INSULIN TRADE PROFILE

April 2016

acciss
Addressing the Challenge and Constraints of Insulin Sources and Supply

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

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The ACCISS Study is supported by The Leona M. and Harry B. Helmsley Charitable Trust and Stichting ICF. The analysis included in this report is that of the authors alone and does not necessarily reflect the views of the Helmsley Charitable Trust or Stichting ICF. All references and conclusions are intended for educational and informative purposes and do not constitute an endorsement or recommendation from the Helmsley Charitable Trust and Stichting ICF.

Contents

Acronyms

ACCISS	Addressing the Challenge and Constraints of Insulin Sources and Supply
COMTRADE	UN Commodity Trade Statistics
IU	International Units
NAFTA	North American Free Trade Agreement
UK	United Kingdom
UM	United Nations
US	United States
WITS	World Integrated Trade Solution

Executive Summary

The Insulin Trade Profile is a summary of information on global trade of insulin, both in retail and bulk formulations. The profile aims to determine the key importing and exporting countries of insulin and their importance in global insulin trade. In addition it attempts to understand if the present trading network has an impact on access to insulin. To do this, we will designed including collect information on cross-border flows of insulin as well as identifying countries most vulnerable to disruptions in supply.

Our research is based on a literature review and a review of the available trade databases from the United Nations (UN) statistical division. The biggest limitation of this study is that the international trade dataset we used cannot distinguish human from analogue insulin.

Within the profile, our key findings were as follows:

- At present, access to insulin is primarily contingent on a supply from Germany, Denmark and France. These three countries currently export between 84.6 – 95.8 percent of the global retail insulin by value. The United States (US) contributes relatively little towards global exports of retail insulin by value. Brazil and Italy have been increasing their export share (by value) over time.

- Similarly, the global trade in imported insulins is dominated by high-income countries. Approximately 50 percent of the global imports of retail insulin between 2004 and 2013 were from the US, United Kingdom(UK), Germany, and Japan, with the US being the predominant importer. The imports of retail insulin (by value) into the US have doubled since 2004. Small countries and islands are particularly vulnerable to disruptions in supply of retail insulin (e.g., Azerbaijan, Botswana, Cape Verde, Fiji, Gambia, Mali, Malta, Mauritania, Mozambique, Namibia, and Vanuatu)

- Since only a few companies dominate the market, without large scale manufacturing/export from India or China or any other emerging economy, it is unclear whether the three main multinational companies can meet the global demand for insulin.

Although not analysed in this report, we raise a number of questions for further research agendas.

1. Are imports of retail insulin (by weight) to countries that have no local production capacity (e.g., most of Africa) enough to supply what we think is the in-country need?
2. What is the difference between the unit price of imported insulin into a country and the retail selling price?
3. What are the factors (e.g., number of persons with diabetes in importing country, volume of insulin imported, gross national income) that impact the unit price of imported retail insulin?

1. Introduction

1.1 The ACCISS Study

Today, approximately 100 million people around the world need insulin, including all people living with type 1 diabetes and between 10-25 percent of people with type 2 diabetes. Although insulin has been used in the treatment of diabetes for over 90 years, globally more than half of those who need insulin today still cannot afford and/or access it. Without insulin, people living with type 1 diabetes will die. Many more will suffer from diabetes-related complications, like blindness, amputation and kidney failure, and, ultimately, premature death.

There are many complex issues that affect access to this life-saving medicine, creating inequity and inefficiency in the global insulin market. These issues include the global insulin market domination by three multinational manufacturers, import duties affecting the price insulin entering different countries, and mark-ups, taxes and other charges in the public and private sector supply chains that affect the final patient price.

The innovative global study, Addressing the Challenge and Constraints of Insulin Sources and Supply (ACCISS), sets out to identify the causes of poor availability and high insulin prices and develop policies and interventions to improve access to this essential medicine, particularly in the world's most under-served regions. The three-year study involves a unique group of leading international experts as members of the study's advisory and technical groups. ACCISS is co-led by Margaret Ewen at Health Action International, David Beran from Geneva University Hospitals and the University of Geneva, and Richard Laing from Boston University School of Public Health.

The study will be carried out in three phases. The first phase was mapping the global insulin market from various angles including trade issues, patents on insulin, market issues (including which pharmaceutical companies manufacture and distribute insulin) prices, trade issues, tariffs and taxes on insulin, and current initiatives to improve access to insulin. This Insulin Trade Profile is a result of the mapping work completed in phase one, and is one of several profiles on the global insulin market to be published. All profiles can be accessed on the ACCISS Study section of HAI's website: http://haiweb.org/what-we-do/acciss/

1.2 The Insulin Trade Profile

Insulin is an essential medicine that is needed to treat type 1 diabetes and in some cases type 2 diabetes.(1) Access to insulin and related devices is particularly difficult in many low- and middle-income countries. (2-4) In high-income countries such as the United States (US), patients without health insurance or with high co-payments are also unable to afford insulin. (5)

Over ninety years ago the first animal-extracted insulin was used to treat a patient with type 1 diabetes, although production was hampered by a limited supply.(6) Since the 1980s, recombinant human insulin has been produced using genetically modified microbes. In the last decade, this recombinant human insulin has undergone chemical modification into various "analogue" insulin products, which have replaced unaltered human insulin in many high-income country markets.

The global insulin market is dominated by a very small number of companies (i.e., Novo Nordisk, Eli Lilly, Sanofi Aventis) that, according to the ACCISS Study Profile on Insulin Markets, hold a 88.7 percent value share of the insulin market. Compounding this, there is growing concern about the affordability of insulin in both upper-income and resource-restricted settings, the latter countries having experienced an unprecedented increase in the prevalence of diabetes over the last two decades. (7)

The aim of this profile is to increase the needed awareness of the global insulin trade market. At the moment, available trade information within market research documents can be expensive and difficult to understand, particularly from a public health context. Further, it is important to

identify the countries receiving insulin that are most subject to "shocks" to the trading system. If we could identify a particular country that imports insulin from just a single other country, this might have an influence both on the price and the availability of insulin. Countries importing insulin from many other countries need to be understood as well, as they have advantages but also challenges, for example, more investment is needed to ensure oversight over quality and safety of the products if they come from many different sources.

