered in UMICs, and 14 in LICs. In HICs, 91 percent of registered insulin products were made by Eli Lilly, Novo Nordisk, and Sanofi, with only one other company (Wockhardt) having products registered in this income group.

2.3. Is Insulin on NEMLs?

Only human insulin is included on the WHO's model EML. A total of 100 NEMLs were identified (using Ministry of Health/country contacts when most recent list not available on WHO website).(Annex) Soluble insulin was listed by 98 countries and 97 countries listed intermediate-acting human insulin. Syria was excluded from the insulin analysis since it did not specify any insulin type. Burundi and Djibouti from the WHO AFRO and EMRO regions were the only two countries that did not list soluble insulin injection on their NEML. Across the 100 countries, Bangladesh, from the WHO SEARO region, is the only country that does not list intermediate-acting human insulin. Of these countries, nine included a rapid-acting analogue and 13 included a long-acting analogue on their NEML.

2.4. Use of Insulin in Type 2 Diabetes

As noted by Holden et al. (10) in 1991 in the United Kingdom (UK) most insulin was used by people with type 1 diabetes. However, by 2010 type 2 diabetes represented about 90 percent of diabetes cases, and most insulin was being used by people with type 2 diabetes. To uncover more about the use of insulin in people living with type 2 diabetes, PubMed was used to

identify relevant literature including cross-sectional database studies, case series and cohort studies containing outcome data for the period between 2000 and 2015.

Use of these studies was challenging, as many were not specific between use of insulin in people with type 1 and type 2 diabetes. There were no clear trends in insulin consumption levels across the six WHO regions. While two publications regarding countries in the WPRO region showed low consumption levels (Malaysia 6.5 percent and Taiwan 2.4 percent), all other regions with more than one publication had large variations between studies. For example, in the United States (US), values ranged from 15.1 percent to 27.1 percent, and European studies ranged from 6.9 percent in France to 40.5 percent in Italy. Countries in the SEARO region also exhibited a significant range of values, with a low of 2.8 percent in Thailand to a high of 36.8 percent in Indonesia. Use of insulin specifically for type 2 diabetes was found to range from 2.4 percent in Taiwan to 23.5 percent in the US.

3.The Intellectual Property Landscape

To investigate the insulin patent landscape in the *Insulin Patent Profile*, the US Food and Drug Administration's Orange Book (Orange Book) and the Canadian Online Drug Product Database Online Query and its Patent Register (Canada Drug Product Database) were used, searching the word "insulin".(11,12) In identifying the companies who had patents for insulin, the search was extended to include the World Intellectual Property Organization PatentScope database, the European Patent Office's International Patent Documentation database, and various country-specific patent offices to give a more global view of the issue.

In general, the search found no patents listed for human insulin. For analogue insulins, 61 patents were found in the Orange Book and eight patents were listed in Canada Drug Product Database.(13) The detail of these, by company, is given in Table 1.

Table 1. US and Canadian patents on analogues by company.

Company	US patent	Canadian patent
Eli Lilly	45	3
Novo Nordisk	13	2
Pfizer	0	1
Sanofi	3	2

Data from the global databases show that most patents on insulin are filed in HICs and UMICs, with very few in low- and middle-income countries (LMICs).

In looking at the expiry of patents, an analysis was done for insulin products already marketed in the US and Canada (Figure 5). Three companies (Eli Lilly, Novo Nordisk, and Pfizer) will have many of their patents expire by 2023. Sanofi has an additional 10 years of patent protection for their products. For products in development, Novo Nordisk and Sanofi both have patents that will expire in the early 2030s, whereas Pfizer and Eli Lilly's patents expire in 2023 and 2024, respectively. (Figure 6)

Figure 5. Cumulative percent of patent expiries of insulins marketed in the US and Canada by company.

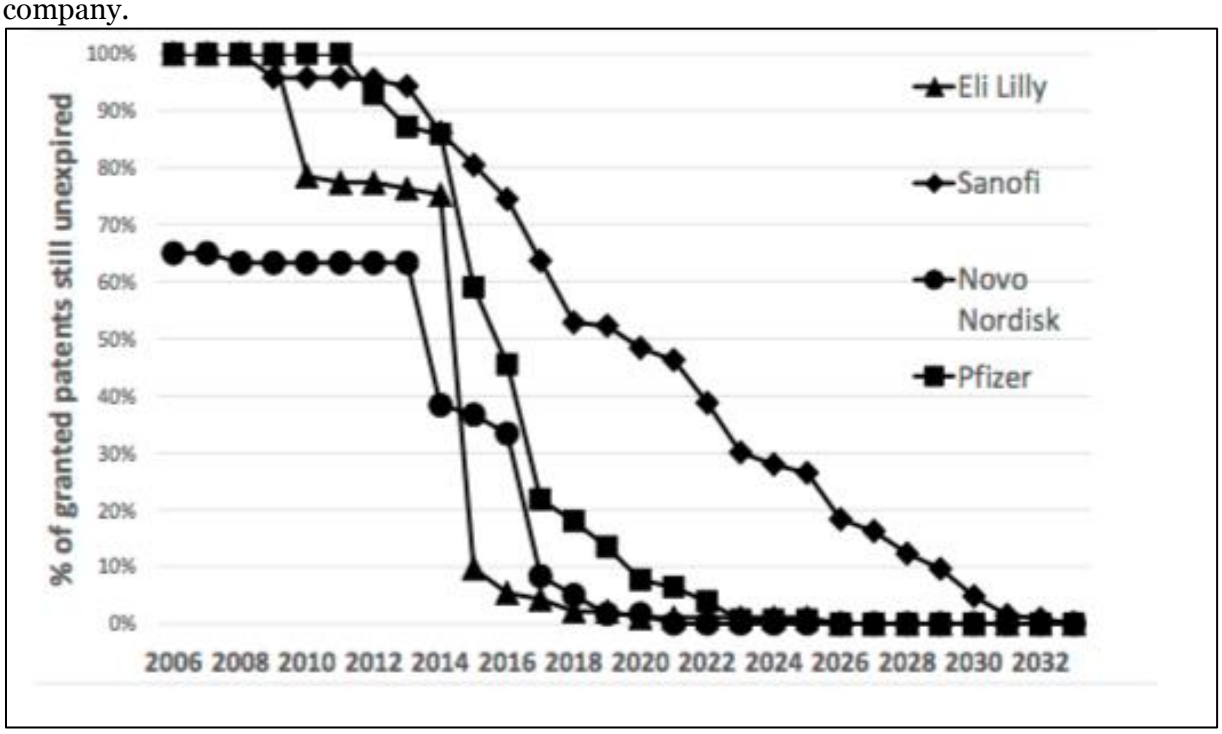
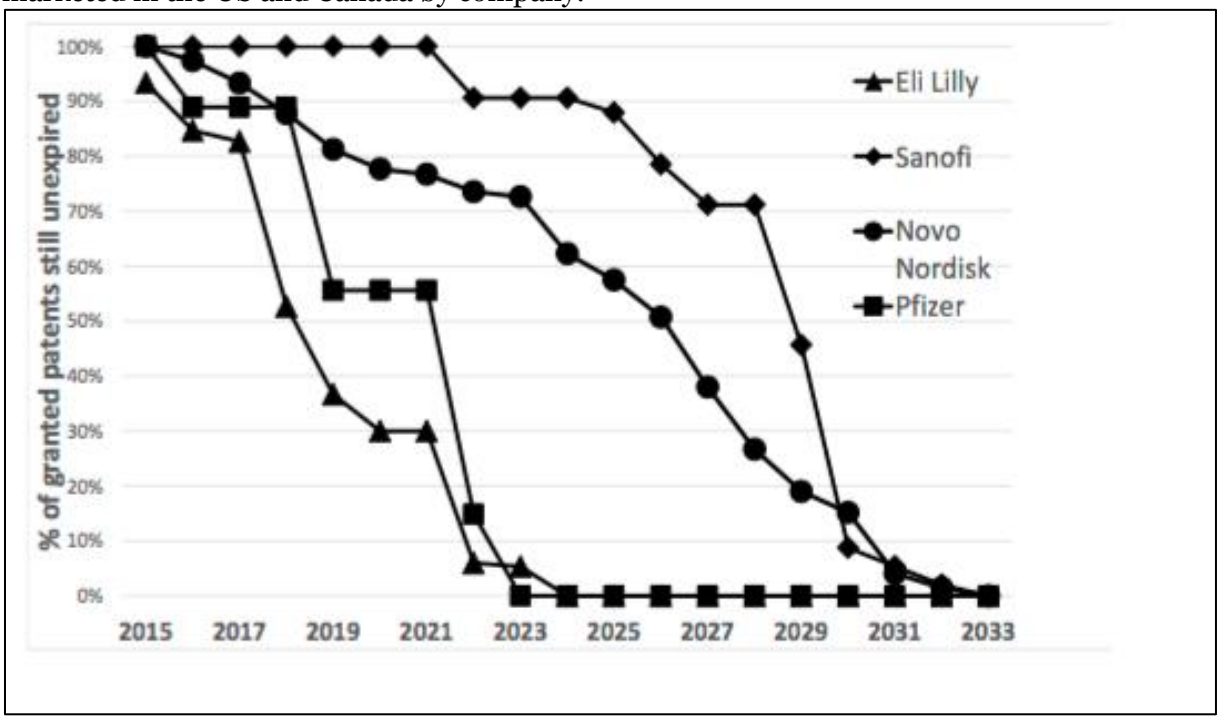


