


Research: Health Economics

A perspective on global access to insulin: a descriptive study of the market, trade flows and prices

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Abstract

Aim To describe the global insulin market.

Methods Market intelligence data, United Nations Commodity Trade Statistics for insulin trade, the International Medical Products Price Guide for prices of human insulin and additional web searches were used as data sources. These sources were combined to gain further insight into possible links among market, trade flows and prices. Descriptive statistics and Spearman's rank order correlation were used for the analysis.

Results A total of 34 insulin manufacturers were identified. Most countries and territories are reliant on a limited number of supplying countries. The overall median (interquartile range) government procurement price for a 10-ml, 100-IU/ml vial during the period 1996–2013 equivalent was US\$4.3 (US\$ 3.8–4.8), with median prices in Africa (US\$ 4.7) and low- (US\$ 6.9) and low- to middle- (US\$ 4.7) income countries being higher over this period. The relationships between price and quantity of insulin (Spearman's $r=0.046$; $P>0.1$) and number of import links (Spearman's $r=0.032$; $P>0.1$) were weak. The links between price and percentage of total insulin from a country where a 'big three' manufacturer produces insulin (Spearman's $r=0.294$; $P<0.05$) and total insulin from the main import link (Spearman's $r=-0.392$; $P<0.05$) were stronger.

Conclusions This research shows the high variability of insulin prices and the reliance on a few sources, both companies and countries, for global supply. In addressing access to insulin, countries need to use existing price data to negotiate prices, and mechanisms need to be developed to foster competition and security of supply of insulin, given the limited number of truly global producers.

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Introduction

The WHO defines access to medicines as 'the reliable and consistent availability of appropriate essential, quality medicines at health facilities, the rational prescribing and dispensing of such medicines, and ensuring that they are affordable. Out-of-pocket payments, if any, should be well within patients' capacity to pay, and protection against catastrophic expenditure should be ensured.' [1] There are large gaps in access to medicines for non-communicable diseases worldwide [2] and insulin provides a unique lens through which to assess barriers to access to medicines.

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Insulin was discovered in 1921 and first used in 1922. Patents on human insulin expired many years ago, and by the end of 2015, 11 of the most commonly sold insulin products in the USA were not protected by patents [3]. The global insulin market remains dominated by three multi-national companies, Eli Lilly, Novo Nordisk and Sanofi, identified in the present study as the 'big three', with these companies controlling 99% of the market by value and 96% of the market by volume [4,5].

High prices for insulin in low- to middle-income and high-income countries have been described [5,6]. The affordability of insulin for individuals and health systems has been affected by the shift from human to analogue insulin [5–8]. In the UK the amount spent by the National Health Service on insulin between 2000 and 2009 increased 130% as a result of the shift from human to analogue insulin, with a potential saving of £625 m if all individuals using analogue insulin had used human insulin instead during this period of time [8].

What's new?

- Very little is known about the global insulin market and its possible impact on access to insulin in a given country.
- Current evidence, using traditional methodological approaches, suggests poor availability and affordability of insulin in specific contexts.
- Insight is provided into the insulin market in terms of numbers of insulin-producing companies, trade flows of insulin, global prices of insulin and the possible impact of different factors on the price of insulin for individual countries.
- This study uses data sources traditionally not used in health research and offers a perspective on how to gain a better understanding of the global pharmaceutical market and access to medicines.

Availability is also an issue, with the mean (range) availability of different formulations of human insulin across 14 countries being 56 (17–100)% in the public sector and 39 (0–95)% in the private sector [5].

Most research to date has focused on barriers to access to medicines at a country level, concentrating on health system factors or availability and affordability [9,10]. Some studies have looked at market-shaping measures put in place by donors for HIV/AIDS and vaccines and their impact on price or access [11,12], but these markets are heavily reliant on donor funding. The aim of the present study, therefore, was to provide a perspective on the global insulin market by identifying manufacturers, and describing trade flows and government procurement prices with a view to filling the gap in the understanding of the global insulin market.