Finally, we note what this particular paper is not, which is an analysis of the number of different insulin manufacturers and intermediaries in the global insulin supply chain. We are primarily interested in a descriptive analysis of the global insulin trading relationship itself.

2. Specific Objectives

The overall objective of this paper is to provide a preliminary understanding of the patterns of insulin trade among nations and its implications for security of supply and access. Further, by analysing the changing relationships of insulin trade over time one can learn about which countries have become more or less vulnerable to potential disruptions in supply, and which middle-income countries are becoming increasingly important in the global insulin trading network. The specific objectives are the following:

1. Identify key countries within the global insulin trading network who have a particularly strong influence on the remainder of the network:
    a. What is/are the public health implications of these strong influencers?
    b. Determine the top 20-30 countries in terms of value of trade and their respective fraction of total global insulin imports and exports.
    c. Identify the countries with trade connections that are most vulnerable to supply security problems, defined as countries with at most two suppliers of insulin and that are not domestic producers
    d. Analyse the impact of disrupting supply of one or more of the major exporters of insulin.
2. Identify from a public health/access to medicines perspective in what sense the global insulin trading network has changed between 2004 and 2013.

3. Brief Literature Review

Social network models have been developed in recent years to explain and predict a variety of phenomena, ranging from the spread and control of infectious disease (8-10), to obesity and smoking prevalence (11,12), to global trade itself (13-19) including the public health implications of trading networks of illicit drug traffic (21-24).

A social network model visually represents the role of multiple actors in determining patterns and flows of material and information, and providing insights into the underlying structure of such as identifying key actors within the network whose behaviours may have especially strong influences on the remainder of the network. This present document appears to be the first time that such analyses have been applied to a specific pharmaceutical in trade network.

4. Methods

4.1 Data Sources and Definitions

We used the UN Commodity Trade Statistics (COMTRADE) database (http://comtrade.un.org/), which registers commodity import and exports by value and volume and country over time.

National law usually requires that importers and exporters of goods report particulars of their transactions to customs for the purposes of collection of duties and taxes and for health, environmental, and/or other control and statistical purposes. This makes customs records a readily available and generally reliable source of data. The benefits of using customs records include, for example, wide coverage, particularly in the case of imports. Data found in COMTRADE is primarily, although not exclusively, from customs records. Fortunately, insulin is one of the very few pharmaceutical products that are specifically included in this database. We performed various database queries using the World Integrated Trade Solution (WITS) software (http://wits.worldbank.org/) which provides free access to COMTRADE data.

4.1.1 Classification of Insulin

The choice for a classification system is an important step as we required consistent data among several years and/or countries. We chose a common nomenclature (Standard International Trade Classification: SITC version 3) for all selected years, countries and/or types of data (imports and exports).

Retail insulin
For this profile, we downloaded all data coded for "medicaments containing insulin, put up in measured doses or in forms or packings for retail sale" (SITC 3 code: 542.23). This coding would encompass a fixed dose combination medicine containing insulin and one or more non-insulins, but we are aware of no such medicine. This coding does encompass all purified human, animal and recombinant (analogue) insulins including insulin combinations such as Humalog® Mix 75/25 (75 percent insulin lispro protamine suspension and 25 percent insulin lispro injection) and NovoLog® Mix 70/30 (70 percent insulin aspart protamine suspension and 30 percent insulin aspart injection).

Bulk insulin
For this profile, we downloaded all data coded for "medicaments containing insulin, not put up in measured doses or in forms or packings for retail sale" (SITC 3 code: 542.21). We interpret this to mean all purified human, animal and recombinant (analogue) insulins including insulin combinations but that are in bulk formulations and/or are not placed in vials, pens, cartridges for retail sale.

4.2 Metrics

In September 2014, we downloaded data for total value (USD) and total net weight (kg) of insulin trade on a nation-by-nation basis for the years 2004–2013. We obtained the data records from the COMTRADE site on yearly global trade of "retail insulin" (commodity code: 54223) and "bulk insulin" (commodity code: 54221). This data is the compilation of imports and exports of retail and bulk insulin, by value (in USD), by "net weight" and by the trading "dyad" (importing and exporting country), reported by the national statistical agencies of over 150 countries and standardised by the UN Statistical Division. Each country can act as a named "Reporter"' in the database. We eliminated data from "free trade zones", "other nes" and "unspecified" designations.

4.2.1 Imports and Exports (Reporters and Partners)

Reporter countries provide the insulin "trade-flow" (value in USD, net weight) to be either export/ outgoing or import/ incoming, along with its dyadic named "Partner" country that is importing from or exporting to the Reporter country, respectively.

Several points are noteworthy. Ideally, an importing Reporter country A listing imports A from Partner country B would match with country B's reported exports to country A. Consequently, this would make mirroring (using information from the Partner when a country does not report its trade) a transparent and error-free process. However, this is not the case for the following reasons, listed below.

1. Difference in the way COMTRADE records imports and exports. Imports are recorded as CIF (cost insurance and freight). CIF-type values include the transaction value of the goods, the value of services performed to deliver goods to the border of the exporting country, and the value of the services performed to deliver the goods from the border of the exporting country to the border of the importing country. Exports are FOB (free on board). FOB-type values include the transaction value of the goods and the value of services performed to deliver goods to the border of the exporting country. This may represent a 10 to 20 percent difference in value. (25)[1]

2. Despite all efforts made by national and international agencies, data quality varies among countries.

3. For a given country, imports are usually recorded with more accuracy than exports because imports are intended to generate tariff revenues while exports do not. Therefore, it is widely assumed that in general, the customs valuation of imported goods is more reliable than the valuation of exported goods, since imports from Partners will determine the value of tariff revenue for Reporters.