Figure 6. Cumulative percent of patent expiries of insulins under development and/or not marketed in the US and Canada by company.



This data shows that for insulin products already on the market, key patents on analogue insulin have already expired. This was reinforced by the recent work of Luo and Kesselheim (14) and Beall et al. (15) in the US, which found that intellectual property cannot be seen as a barrier to entry for biosimilar manufacturers. In looking at patents in the US, Luo and Kesselheim found 19 active patents on insulin in 2014, with 10 filed by Novo Nordisk, six by Sanofi, and three by Eli Lilly. Of concern was that more than half of these patents were for insulin delivery devices, rather than the insulin itself.

4. Insulin Trade

To create the *Insulin Trade Profile*, insulin imports and exports by value and volume were analysed by country from 2003-2013 using the United Nations Commodity Trade Statistics (COMTRADE) database. Insulin is a unique case for medicines, as a specific category exists to track global trade.

In looking at exports over the time period 2003-2013, 10 countries made up 98 percent to 99 percent of the global value of retail insulin exports. Denmark, France, and Germany collectively exported between 85 percent to 96 percent of global retail insulin by value. In 2013, Germany represented 46 percent of total insulin by value, Denmark 24 percent and France 15 percent. Brazil and Italy increased their exports over this time period, but they remained low at 6.5 percent and 3.7 percent respectively in 2013.

For imports, 20 countries made up 85 percent to 87 percent of the global value of retail insulin imports from 2004-2013. Fifty percent of global imports were to the US, UK, Germany and Japan. Imports to UK, Germany and Japan remained constant from 2003-2013, but doubled over the same period in the US and increased in China and India as well.

Based on this trade data, certain vulnerable countries were identified. Around 60 countries, mostly LMICs with no local insulin manufacturing, imported insulin from only one country for at least one year. This data also showed that only 17 percent of sub-Saharan African countries purchased insulin every year during the period 2004-2013. Worryingly, 29 percent of countries did not report buying insulin at all over this period.

5. The Price and Affordability of Insulin

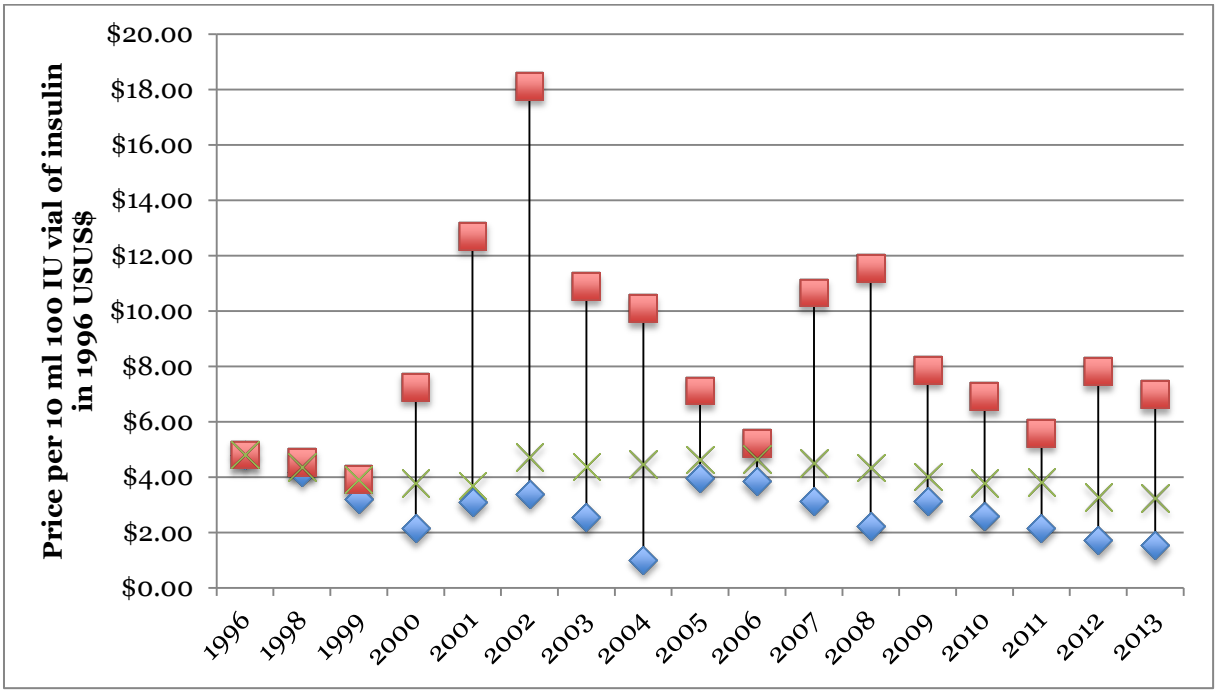
To create the Insulin Price Profile, different resources were used to gain as much information as possible on the price of insulin at different levels of the health system. These sources included: Management Sciences for Health (MSH) data from 1996-2013 (from the online *International Drug Price Indicator Guide);* government procurement prices (from national medicine procurement officers in 26 countries and two organisations: Gulf Cooperation Council (GCC) and the United Nations Relief and Works Agency for Palestine Refugees (UNRWA); patient prices (via list serv requests, contacts and other informants from 43 countries) and reimbursement prices (from publicly-accessible databases on national social insurance schemes from 28 countries).