Methods

To describe the global insulin market a variety of data sources were analysed and combined.

Insulin manufacturers

Information on insulin manufacturers and distributors was collected from IQVIA (formerly IMS Health) data and Pharmaceuticals and Healthcare Reports, published by Business Monitor International and available through ProQuest [13]. The two most recent market reports for each country were collected (usually Quarter 1 and Quarter 2 for 2014); if neither referenced 'insulin' or 'diabetes', the most recent report containing one of those terms was also included. Within each report, a list of all insulin manufacturers in a given country, as well as other pharmaceutical companies potentially related to insulin manufacturers, was extracted. The Global and Chinese Insulin Industry Report

2014 [14] was used to verify findings on each company identified. Additional information was obtained through web-based searches of medicine regulatory authorities and ministries of health for each country, pharmaceutical company websites and additional sources from web and database searches. Companies for which no information could be found were disregarded for the purposes of this study.

Trade data

The United Nations Commodity Trade Statistics (COMTRADE) database [15] provides information by country and territory on imports and exports of commodities by value and volume over time. There is a specific commodity category for insulin, both in retail form as well as bulk insulin; bulk insulin is the unfinished product, for example, insulin crystals, whereas retail insulin is ready for sale to individuals and health systems. For any given country and for any year listed in its database, COMTRADE provides information on the number of different countries that provide insulin to a specific country (import link), or exports from a given country to another (export link).

Websites of the three main insulin producers and Google searches were used to identify countries where the main global insulin producers have manufacturing capacity. This allowed some exporting countries to be linked to specific companies.

Price data

The Management Sciences for Health International Medical Products Price Guide, provides a variety of prices from different sources, including large pharmaceutical suppliers, international development agencies and governments [16]. The guide allows comparison of prices of medicines and is used as a reference in many approaches looking at access to medicines [17]. Nineteen countries reported their procurement price for lente, mixed, NPH or regular insulin from 1996 and 2013 to the International Medical Product Price Guide. A total of 173 total single purchases of insulin were included in the analysis.

Comparing data sources

We combined the list of identified companies and their primary manufacturing site countries with trade data on exports from these countries. Germany was chosen as a benchmark because it is known that only one of the main three producers produce their insulin there. For each country price point for a given year, the equivalent import data [quantity, number of import links, insulin export (source) countries] were identified when possible. This resulted in 61 data points being included where all the necessary numbers were available. (Appendix S1).

Data analysis

All trade and price data were entered into a Microsoft Excel (version 2016 for Mac, Microsoft, Redmond, WA, USA)

spreadsheet. For the trade data, both total value (US\$) and total weight (kg) by country from 2004 to 2013 for both retail and bulk insulin were extracted, and the database was queried as to whether any given 'country/territory' imported insulin from (import link), or exported insulin to (export link) any other country/territory in the database. Total exports and imports by country/territory and proportions were calculated in terms of total exports/imports per country/territory compared with the global total. The number of import links were also calculated by totalling the number of countries from where a given country received its insulin. This was analysed according to WHO region and World Bank Income Group. To assess reliance on suppliers, the percentage of total insulin provided by a given supplying country was calculated. The mean total insulin quantity per import link was also calculated.

Government procurement prices (actual prices paid by governments) for human insulin from 1996 to 2013 were obtained from the online version of the International Drug Price Indicator Guide. Data from 1996 to 2010 were extracted from the International Drug Price Indicator Guide in 2011 and data from 2011 to 2013 were extracted from the International Drug Price Indicator Guide in early 2015. These were divided by type of human insulin and standardized to be equivalent to a 10-ml, 100-IU/ml vial. All prices were adjusted to 1996 prices using the US Department of Labor Bureau of Labor Statistics consumer price index. Analyses were carried out overall, by WHO region, and by World Bank Income Group. Median, minimum and maximum price data were analysed.