As a result of the fact that imports are usually recorded more accurately, we employed the following method:

- Imports: To determine imports into country A from its dyadic trading Partner(s), we set country A as a named Reporter in the "import" mode of the database. In other words, we consider imports to be what country A is reporting to have imported from others.

- Exports: To determine exports from country A, we set country A as a Partner in the "import" mode and determined all Reporter countries that were importing from country A. In other words, the exports from country A were determined by what all other countries were reporting to have imported from country A.

We downloaded and developed the yearly datasets such that all the Reporter countries are importers, i.e., incoming retail insulin trade-flow, and that all their dyadic Partners were necessarily exporting insulin to the Reporters.

4.2.2 Net Weight (kg)

The definition of net weight adopted by China for those "..goods contained in a package for retail sale, such as …medicine and other similar products…" should exclude the "..outer package, but

1We empirically confirmed this by regressing values of retail insulin imported into individual top 40 'reporter' countries in a given year against the value of retail insulin exported to the same country by these its "Partners". If the dyadic symmetry is perfect, we would expect a slope of 1.0 for the regression. We found that there is a 14 percent difference in value (slope of 0.86: data not presented), consistent with COMTRADE assertions. We obtained this 'top 40' league table by picking the top 20 countries in terms of import dollar value for each year between 2004-2013, and then identifying unique countries which led to a list of 40 countries. This means that if a country was among the top 20 in even one year, it was included in the list.

include the inner package for retail packing…" but "…for goods like beverages, spirits or similar products, the net weight of goods is the weight of the liquid, which should exclude the packaging, even if for retail packing." [25]

In the European Union, completion of information on net weight is, in general, obligatory for all customs procedures. The net weight is the mass of the goods *without any packaging* (italics added). As stipulated, "…A company imports 1,000 bottles of wine. Each bottle of wine weighs 1.25 kg and the wine in each bottle weighs 0.75 kg. The figure "750" must be entered … [in the customs document]".

We confirmed with the U.S. Customs office in Boston, MA who asserted that "net weight" means just the weight of insulin.

4.2.3 Unit Price Calculations

We calculated an aggregated global unit price as follows: globally we took the total sum value of imported retail and bulk insulin per year and the sum of the total weight of this same insulin and divided (total global value/total global weight) to get a crude estimate of the unit price (US dollars per kilogram of insulin) for each year. We normalised this unit price to 10 grams of insulin and estimated this to be the unit price for 10ml of insulin (density insulin = 1gm per ml). (See Appendix 1 for calculations). This is, in effect, a global weighted average unit price because this is independent of the unit price for individual imports into any country for any year.

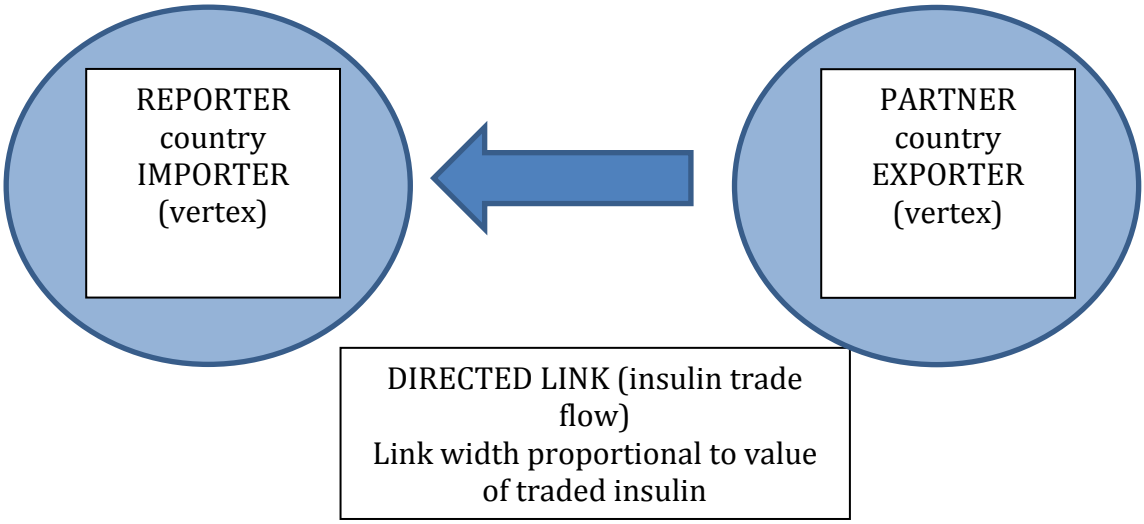
In a second method, we estimated a "country-specific" unit price for each year by taking each of the top 30 retail insulin importers by value (about 95 percent of global imports by value) and each of the top 20 bulk insulin importers (about 98 percent of global imports by value). With this information we then divided the total value of insulin by the total weight for insulin for each country. This equaled the weighted average yearly unit price for retail or bulk insulin for that country-year. For each year, we took the median of all 20 countries and for retail insulin we took the median for all 30 countries. We used medians because of the country-to-country variation in weighted unit price.

We disaggregated these 30 top importing countries by region and included four additional countries; Brazil and Argentina as representing Latin America, Mexico as the third North American Free Trade Agreement (NAFTA) country, and India an the additional country in South East Asia/Pacific region. Data is in Annex 2.

4.2.4 Retail Insulin Trading Network: Data Analysis

The fundamental networking concept we wish to emphasise is that within a trading network, the dyadic trading relation between two countries (A and B) is analysed, not by itself, but in relationship to other countries. We developed a network representation of the global insulin trade for retail insulin. In the jargon of network analysis, each trade relationship acts as a directed graph unit: consisting of two countries (two "vertices" of an importing Reporter and an exporting Partner) connected by the insulin trade-flow (directed "link") towards importing Reporter, as seen in Diagram 1.

Diagram 1. A directed graph unit.