Procurement prices were adjusted, according to the INCO term, to cover costs to the national central store. All prices were standardised to 10ml of 100IU/ml insulin in US dollars. Where more than one price was recorded for a product, the mean price was taken. Based on median patient prices, affordability was expressed as the number of days the lowest paid unskilled government worker would have to work to buy 10ml of insulin (approximately 30 days' supply).

5.1. Management Sciences for Health Data

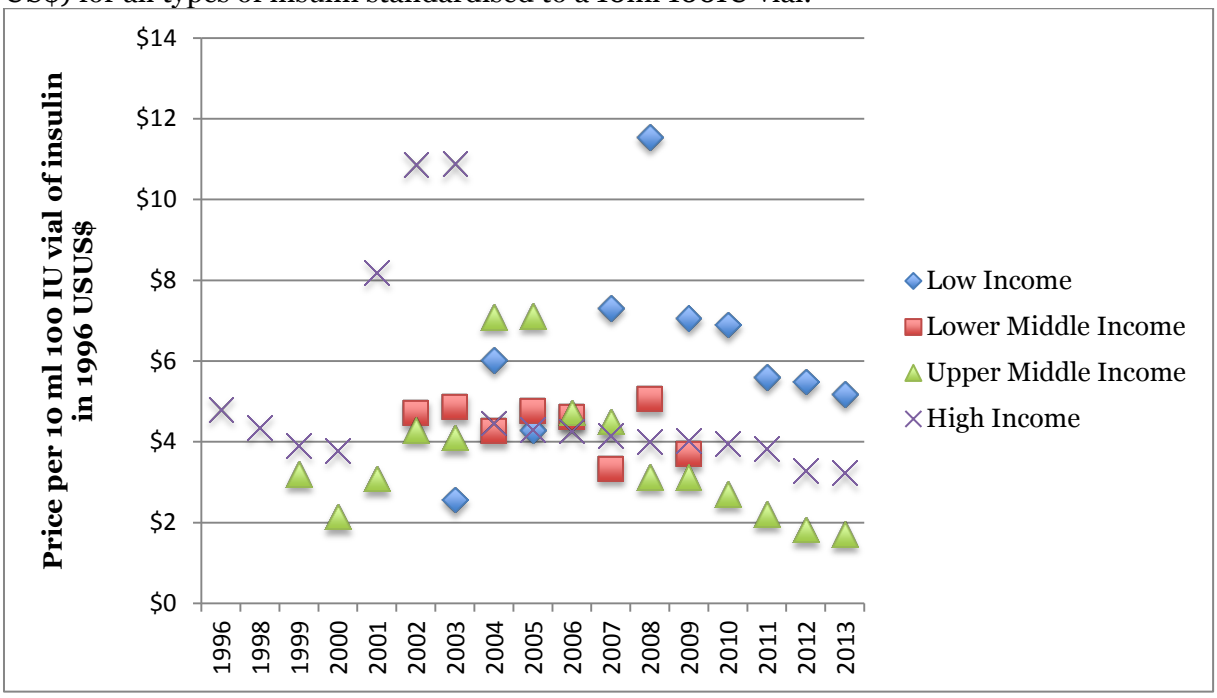
Between 1996 and 2013, prices for 11 different suppliers were listed and purchases were made by 18 countries and the Organisation of Eastern Caribbean States. Both the supplier list and the buyer list included four human insulins. Overall, the median supplier and buyer prices were US$5.30 and US$4.31, respectively. While in some years the range in supplier and buyer prices was wide, median prices of each were fairly steady over the 17 years.
Figure 7 presents this for buyer prices.

Figure 7. Range of adjusted buyer prices from 1996-2013 (in US$) for all types of insulin standardised to a 10ml 100IU vial.



It is interesting to note that buyers in the WHO AFRO region, and those from LMICs, had median prices above the overall median price for seven and eight years, respectively, as shown in Figure 8.

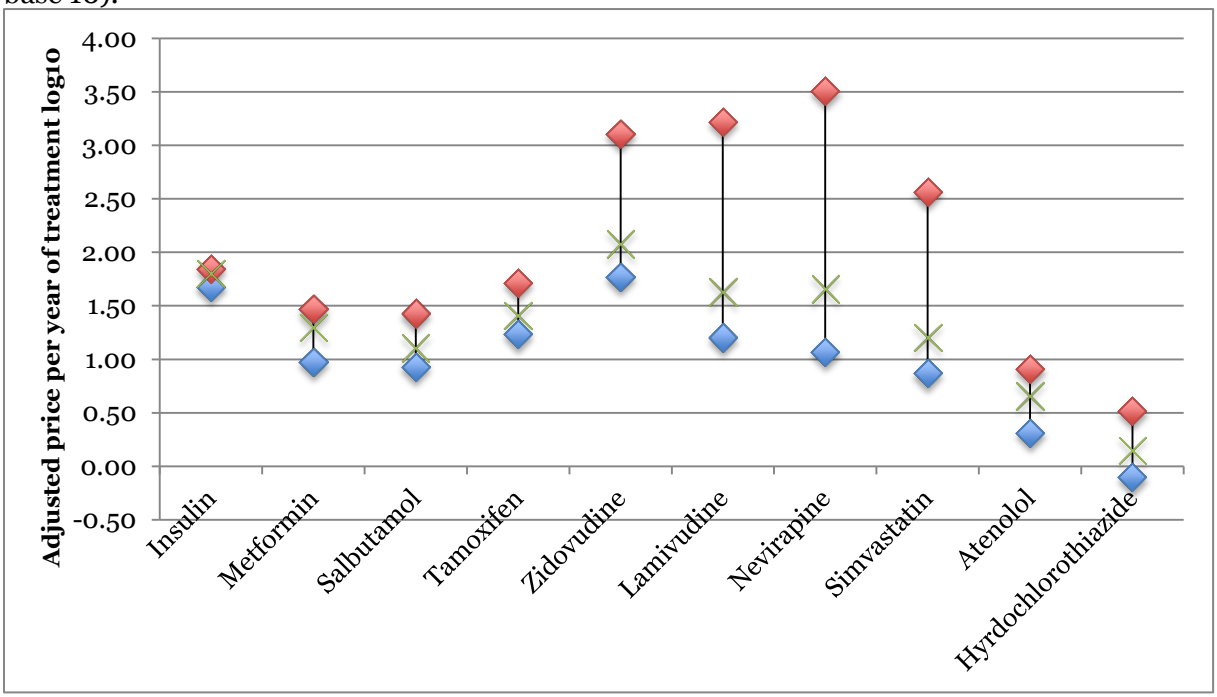
Figure 8. Adjusted median buyer prices by World Bank Income Group from 1996-2013 (in US$) for all types of insulin standardised to a 10ml 100IU vial.