For each country identified as producing insulin, in addition to countries where the big three are known to have production sites, data on the total exported insulin, the number of export links and to which WHO regions they exported were extracted for the period 2000–2013. Germany was used as a comparator for these data.

Using Microsoft Excel (Version 2016 for Mac, Microsoft), simple scatter plots for the relationships between price of insulin and number of import links, quantity imported, percentage of insulin from main import link, and percentage of insulin from countries where the big three are known to produce insulin were created, and a trendline added using the inbuilt function. For each of these relationships the Spearman rank order correlation was calculated to measure the strength of association between the two variables.

Results

The number of insulin manufacturers, trade flows between countries, government procurement prices and relations among these different data sources are presented below.

Insulin manufacturers

Forty possible insulin manufacturers were identified. Further discussions with leading experts enabled us to ascertain that

some were not insulin producers, were affiliates of larger companies, or were no longer producing insulin. This resulted in 34 potential insulin manufacturers globally in 2016 (Appendix S2). The largest number of possible insulin producers were located in Asia (15), followed by Europe (10) and Latin America (seven).

Trade data

Denmark, France, USA, Brazil, China, Japan and Russia were identified as production sites for Novo Nordisk [18]. Eli Lilly has production sites in the USA, France, Italy, China and Russia [19–21]. Germany, Russia and Ireland are where Sanofi produces its insulin [22,23]. There is overlap between companies and countries where insulin is produced; for example, Eli Lilly and Novo Nordisk both produce insulin in the USA and France as well as between these two companies and manufacturers of biosimilar insulin in Russia and China.

The median (range) total value of global exports of retail insulin over the period 2004–2013 from Denmark, Germany, France and USA was 89 (81–90)% and was 50 (16–70)% for volume. Adding in other manufacturing sites for the big three, located in Brazil, Ireland and Italy, where only those three companies produce insulin, increased the median total value of insulin to a median (range) of 90 (90–92)% and a median (range) volume of 51 (19–71)%.

In the period 2004–2013, five countries, the USA, Germany, Japan, China and the UK, represented 38–48% of total global insulin imports by volume and 50–62% of total global insulin by value. These five countries increased their imports of insulin by 143% in terms of volume and 255% in terms of value over this period.

On average, countries/territories imported insulin from 5.8 (range 1–13) countries. Low-income countries (3.5) and countries in Africa (3.3) had the lowest number of import links. On average the main import link to a country provided 67.8% of total insulin (range 61.1–73.9%), with the second link being only 22.8% (range 20.9–24.6%) by volume (Appendix S3). In six of the 10 years analysed the two main import links provided >90% of total insulin. For 70% of countries in 2004–2013 the main import link for insulin was a country where one of the big three had manufacturing capacity. For the period 2004–2013, 62 countries/territories (28%) bought insulin from only one source country and 35 countries/territories (16%) reported buying no insulin at all over this period.

Reported government procurement prices

The overall median (interquartile range) price for a 10-ml, 100-IU/ml vial equivalent was US\$4.3 (US\$3.8–4.8) and little variation in this median price was seen in the period 1996–2013 (Fig. 1); however, a wide range of prices was seen overall: from US\$1.0 to US\$18.1 per 10-ml, 100-IU/ml vial equivalent. Wide ranges were also seen within different

regions: US\$1.0–11.5 (median US\$ 4.7) in the WHO Regional Office for Africa; US\$3.7–7.2 (median US\$4.4) in the WHO Regional Office for the Eastern Mediterranean; and US\$1.5–18.1 (median US\$4.0) in the WHO Regional Office for the Americas. Variability was also seen among World Bank Income Groups, with the highest median prices in low-income and low- to middle-income countries. The range of prices in low-income countries was US\$2.5–11.5 (median US\$6.9) and in low- to middle-income countries it was US\$1.0–12.5 (median US\$ 4.7). By contrast these values for upper middle-income and high-income countries were US \$1.5–7.1 (median US\$ 3.1) and US\$3.2–18.1 (median US \$4.0), respectively.