We quantified a set of attributes of the yearly global insulin trade for of each constituent country (node) for years 2004 to 2013, using "R (igraph package) 3.0.3" statistical software [26]. R version 3.0.3, along with the 'igraph' package, were used to make all plots. R codes are found in Appendix 2.

Using the statistical software R version 3.0.3 (Igraph package), we plotted the global insulin trade network maps for certain years. We placed the countries (vertices) relative to their approximate geographic position. Vertex size is proportional to the log (base 10) of the diabetes prevalence (number of persons with type 1 and 2 diabetes) in the country in a given year. Diabetes prevalence was obtained from annual reports of the International Diabetes Federation. (27) We linearly interpolated to obtain prevalence for years with missing data (e.g. linear interpolation between 2009 and 2011 to obtain prevalence for 2010).

We constructed each vertex as a pie chart with the fraction of the total dollar amount in insulin trade due to imports (in red) represented as one slice and exports represented as the other slice (in yellow).

The width of each link is proportional to the dollar amount of trade the link represents. In order to adjust for inflation and to have results comparable over years, the insulin trade value was converted in 2013 constant dollars using the U.S. Consumer Price Index (28). For the purposes of creating a network diagram, we experimented with different link width dimensions and settled on the link as being the square root of the trade value divided by 50. The shading of each link also corresponds to trade value, with darker links having a higher trade amount and lighter links having a smaller trade amount.

For each year, irrespective of whether we created a map, we quantified a set of attributes of the yearly global insulin trade. We calculated the total number of (a) trading countries (nodes), (b) importer-only countries (nodes which only have incoming links), (c) exporter-only countries (nodes which only have outgoing links) and (d) trade-relationships (total links) in the global trade network.

We also calculated country-specific trade attributes, for each year 2004-2013, namely (a) in-degree (number of incoming/import links), (b) out-degree (number of outgoing/export links), (c), in-strength (import dollar value), and (d) out-strength (export dollar value).

We also calculated the frequency (average number of countries) for each import and export link. Put another way, for each year between 2004 and 2013, we determined the number of countries

with one import link and then took the average of these particular countries over all years. We continued with this procedure for each number of import links, where "n" was the maximum number of import links in the network. In addition, for each year between 2004-2013, we determined the percentage of the total global import (by value) of retail insulin that was relegated to those countries with one import link and then took the average of these values overall years.

In effect, we calculated the average percentage of total global import and export trade value relegated to a given import link and export link.

Note that we did not create network maps for bulk insulin as the dollar value and weight of bulk insulin was a relatively small fraction of the total insulin traded (bulk and retail).

4.2.5 "Vulnerable countries" and the "Denmark model"

In principle, if a nation has a high number of different export links, problems with insulin production in that nation could potentially affect multiple other nations. These other nations are even more vulnerable if they do not regularly import insulin from other nations and are most vulnerable if they do not manufacture insulin. However, a nation that has a high import linkage or "degree" (importing insulin from many nations worldwide) is less at risk of jeopardised insulin supplies in the event of insulin shortages in one exporting region or nation.

Denmark model

Given that Denmark is one of the primary suppliers of global insulin, we developed a simple model which asked how much the global supply of insulin would be disrupted if Denmark's exports of retail insulin were to be eliminated. In one counterfactual model, we assumed exports of retail insulin from Denmark to diminish by either 100 percent, or 50 percent for 2012 and calculated the resulting global import value and import weight of retail insulin. We then calculated the difference between this altered imports scenario versus the actual global trade activities of Denmark in that year. From the difference between these scenarios, we estimated how many people in different regions would be affected. The assumptions are based on the weight of retail insulin are in Appendix 1.

We did this for a single year as a full 10-year model would be unrealistic.

4.3 Limitations of the Data/Analyses

4.3.1 Specific Limitations

The database does not distinguish between human or analogue insulin. Nor do we know whether the insulin is packaged as a vial, pen or other container, although we think this irrelevant as net weight is liquid only. We note, however, that the UN only recommends that net weight be the shipping weight in kilograms excluding all/any packaging but this may vary among countries. (25) We assumed that 10ml of insulin contains 100 International Units (IU) but it might contain 40 IU as this is the other standard dosage. (see Appendix 1) We interpret the y axis of Figure 15 therefore as a lower limit.

Although each country is free to ignore it, the UN recommends that a Partner country in this dyadic configuration identify itself as the country of origin of a good, and the importing Reporter be the "country of last known destination, i.e., the last country - as far as it is known at the time of exportation - to which goods are to be delivered…" (25, page 205) Thus, a trading Partner (exporting) is the country of origin of the trade activity that is recorded and there may be one or more intermediary countries between the dyad. Put another way, the Reporter country X is saying that "we have received insulin that was exported from Partner country Y but we have no information on the actual pathway it took to get here- we only report that it originated from country Y." However, each country may be a node in one or several trade-relationships depending on its trade activity but we have no way of identifying these intermediate trading nodes.

4.3.2 General Limitations

In industrial economies trade volumes are known to be highly dynamic and characterised by relatively large fluctuations depending on a number of national and international economic factors. Consequently, time series data of physical and also monetary trade flows normally do not reveal smooth trends. Nonetheless, fluctuations in physical trade data compiled in material flow categories can also be the result of changes or flaws in the physical data reported. Reasons for this may be among the following: general problems in data reporting, changes in trade classifications, changes in the physical units reported, changes in conventions of trade statistics (such as whether packaging material is included), and suppressed data due to reasons of confidentiality.

Multiple factors that are not included in this analysis can influence access to insulin. Trade agreements, policies among various trading parties, as well as individual corporate "access to medicines" corporate policies play an important role in determining the social network structure of trade in pharmaceuticals generally. These would affect not only which nations trade with each other, but also whether nations may be dependent upon exports or imports from certain other nations.