The buyer price for insulin in cartridges was about three times the price of insulin in vials. There was little difference in median buyer prices for the different types of human insulin.

A difference between the price of insulin versus other non-communicable disease (NCD) medicines was seen when looking at the overall range of prices for defined daily doses. Insulin had the smallest range over the period of analysis as shown in Figure 9. This data is presented using the median prices at logarithmic base 10 for easier presentation. Over the time period, all antiretrovirals (ARV) and simvastatin were at one point higher priced than insulin, but by 2013 only zidovudine remained higher priced than insulin.

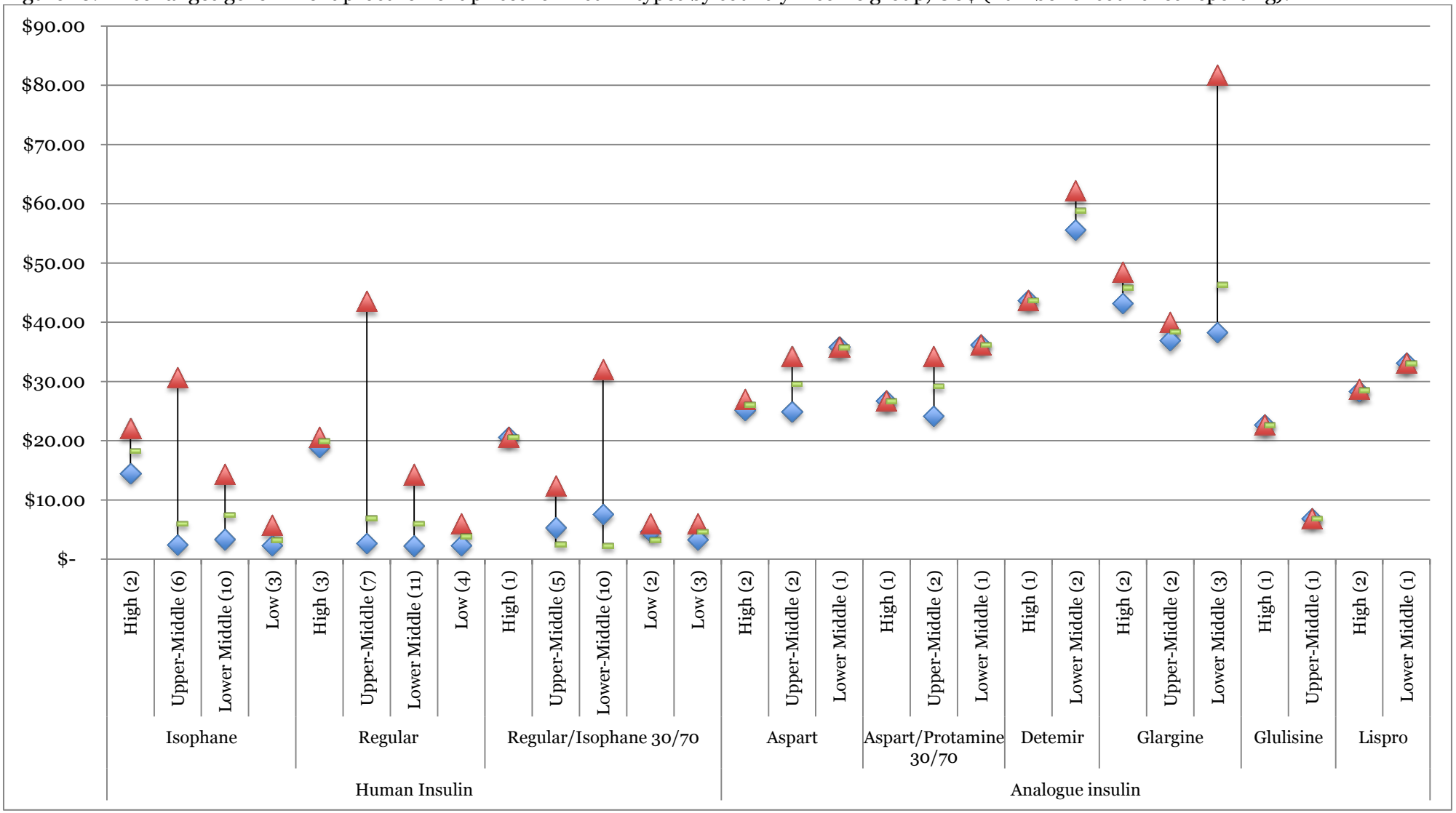
Figure 9. Price ranges for defined daily doses for selected medicines (adjusted prices at Log base 10).



5.2. Government Procurement Prices

Human insulins were more often procured and lower priced (median US$5.99) than analogues (US$34.20). UNRWA (US$2.92) and GCC prices (US$4.20) for human insulin were lower than the median national prices. Procurement prices varied across countries e.g. regular/isophane (premixed) 30/70 insulin ranged from US$2.24 in Pakistan to US$32.00 in Kyrgyzstan (Figure 10 shows government procurement price for insulin type). Presentation of insulin also had an impact on price. Across the five insulin types with the most price points (aspart, glargine, isophane, regular and premixed 30/70), vials (US$5.84) were lower priced than cartridges (US$17.93) and prefilled pens (US$27.31). Not all analogue insulin formulations are included in Figure 10.

Figure 10. Price ranges government procurement prices for insulin types by country income group, US$ (number of countries reporting).



According to the data, significant savings would result in some countries if they only purchased human insulin e.g. Iran would save US$49 million (Table 2). An analysis of government procurements in Iran, Dominican Republic, Moldova, and Kyrgyzstan showed analogue insulin made up only 27 percent, three percent, nine percent and six percent respectively of their insulin purchases by volume, but represented 75 percent, seven percent, 38 percent and 34 percent, respectively, of value.

Table 2. Expenditure and potential savings on insulin purchases in four countries.