Market, trade flows and prices

Of the countries identified as local producers of insulin (Appendix S2), Indonesia and Iran did not export any insulin during the time period 2004–2014 (Table 1). Apart from countries where the big three companies are present, only companies based in Bangladesh, China, India and Poland exported to all WHO regions. Compared with India or Germany other countries included in Table 1 exported a fraction of the insulin that these larger countries exported and also exported to fewer countries. The three Latin American countries identified as having insulin producers had a more restricted geographical reach than other countries.

Figure 2 shows a possible inverse relationship between price and increasing quantity of insulin purchased. To make the relationship between price and quantity clearer, the quantity of insulin imported was logged because a wide price range is seen at small quantities of insulin purchased. This relationship was found to be weak (Spearman’s $r=0.046$; $P>.10$). In looking at the impact of the number of import links on the price of insulin, a lower number may increase prices, with a wide variation seen across a number of import links (Fig. 3); however, this association was also shown to be weak (Spearman’s $r=0.032$; $P>.10$). Figure 4 shows how dependency on a given source of insulin might impact price. This dependency is both for a country where the big three companies are manufacturing insulin or a given import link. The link between price and percentage of total insulin from a country in which one of the big three is present was stronger (Spearman’s $r=0.294$; $P<0.05$), as was the percentage of total insulin from the main import link (Spearman’s $r=-0.392$; $P<0.05$).

Discussion

Insulin manufacturers in addition to the ‘big three’ companies were identified in the present study, but their contribution to the global insulin market is small. The present study confirms that the countries with the largest exports are those in which the big three manufacturers are located [4,5]. The trade data also highlight how certain large countries import a