5. Results

5.1 Map

Four networking maps (Figures 1-4) are provided, one for each year of 2004, 2007, 2010, and 2013. Tables 2 and 3, in addition, provide league tables for 2004 and 2013, respectively, listing the top 15 countries in terms of number of total trade partners, their percentage of the total global trade links, their number of import partners, their number of export partners and their total trade value as percent of global insulin trade. Table 1 lists the key trade relationships among the top 20 countries (by trade value) for each of 2004, 2007, 2010, and 2013.

Overall, there are several qualitative trends that can be seen even in the maps. The clearest trend is that the US - Germany retail insulin link is increasing by the year (See e.g., Table 1). Retail insulin flow between Germany to the US for 2004, 2007, 2010, and 2013 represents 9.5, 14.9, 15.8 and 32.1 percent of the global retail insulin trade dollar value, respectively. There are some countries that, over time, have increased their exports of retail insulin, notably Brazil. Africa and the Western Pacific generally have the fewest links in these maps.

India and China are becoming increasingly important traders of insulin (See Tables 2 and 3, below). In 2004, India had 21 retail insulin trade links (import plus export) links which represented 3.3 percent of global trade links. In 2013, the links grew to 42 representing 7.6 percent of the total 2013 links. Similarly in 2004, China had eight retail insulin trade links (import plus export) which represented 1.2 percent of global trade links. In 2013, the links grew to 19 representing 3.4 percent of the total 2013 links.