		Iran	Dominican Republic	Moldova	Kyrgyzstan
Human insulin	**Volume**	4 235 000	200 400	13 104	189 500
	Value (USUS$)	US$18 479 846	US$495 405	US$94 110	US$933 442
Analogue insulin	**Volume**	1 569 000	5 200	1 333	11 250
	Value (USUS$)	US$56 029 008	US$35 786	US$58 087	US$477 694
Total	**Volume**	5 804 000	205 600	14 437	200 750
	Value (USUS$)	US$74 508 854	US$531 191	US$152 197	US$1 411 136
Analogue insulin	**Percentage of Volume**	27%	3%	9%	6%
	Percentage of Value	75%	7%	38%	34%
Only purchasing human insulin	**Weighted mean average per vial**	US$4.36	US$2.47	US$7.18	US$4.93
	Total value (USUS$)	US$25 305 440	US$507 832	US$103 658	US$989 698
	Savings	US$49 203 414	US$23 359	US$48 539	US$421 439
	Savings as a percentage of current insulin expenditure	66.0%	4.4%	31.9%	29.9%

The range of savings as a percentage of current insulin expenditure is 4.4 percent in the Dominican Republic to 66.0 percent in Iran, which shows the potential for more rational use of resources.

5.3. Patient Prices and Affordability

In most countries, patient prices were collected from a single medicine outlet, therefore they should not be considered representative of the country. Median patient prices in the public sector (in countries where insulin is not supplied free-of-charge) were US$7.64 for human insulin and US$45.03 for analogue. In the private sector a similar picture was seen with analogue insulin higher priced (US$39.35) than human insulin (US$16.65).

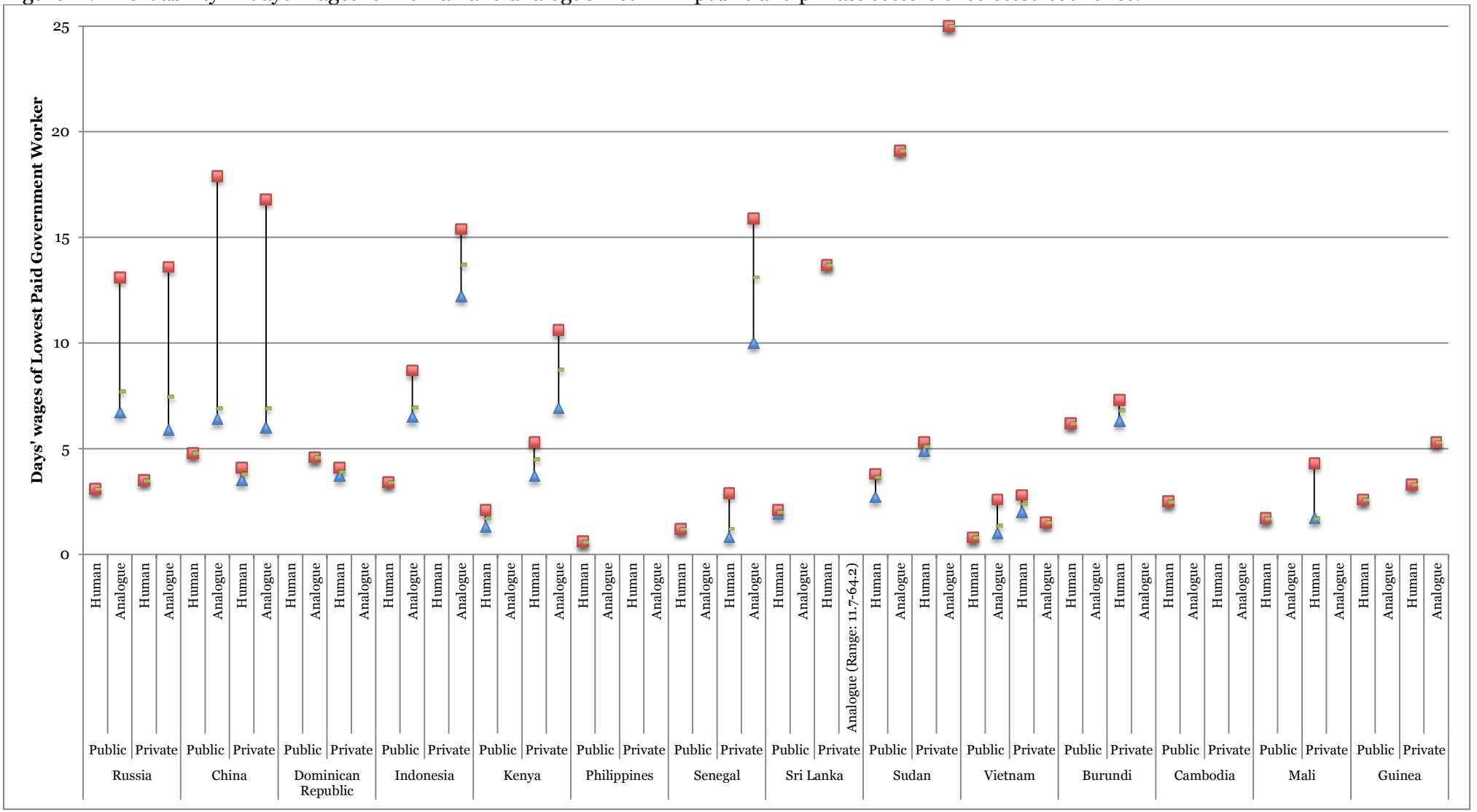
For human insulin, median prices were highest in HICs in the public (US$35.77) and private (US$21.69) sectors. They were lowest in UMICs in the public sector (US$6.17), and in LICs in the private sector (US$8.00). In both sectors, some large price variations were seen across the countries e.g. premixed 30/70 insulin ranged from US$2.16 (Sri Lanka) to US$36.47 (Germany) in the public sector, and US$3.72 (Venezuela) to US$39.08 (New Zealand) in the private sector. Some large price variations for brands of human insulin were seen even within income level e.g. in the private sector, both Insulatard® and Humulin R® ranged from about US$6 to US$50 across five LMICs, respectively.

For analogue insulins, median prices were highest in HICs in the public (US$49.31) and private (US$44.28) sectors. Prices were lowest in LMICs in the public sector (US$25.69) and private sector (US$23.57). As with human insulin, some large price variations were seen across the countries e.g. glargine ranged from US$16.60 (Vietnam) to US$112.93 (China) in the public sector, and US$8.32 (India) to US$196.46 (Venezuela) in the private sector.

An analysis of prices by presentations was not possible for the public sector due to insufficient data, so was undertaken for private sector patient prices only. For each type of human insulin, the median patient price of vials was lower than those of pens and cartridges. There were more price points for analogues sold as cartridges or pens compared to vials. For the five analogues with prices for vials, only two (aspart and lispro/protamine 25/75) had lower prices compared to both pens and cartridges. For the other three analogues, pens were lower priced for glargine, and cartridges were lower priced for glulisine and lispro.