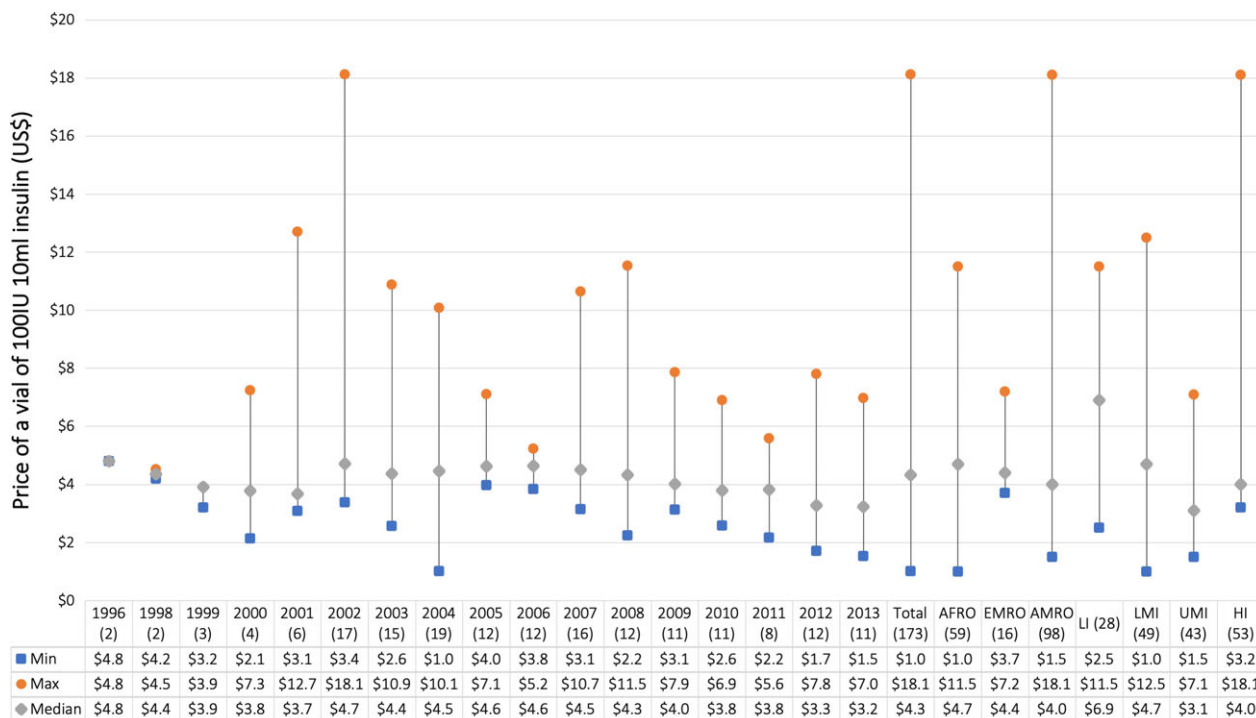


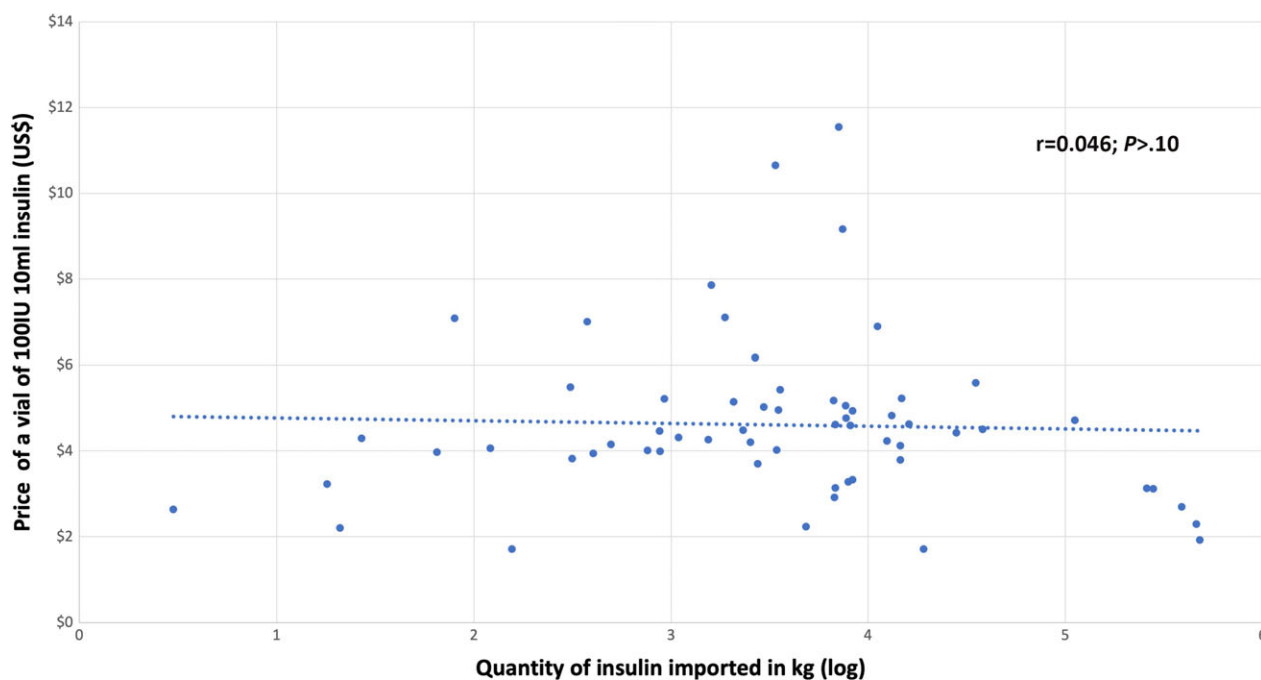
FIGURE 1 Prices for insulin by year, WHO Region and country income group for the period 1996–2013 (number of data points) per 10-ml, 100-IU/ml vial, adjusted to 1996 US dollars.