Figure 1. Trade network map for 2004.
Yellow = export; Red = imports

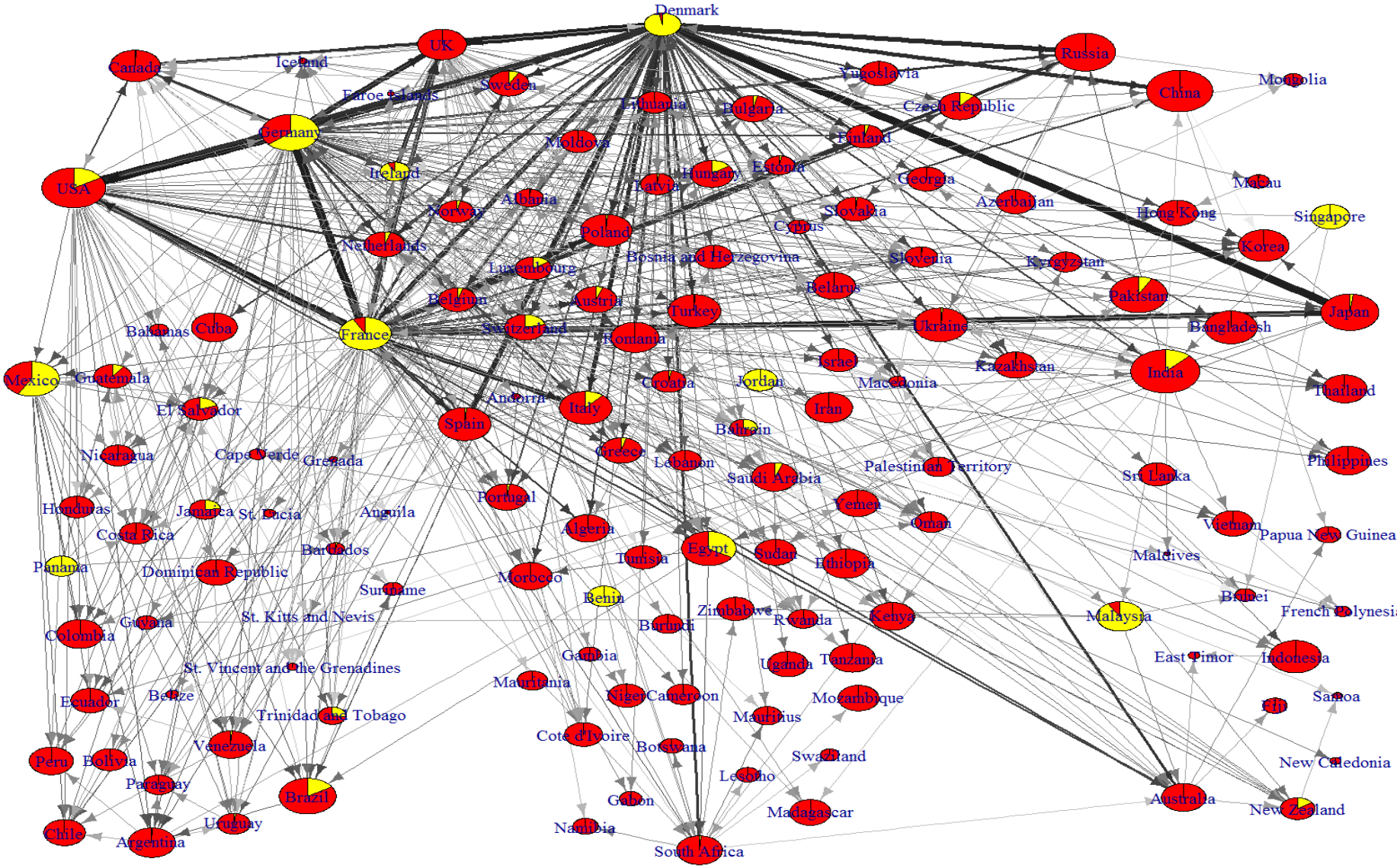


Figure 2. Trade network map for 2007.
Yellow = export; Red = imports

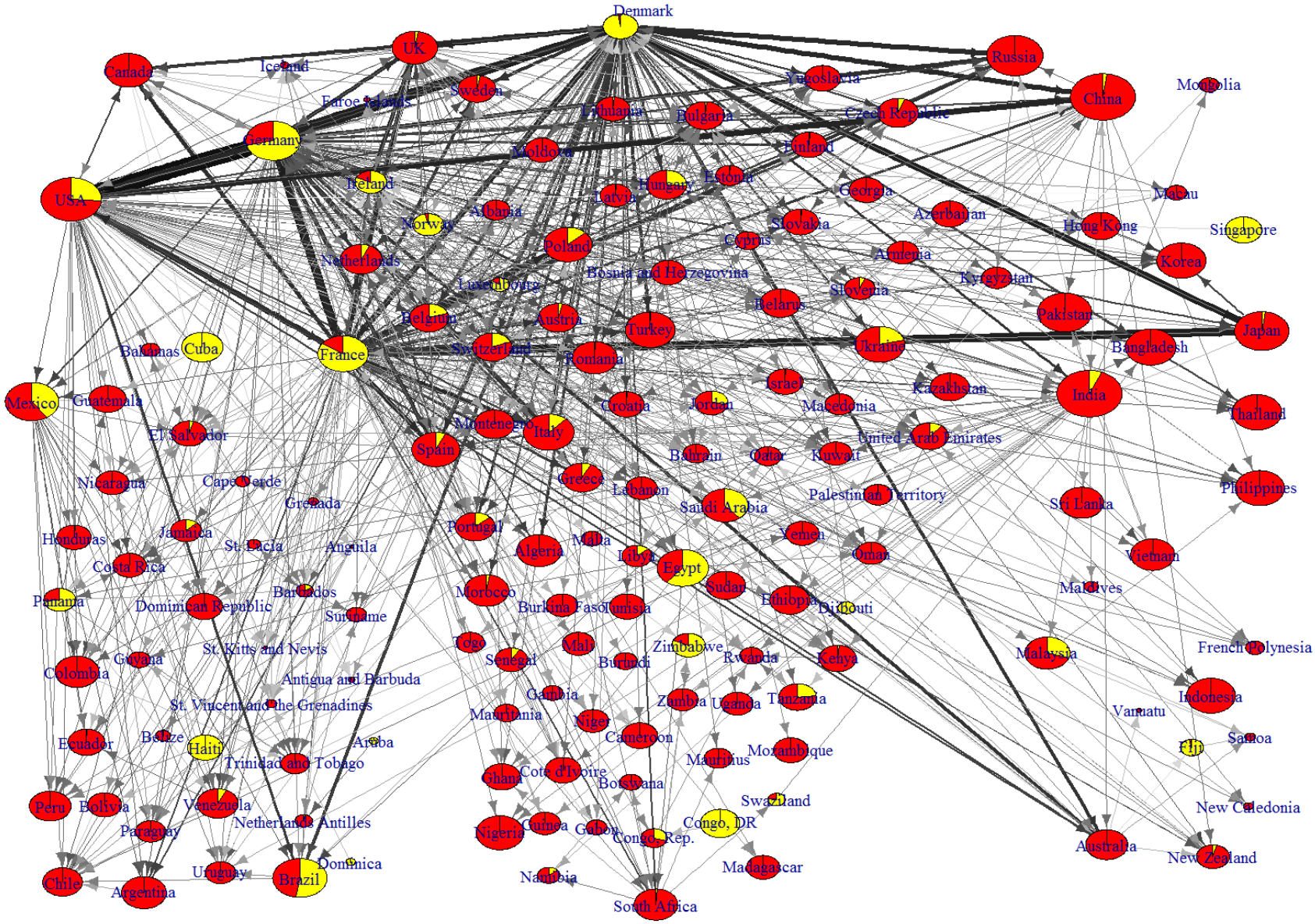


Figure 3. Trade network map for 2010.