Insulin was largely unaffordable for those on low incomes. On average, insulin was less affordable in the private sector compared to the public sector, and analogue insulin was less affordable than human insulin. Mean affordability in the public sector was 2.5 days' wages for human insulin, and 7.5 day's wages for analogue. In the private sector, it was 3.5 and 9.5 days' wages for human and analogue insulin, respectively. In a number of countries, every insulin cost more than three days' wages to purchase even in the public sector. (Figure 11) It is interesting to note that in some countries there was little difference in insulin affordability between the public and private sectors where people have to pay out-of-pocket, e.g. Russia, China and Vietnam, whereas in other countries there is a significant difference, such as Indonesia, Senegal and Sri Lanka. For example, in Sri Lanka the maximum days' wages an individual would have to pay was 64 for analogue insulin (Range: 11.7 to 64.2 days' wages; Median 28 days' wages). In many countries, public sector availability is crucial as insulin is supplied free-of-charge or is more affordable e.g. in Sri Lanka the difference in affordability of human insulin was two days' wages in the public sector versus 13.7 days' wages in the private sector.

Figure 11. Affordability in days' wages for human and analogue insulin in public and private sectors of selected countries.



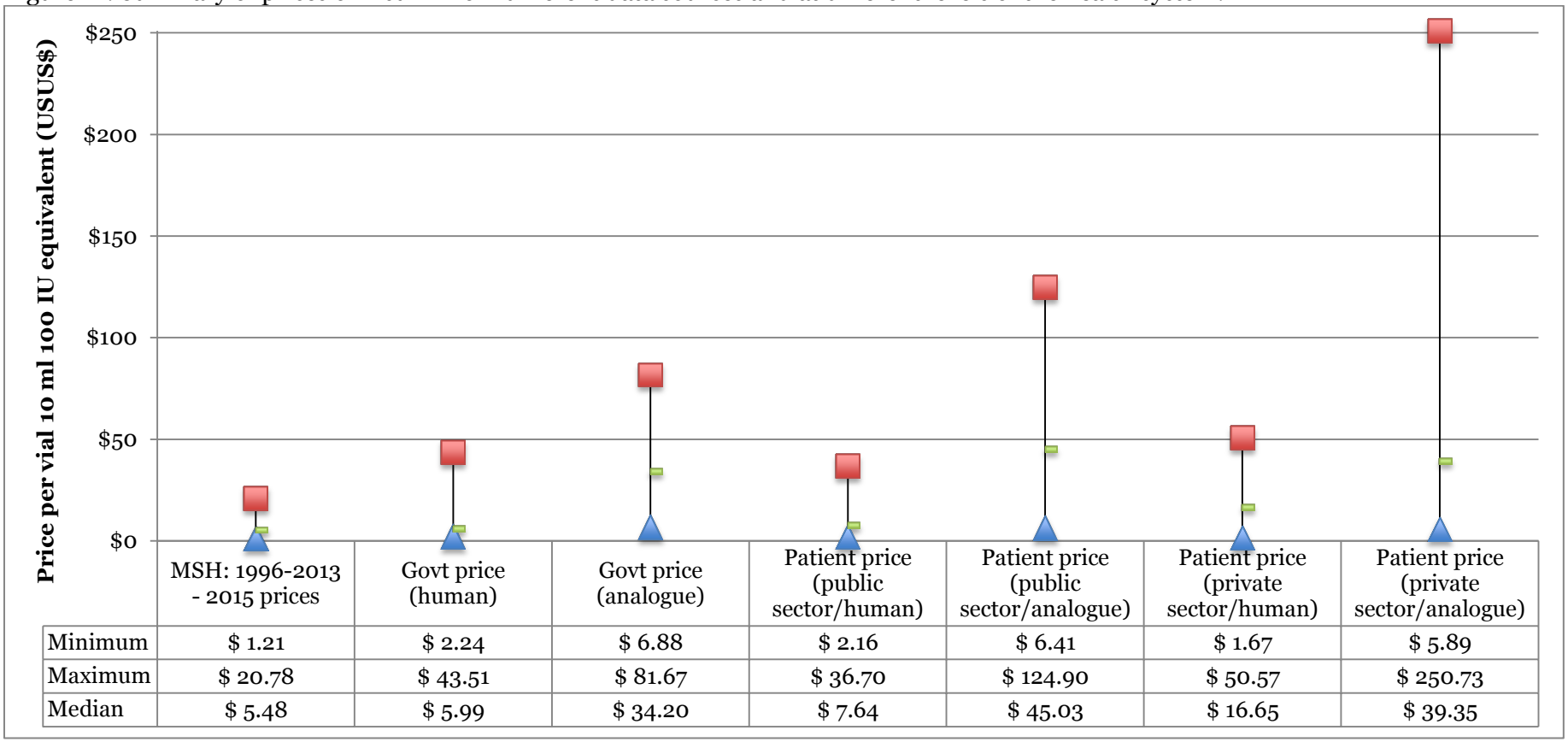
5.4. Reimbursement Prices

The median reimbursement price for human and analogue insulin was US$19.14 and US$27.90, respectively in 28 countries. In the few countries reimbursing animal insulin, the median price was US$65.67. Median prices of human insulin ranged from US$17.75 (premixed 25/75) to US$22.94 (premixed 15/85). For analogue, median prices ranged from US$24.52 (glulisine) to US$49.88 (degludec).

Figure 12 summarises the different price data showing:

- Some countries are procuring efficiently compared to MSH prices (which are often used as a global reference price)
- Analogue insulin is higher priced than human insulin (for government procurement prices, patient prices and reimbursement prices)
- In many contexts there is poor affordability for individuals
- Poor availability in public sector outlets forces insulin users to purchase in the private sector, where prices are usually higher priced (but not in all countries)

Figure 12. Summary of prices of insulin from different data sources and at different levels of the health system.



	MSH: 1996-2013 - 2015 prices	Govt price (human)	Govt price (analogue)	Patient price (public sector/human)	Patient price (public sector/analogue)	Patient price (private sector/human)	Patient price (private sector/analogue)
Minimum	$ 1.21	$ 2.24	$ 6.88	$ 2.16	$ 6.41	$ 1.67	$ 5.89
Maximum	$ 20.78	$ 43.51	$ 81.67	$ 36.70	$ 124.90	$ 50.57	$ 250.73
Median	$ 5.48	$ 5.99	$ 34.20	$ 7.64	$ 45.03	$ 16.65	$ 39.35

6. Taxes and Tariffs on Insulin

The United Nations Conference on Trade and Development World Integrated Trade Solution website, the Trade Analysis Information System database, was accessed and the weighted and simple average of measured tariffs was extracted for insulin. It was found that the majority of countries have no import tariffs on retail insulin. The proportion of countries without tariffs has increased since 2004 from 52 percent to 77 percent. Global weighted average import tariffs have decreased from slightly less than 3.5 percent (2004) to about 1.9 percent (2013). In 2012 and 2013, most of the countries with the highest import tariffs were from Latin America. For example, Argentina, Brazil, Paraguay and Uruguay consistently have import tariffs on retail insulin in excess of 10 percent. Value Added Tax (VAT) on insulin ranged from 0-24 percent. Average VAT levels were:

- 8.3 percent in OECD countries (Range: 0-25 percent)
- 4.6 percent in non-OECD HICs (Range: 0-21 percent)
- 7.0 percent in both upper- (Range: 0-24 percent) and lower-middle income countries (Range: 0-20 percent)
- 7.0 percent in low-income countries (Range: 0-18 percent)

7. Discussion and Possible Interventions

The profiles and data within this report provide a unique addition to the information presented previously by the ACCISS Study.(4, 5) Although this data needs to be complemented by on-going work, it highlights some areas of possible intervention. For example, some targeted interventions at country level might be necessary for countries. This could include Burundi and Djibouti for the inclusion of insulin on their NEMLs and Argentina, Brazil, Paraguay, and Uruguay with regards to the import tariffs they have on insulin. Another area of targeted intervention could be for countries identified as not purchasing insulin frequently and those that can be considered vulnerable through the analysis of the trade data as well as those paying high prices.