Table 1 Total (kg) of insulin exports from countries in which local manufacturers were identified

Country	Total quantity of retail insulin exported from country from 2000–2013, kg	Total quantity exported from country in comparison to Germany, %	Number of countries/territories to which insulin exported	Number of WHO regions to which insulin exported
Argentina	34 008	0.3	17	2 (EURO and AMRO)
Bangladesh	25 620	0.2	24	6
China	212 941	1.7	34	6
Egypt	32 218	0.3	10	2 (AFRO and EMRO)
El Salvador	1313	0.0	6	1 (AMRO)
India	21 787 848	168.9	187	6
Mexico	1 085 850	8.4	32	3 (EMRO, EURO and AMRO)
Poland	793 462	6.2	66	6
Russian Federation	27 839	0.2	14	4 (AFRO, EURO, AMRO and WPRO)
United Arab Emirates	114 050	0.9	6	4 (AFRO, EMRO, EURO and SEARO)
Countries where 'big three'* produce insulin				
Denmark [†]	40 106 504	310.9	136	6
France [‡]	45 747 289	354.7	115	6
USA [‡]	20 960 897	162.5	88	6
Germany [†]	12 899 410	100.0	121	6

AFRO, WHO Regional Office for Africa; AMRO, WHO Regional Office for the Americas; EMRO, WHO Regional Office for the Eastern Mediterranean; EURO, WHO Regional Office for Europe; SEARO, WHO Regional Office for South East Asia; WPRO, WHO Regional Office for the Western Pacific.

*Eli Lilly, Novo Nordisk and Sanofi. [†]Only one of the 'big three' produces insulin in this country. [‡]Both Novo Nordisk and Eli Lilly produce insulin in these countries..

**FIGURE 2** Graph showing prices per vial of insulin and quantity (kg) of insulin imported (log).

large proportion of the global insulin produced, and some countries are dependent on just one source for their insulin supply. The data from Management Sciences for Health show that, for human insulin, the median price in the period 1996–2013 remained relatively stable. Overall, however, there were large variations in price among WHO regions and income groups. From comparing the data sources in the

present study, it can be seen that increasing competition, with less reliance on a big three company and on a given import link, decreases prices. Number of import links and quantity of insulin ordered would seem to be moderately and inversely associated with price.

For medicines for which there are a large number of generic manufacturers, the average price for the generic