Yellow = export; Red = import

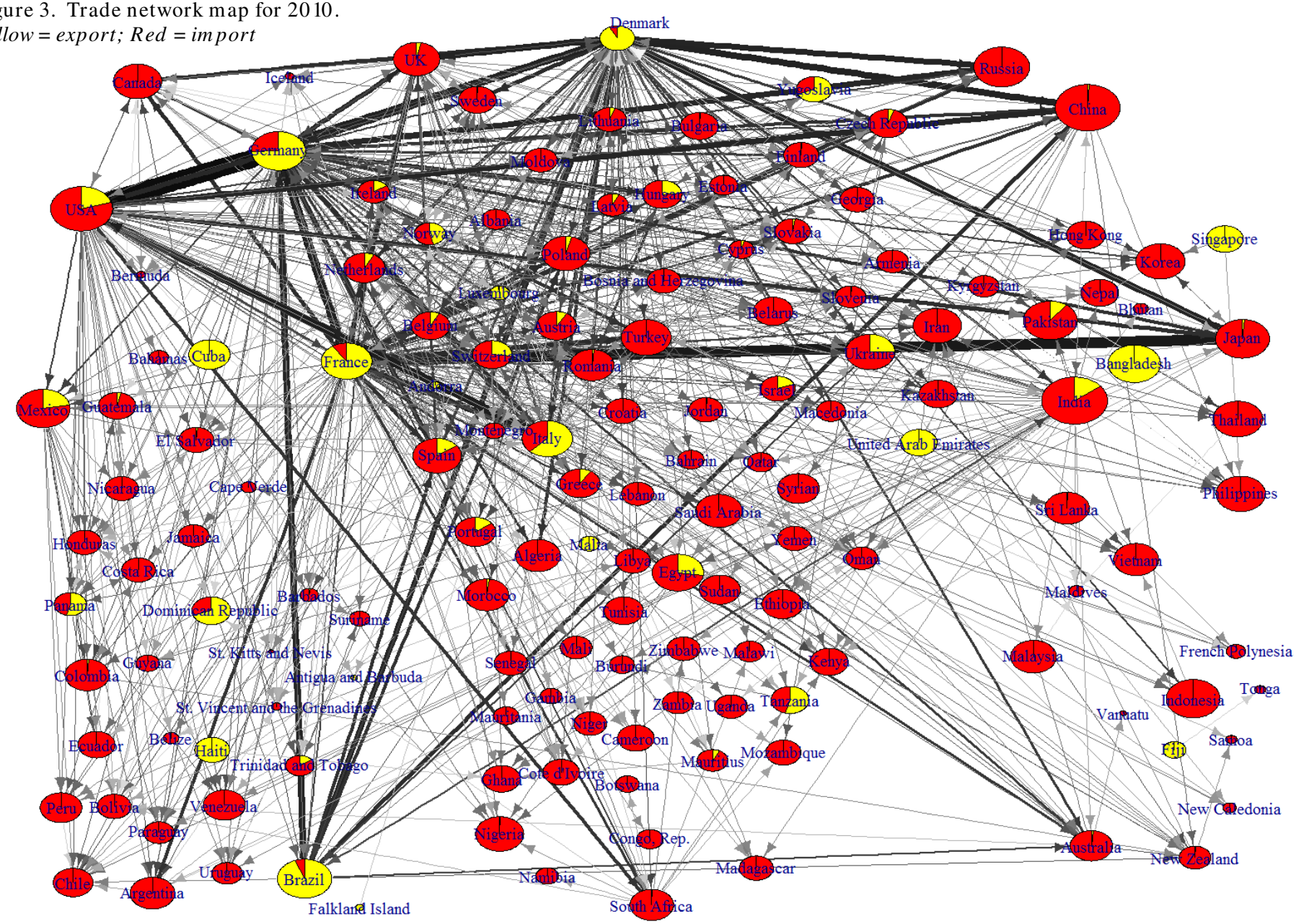


Figure 4. Trade network map for 2013.
Yellow = export; Red = import

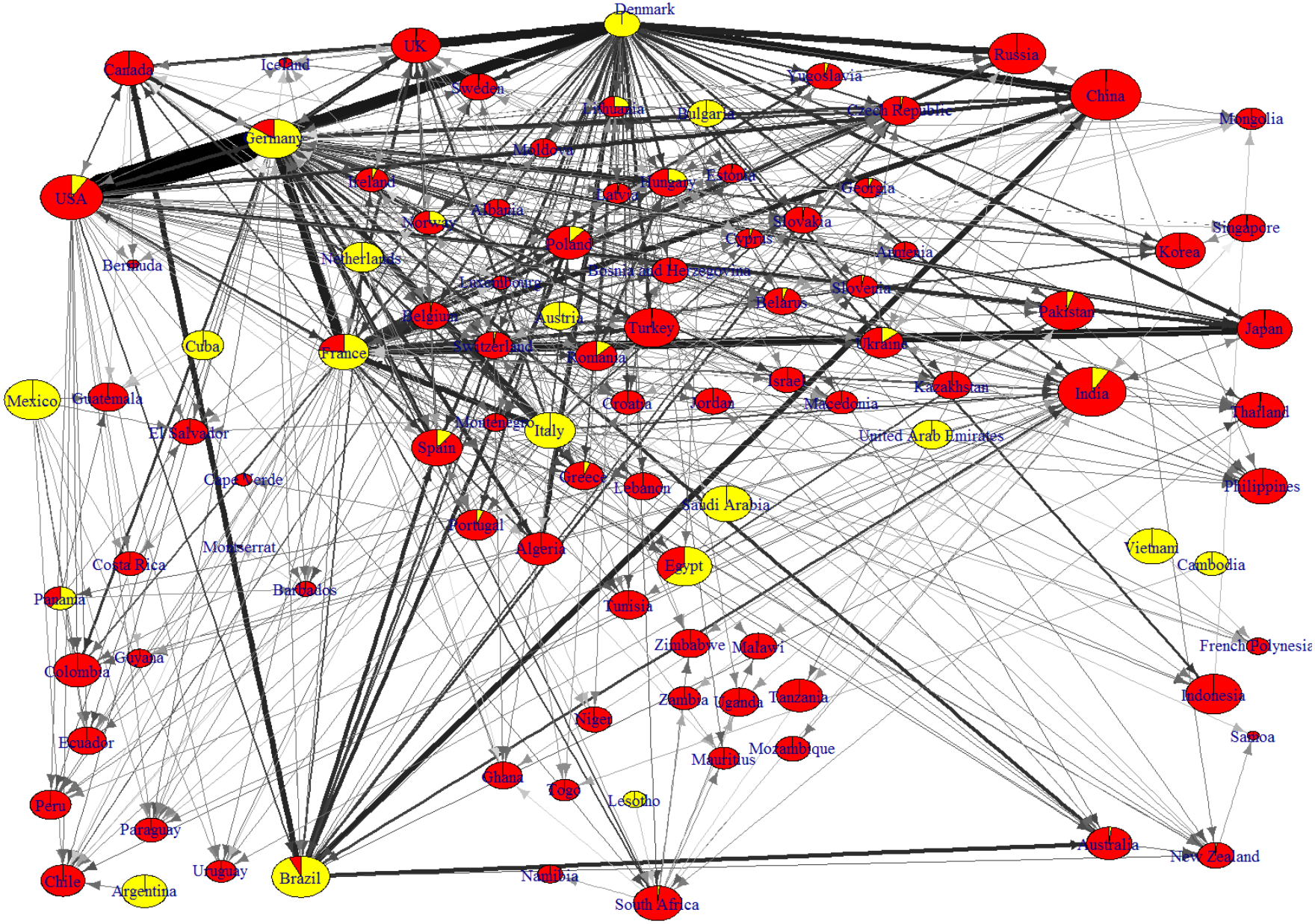


Table 1. Top 20 insulin trade relations (by trade value) in the years 2004, 2007, 2010, and 2013.