This report confirms from different data perspectives the dominance of Eli Lilly, Novo Nordisk, and Sanofi with regards to the global insulin market. Although other insulin manufacturers have been identified based on the data available, their size and market penetration seem to be low. This can be seen looking at the trade and registration data presented. The ACCISS Study is further investigating this with visits to multi-national companies as well as biosimilar insulin manufacturers. Lessons learnt from the visits to the biosimilar companies will soon be published. This will hopefully identify ways of increasing competition. However, a challenge remains in that to date only two companies, Eli Lilly (in a variety of countries) and Biocon (only in Japan) have received approval for their biosimilar glargine formulations in highly regulated markets. Ongoing work of the ACCISS Study on biosimilar regulations will soon be available, providing a comparison of various guidelines, as well as two case studies of the approval process of biosimilar insulin.

Another factor that has again been highlighted by this report is the high price of insulin. The global procurement price of human insulin based on MSH data seems to have remained stable over time in comparison to other NCD medicines and those used in the treatment of HIV/AIDS. Government procurement prices for insulin are highly variable across countries, showing that some governments are paying substantially more than they should.

Patient prices are also high in many countries, particularly in the private sector. In countries with poor insulin availability in the public sector, high prices in the private sector make insulin out of reach to many. Availability data for insulin from 15 countries is currently being analysed, in addition to further price analyses, to complement the information included in this report. A study nearing completion on insulin price components will help illuminate if

the high price of insulin is due primarily to high selling prices by companies or high add-on costs (mark-ups and other charges) in the pharmaceutical supply chain.

Unlike for many other medicines, intellectual property is not an issue for insulin itself. As was shown in this report, human insulin is off patent and many analogue insulin formulations are either already off patent or will no longer be protected in the next few years. Of concern is the increase in patent protection on the delivery devices. This should be monitored as well as the availability of human insulin in vial form. One intervention for this could be a global compact between the WHO and the industry to guarantee the global availability of human insulin in vial form.

Another element to monitor is the use of insulin in type 2 diabetes. Unlike for type 1 diabetes where the need for insulin is absolute, insulin use in type 2 diabetes is not as clearly defined. As seen in this report, use of insulin in type 2 diabetes usually ranges from 10 to 25 percent. This needs to be monitored to, on the one hand, look more closely at the possibility of over use of insulin in type 2 diabetes and to develop a consensus concerning best practices for insulin treatment with these individuals. In addition, policies must ensure that future developments in the area of insulin also take into account type 1 diabetes.

The target established by WHO's Global Action Plan for the Prevention and Control of NCDs 2013-2020 is "80% availability of the affordable basic technologies and essential medicines, including generics, required to treat major NCDs in both public and private facilities."(16) Clearly this target is far from being met for insulin based on the data presented in this report. Therefore the ACCISS Study will continue to gather data on this issue, as well as promote the use of existing guidelines and tools for effective purchasing of quality-assured, safe, efficacious, and cost-effective insulin therapy, as well as policies aimed at addressing different challenges that this report (and further research) identifies.

In 2016, numerous opportunities enabled the research undertaken to date by ACCISS to be disseminated and discussed. Specifically, for World Health Day 2016 which had as its theme diabetes, the ACCISS Study organised a side event to the WHO's main event. This event was attended by approximately 30 guests in person, as well as 118 unique viewers online, and had a distinguished panel which included:

- David Beran, University of Geneva, Co-investigator of the ACCISS Study
- Krystal Boyea, Ambassador & Spokesperson for Diabetes, Barbados
- Katie Dain, Executive Director, NCD Alliance
- Justine Davies, Editor-in-Chief, The Lancet Diabetes & Endocrinology
- Ruth Dreifuss, Former President of Switzerland, Chairperson of the Commission on Intellectual Property Rights, Innovation, and Public Health and co-Chair of the UN High-Level Panel on Access to Medicines
- Hans Hogerzeil, Professor in Global Health at the University of Groningen, former WHO Director for Essential Medicines and Pharmaceutical Policies
- Kaushik Ramaiya, Consultant Physician and Chief Executive Officer at Shree Hindu Mandal Hospital, Dar es Salaam and Mwanza, Tanzania

World Health Day activities at WHO included an intervention by David Beran, at the launch of the Global Diabetes Report in Geneva and press coverage around it prominently featured the issue of access to insulin. Other opportunities included two Lancet Commissions, one on access to essential medicines and the other on diabetes in sub-Saharan Africa, where again different members of the ACCISS Study Team and Advisory Group were involved. The essential medicines report was published in November 2016 and the other report is expected to be published in the first quarter of 2017.

With the completion of this phase of its work, the ACCISS Study has further contributed to a better understanding of the insulin market. Many issues need further investigation. Based on

the findings so far, and discussions of these finding with key opinion leaders, additional research is being carried out looking at perceptions of insulin and its use by users and clinicians and developing a business case for providing insulin to the world's poorest populations. As the ACCISS Study moves into its final year, the information collected, as well as these additional pieces of research, will assist in developing interventions to address the challenge of access to insulin.

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Annex 1. List Companies Identified as Insulin Producers

Company Name	Country of Headquarters	Number per country
Denver	Argentina	1
Popular	Bangladesh	3
ACI Limited	Bangladesh	
Aristopharma	Bangladesh	
Tonghua Dongbao	China	12
Shanghai Fosun	China	
Hongye Biochem	China	
Beier	China	
Shanghai Biochem and Pharma	China	
Nanjing Xinbai	China	
Gan & Lee	China	
Wanbang	China	
United Laboratories	China	
Union Pharmaceuticals	China	
Shanghai Biochemical Research	China	
Jinhua	China	
BCN Medical	Colombia	1
Novo Nordisk	Denmark	1
SEDICO	Egypt	3
Vacsera	Egypt	
Amoun Pharmaceuticals	Egypt	
Soperquimia	El Salvador	1
Sanofi	France	1
Wockhardt	India	3
Biocon	India	
USV	India	
Sanbe	Indonesia	1
Exir	Iran	1
Pisa	Mexico	4
Probiomed	Mexico	
Laboratorios Antibioticos	Mexico	
Laboratorios Cryopharma	Mexico	
Bioton	Poland	2
Polfa Tarchomin	Poland	
CJSC Brinsalov	Russia	3
Medsintez	Russia	
Pharmstandard	Russia	