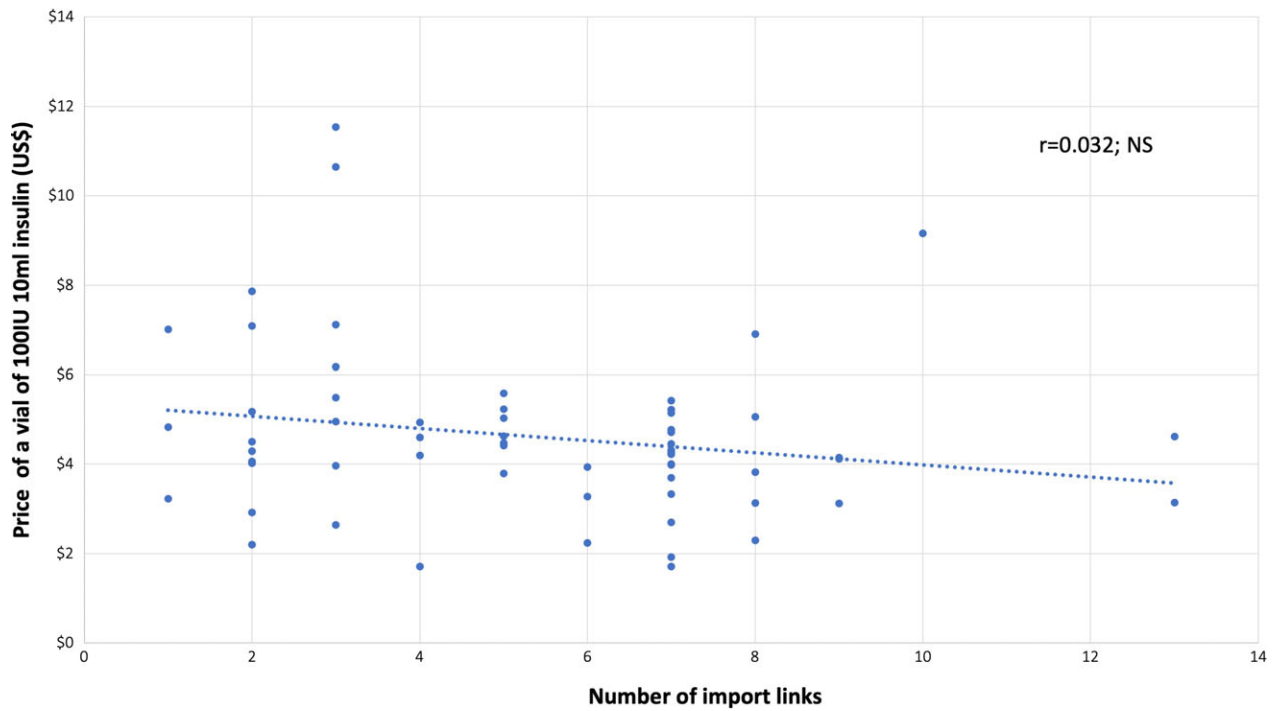


FIGURE 3 Graph showing prices per vial of insulin and number of import links.