Company Name	Country of Headquarters	Number per country
Aspen	South Africa	1
Julphar	UAE	1
Eli Lilly	USA	1

Annex 2. List Countries Included in NEML Analysis (year of NEML)

Inclusion of insulin	WHO Region				
	AFRO (n=31)	**AMRO (n=22)**	**EMRO (n=19)**	**SEARO (n=11)**	**WPRO (n=17)**
NEML Medicine + Product Presentation Listed	Angola (2014) Algeria (2006) Botswana (2012) Burkina Faso (2007) Burundi (2012) Cameroon (2009) Chad (2007) Congo (2013) Cote d'Ivoire (2013) Democratic Republic of Congo (2010) Ethiopia (2010) Eritrea (2010) Ghana (2010) Kenya (2010) Lesotho (2010) Madagascar (2008) Mali (2008) Mauritania (2007) Mozambique (2012) Namibia (2008) Niger (No year) Nigeria (2010) Rwanda (2010) Zambia (2013) Senegal (2008)	Argentina (2005) Bolivia (2013) Brazil (2010) Dominican Republic (2005) Ecuador (2009) Guyana (2010) Haiti (2012) Honduras (2011) Jamaica (2008) Mexico (2009) Nicaragua (2009) Paraguay (2009) Peru (2010) Suriname (2014) Trinidad and Tobago (2010) Venezuela (2004)	Afghanistan (2014) Iran (2013) Djibouti (2007) Oman (2009) Pakistan (2007) Morocco (2012) Egypt (2012) Libya (2005) Lebanon (2014) Yemen (2009) Sudan (2014) Iraq (2010) Saudi Arabia (2012) Somalia (2003) Palestine (2012)	Bhutan (2012) DPR Korea (2012) India (2011) Indonesia (2011) Maldives (2009) Myanmar (2010) Nepal (2011) Sri Lanka (2009) Thailand (2012) Timor-Leste (2010) Vietnam (2008) Republic of Korea (2012)	Cambodia (2012) China (2012) Cook Islands (2008) Fiji (2013) Kiribati (2009) Malaysia (2012) Mongolia (2009) Niue (2006) Papua New Guinea (2002) Solomon Islands (2010) Vanuatu (2007)
NEML Derived from National Formulary	Guinea (2013) Lesotho (2005) Liberia (2011 Malawi (2009) South Africa (2012) Tanzania	Belize (2011) Barbados (2012) Chile (2005) Colombia (2006) Uruguay (2011)	Jordan (2011) Bahrain (2009) Tunisia (2008)		Palau (2006) Marshalls Island (2007) Philippines (2008)Tonga (2007) Tuvalu (2010)

Inclusion of insulin	WHO Region				
	AFRO (n=31)	AMRO (n=22)	EMRO (n=19)	SEARO (n=11)	WPRO (n=17)
	(2007) Zimbabwe (2011)				
NEML Medicine Listed Only without specifying the product presentations (dosage, tablet, etc.)		El Salvador (2011)	Syria (2008)	Bangladesh (2008)	

Annex 3. Registration of Different Insulin Products by Country

Country	Income level	WHO Region	Number of insulin products registered				
			Human	Analogue	Animal	Unknown	Total
Algeria	UMIC	AFRO	3	1	0	0	4
Armenia	LMIC	EURO	19	13	0	0	32
Australia	HIC	WPRO	24	13	2	0	39
Azerbaijan	UMIC	EURO	12	17	0	0	29
Bangladesh	LMIC	SEARO	22	3	0	0	25
Belarus	UMIC	EURO	8	1	0	0	9
Botswana	UMIC	AFRO	5	0	0	0	5
Brazil	UMIC	AMRO	6	0	1	1	8
Brunei Darussalam	HIC	WPRO	5	8	0	0	13
Canada	HIC	AMRO	17	18	2	0	37
Chile	UMIC	AMRO	8	0	0	0	8
China	UMIC	WPRO	141	80	0	3	224
Colombia	UMIC	AMRO	20	2	0	1	23
Costa Rica	UMIC	AMRO	9	8	0	0	17
Croatia	HIC	EURO	12	12	0	0	24
Cuba	UMIC	AMRO	4	3	0	0	7
Dominican Republic	UMIC	AMRO	35	21	0	0	56
Egypt	LMIC	EMRO	54	13	1	3	71
Estonia	HIC	EURO	71	60	0	0	131
Fiji	UMIC	WPRO	3	0	0	0	3
Finland	HIC	EURO	73	56	0	2	131
Guatemala	LMIC	AMRO	35	21	0	0	56
Iceland	HIC	EURO	9	13	0	0	22
India	LMIC	SEARO	28	16	2	2	48
Indonesia	LMIC	SEARO	4	5	0	0	9
Israel	HIC	EURO	9	17	0	0	26
Japan	HIC	WPRO	4	27	0	0	31
Kenya	LMIC	AFRO	35	8	3	1	47
Latvia	HIC	EURO	51	41	0	0	92
Lebanon	UMIC	EMRO	11	0	0	0	11
Lithuania	HIC	EURO	5	0	0	0	5
Malaysia	UMIC	WPRO	3	0	0	0	3
Malta	HIC	EURO	3	0	0	0	3
Mexico	UMIC	AMRO	16	11	0	0	27
Moldova	UMIC	EURO	19	9	0	0	28
Montenegro	UMIC	EURO	6	9	0	0	15
Morocco	LMIC	EMRO	19	22	1	0	42

Country	Income level	WHO Region	Number of insulin products registered				
			Human	Analogue	Animal	Unknown	Total
New Zealand	HIC	WPRO	64	30	7	3	104
Nigeria	LMIC	AFRO	65	7	1	1	74
Norway	HIC	EURO	21	13	0	1	35
Oman	HIC	EMRO	9	23	0	0	32
Panama	UMIC	AMRO	0	1	0	0	1
Peru	UMIC	AMRO	15	18	0	0	33
Philippines	LMIC	WPRO	7	8	0	0	15
Saudi Arabia	HIC	EMRO	16	22	1	0	39
Serbia	UMIC	EURO	20	26	0	0	46
Singapore	HIC	WPRO	12	20	0	0	32
South Africa	UMIC	AFRO	4	1	0	3	8
Sri Lanka	LMIC	SEARO	15	17	0	0	32
Sudan	LMIC	EMRO	12	1	0	0	13
Sweden	HIC	EURO	31	0	0	0	31
Switzerland	HIC	EURO	4	11	3	0	18
Trinidad and Tobago	HIC	AMRO	6	1	0	0	7
UK	HIC	EURO	14	0	7	2	23
US	HIC	AMRO	21	30	28	2	81
Total			**1144**	**757**	**59**	**25**	**1985**