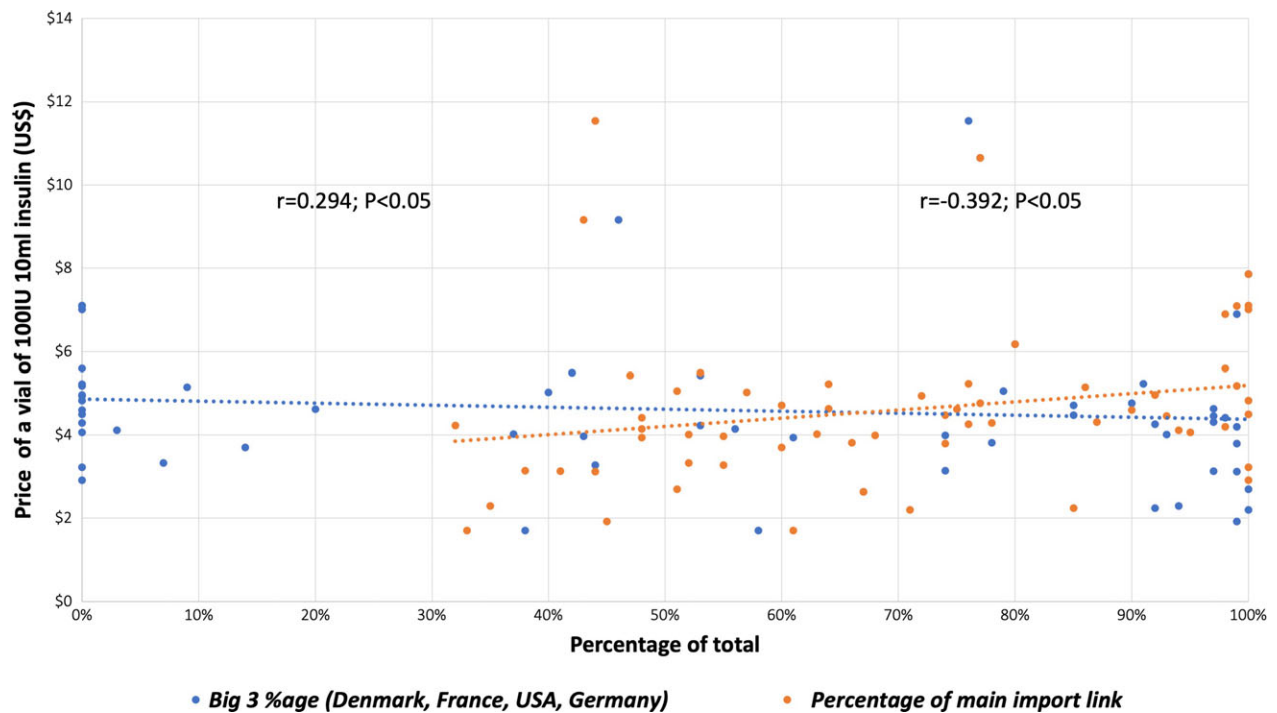


FIGURE 4 Graph showing prices per vial of insulin and percentage of insulin from main import link and percentage of insulin from the ‘big three’ companies.

product falls to 20% of the price of the branded product [24]. For insulin barriers for biosimilar insulin manufacturers to enter markets include the full ownership of the

production process, size of their local market and presence in other markets to generate revenue, overall manufacturing capacity and percentage of this capacity currently being

utilized, regulatory hurdles in that biosimilar products face a more stringent regulatory assessment than that for small molecule generics, entry into markets, perception issues with regards to quality, and overall influence of the big three [25]. The contribution of other manufacturers of insulin to domestic markets needs to be studied further, in particular those in India and China. The recent agreement between Sandoz (the Novartis generic arm) and Gan and Lee, the Chinese insulin manufacturer, may signal that Indian or Chinese manufacturers may become more influential globally [26]. WHO pre-qualification of insulin, the assessment of a producer by the WHO to ensure their capacity to produce a product of consistent quality in agreement with global standards, might enable an increase in reliable sources of quality-assured insulin. A recent pilot study on pre-qualification of biosimilars for cancer treatment is a positive step [27].

The present study has some limitations. Firstly, the sources used were not established for research purposes. With regard to market data, the search approach used and its design, and the fact that only English-language resources were used, are clear limitations. In addition, access to the specific information was difficult in that many market reports are very expensive. A limitation regarding the trade data is that these data are collected for customs purposes and not for the analysis of medicine markets. Furthermore, the export data from Denmark were missing for some of the years evaluated. The trade data do not provide details of any potential trade-related barriers that may hinder insulin imports. Given the global nature of trade and the insulin market it can only be assumed that exports from certain countries are linked to specific companies, although some countries are clearly linked to certain companies, e.g. Denmark for Novo Nordisk and Germany for Sanofi. The data do not give any indication of local production. For prices the present study relied on Management Sciences for Health data. The Management Sciences for Health data on median prices were calculated based on a varying number of data points per year, and do not take into account any impact of concessionary agreements, differential pricing and quantities purchased on price. The data source does not detail any taxes or tariffs added to the price of the insulin reported, is only for certain countries and does not include analogue insulin. For example, some purchasers have only one data point for the whole period whereas others may have many. All data are self-reported by countries.

This study does not look at trade rules and their impacts on access to insulin, but provides an overview of the insulin trade and the limited sources of insulin that countries have at their disposal. It adds to the literature on access to insulin and pharmaceutical markets by analysing three unique data sources. It complements studies conducted in various countries looking at the availability and affordability of insulin. From a methodological perspective this is the first attempt to describe the global market for a medicine using such a variety

of data sources. New ways of looking at medicine markets are essential given the paucity of data and the need for transparency throughout the medicine supply chain [28,29]. Overall, a wide variation in prices was found on the global market and countries need to use these data to negotiate the prices they pay for insulin. Ways need to be developed to foster competition and security of supply of insulin given the limited number of truly global producers. With recent data showing that one in two people globally have access to insulin, with this being only one in seven in Africa [30], the present study shows how the market may influence access to this life-saving medicine and how in addressing this challenge these global factors need to be tackled.

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Competing interests

None declared.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Countries included in comparison of trade and price data.

Appendix S2. Location of company headquarters for insulin manufacturers, numbers and company names.

Appendix S3. Average percentage of total insulin for all countries from four main import links.