	2004			2007			2010			2013		
	Top 20 Trade-relations in terms of value (in USD)		% of 2004 global trade value	Top 20 Trade-relations in terms of value (in USD)		% of 2004 global trade value	Top 20 Trade-relations in terms of value (in USD)		% of 2004 global trade value	Top 20 Trade-relations in terms of value (in USD)		% of 2013 global trade value
S. No. (Rank)	Reporter (Importing)	Exporting		Reporter (Importing)	Exporting		Reporter (Importing)	Exporting		Reporter (Importing)	Exporting	
1	United States	Germany	9.48	United States	Germany	14.92	United States	Germany	15.79	United States	Germany	32.13
2	Germany	France	5.99	Germany	France	4.69	Japan	France	5.1	United States	Denmark	4.17
3	Japan	Denmark	5.79	Germany	Denmark	4.19	Germany	France	4.25	Germany	France	3.72
4	United States	France	5.09	Japan	France	3.85	United States	Italy	3.6	United Kingdom	Denmark	3.51
5	United Kingdom	Denmark	5.08	Japan	Denmark	3.5	United States	Denmark	2.55	China	Denmark	3.28
6	Japan	France	3.44	United States	Denmark	3.36	China	Denmark	2.28	Japan	France	3.23
7	Germany	Denmark	3.13	China	United States	2.38	France	Germany	2.21	France	Germany	2.56
8	United Kingdom	Germany	2.93	United Kingdom	France	2.19	United Kingdom	Denmark	2.16	Germany	Denmark	2.18
9	Poland	France	2.72	France	Germany	2.07	Italy	France	2.16	Russia	Denmark	1.8
10	Italy	France	2.67	United States	France	2.01	Japan	Denmark	2.01	China	France	1.55
11	Spain	Denmark	2.33	Poland	France	1.92	Germany	Brazil	1.95	China	Brazil	1.47
12	France	Denmark	2.33	France	Denmark	1.88	Russia	Denmark	1.9	France	Italy	1.42
13	Russia	Denmark	2.27	Germany	United States	1.84	Denmark	Brazil	1.81	Canada	Brazil	1.34
14	United States	Denmark	2.09	United Kingdom	Denmark	1.74	United Kingdom	France	1.76	United Kingdom	Germany	1.13
15	Italy	Denmark	1.99	China	Denmark	1.7	China	United States	1.75	Spain	Germany	1.12
16	Spain	France	1.88	Spain	France	1.64	Russia	Germany	1.69	Algeria	Denmark	1.08
17	China	Denmark	1.68	Italy	France	1.55	Germany	Denmark	1.52	Germany	Italy	1.04
18	United Kingdom	France	1.54	Russia	Denmark	1.44	United Kingdom	Germany	1.46	Hungary	Germany	1.03
19	United Kingdom	Ireland	1.49	Italy	Denmark	1.32	Germany	United States	1.37	China	United States	0.88
20	Sweden	Denmark	1.24	United Kingdom	Ireland	1.21	Turkey	France	1.72	Japan	Germany	0.86
	% of 2004 insulin trade represented by top 20 links		65.16	% of 2007 insulin trade represented by top 20 links		59.43	% of 2010 insulin trade represented by top 20 links		58.49	% of 2013 insulin trade represented by top 20 links		69.51

Table 2. Trade characteristics of top 15 countries ranked on basis of trade partners in 2004.

	Country	Number of total trade partners (% of global trade links = 643)	Number of import partners	Number of export partners	Total trade value as % of 2004 global insulin trade
1.	Denmark	111 (17.26)	9	102	43.7
2.	France	92 (14.31)	10	82	34.4
3.	Germany	90 (14.00)	14	76	27.3
4.	United States	58 (9.02)	5	53	19.9
5.	United Kingdom	49 (7.62)	9	40	11.0
6.	Netherlands	34 (5.29)	12	22	2.73
7.	Belgium	26 (4.04)	6	20	0.99
8.	Switzerland	26 (4.04)	6	20	0.71
9.	Italy	24 (3.73)	7	17	5.77
10.	India	21 (3.27)	7	14	0.38
11.	Canada	19 (2.95)	12	7	2.11
12.	Egypt	18 (2.80)	13	5	0.35
13.	Ireland	18 (2.80)	8	10	2.55
14.	Mexico	18 (2.80)	5	13	0.55
15.	Slovenia	17 (2.64)	11	6	0.26

Table 3. Trade characteristics of top 15 countries ranked on basis of trade partners in 2013.

	Country*	Number of total trade partners (% of global trade links = 553)	Number of import partners	Number of export partners	Total trade value as % of 2013 global insulin trade
1.	Germany	103 (18.62)	37	66	5.3
2.	France	74 (13.38)	10	64	19.0
3.	Denmark	71 (12.83)	0	71	23.9
4.	United States	54 (9.76)	5	49	39.7
5.	India	42 (7.59)	12	30	1.6
6.	United Kingdom	34 (6.15)	16	18	5.6
7.	Italy	34 (6.15)	0	34	3.7
8.	Czech Republic	24 (4.34)	20	4	1.2
9.	Brazil	22 (3.98)	6	16	6.9
10.	Switzerland	21 (3.80)	14	7	0.5
11.	Poland	21 (3.80)	9	12	1.9
12.	Hungary	21 (3.80)	13	8	2.1
13.	Spain	19 (3.44)	12	7	3.0
14.	China	19 (3.44)	8	11	7.92
15.	Canada	18 (3.35)	11	7	3.36

5.2 Exports of Retail Insulin over Time

Appendix 3 contains the year-specific list of countries ranking in terms of their absolute value (constant 2013 dollars) of the respective year's global value of retail insulin exports. Appendix 4 contains the year-specific list of countries ranking in terms of their fractional share in the respective year's global value of retail insulin exports. The top 10 countries in this league table in Appendix 4 make up between 97.9 and 99 percent of the global value of retail insulin exports over any given year (2004-2013). Several points are noteworthy:

- The largest global market share in retail insulin exports (by value) relegated to Germany, France and Denmark (Figure 5) which export 84.6 to 95.8 percent of global retail insulin by value. The US contributes relatively little towards global exports of retail insulin by value (See also Appendix 4).
- A second "tier" of exporters (Brazil, Italy) is increasing its export share over time (Figure 6). Italy has increased its percent market (by value) by a factor of five to eight as compared to its original share in 2004.
- A third "tier" (Figure 7) consists of India, Spain, Hungary and Egypt, although in comparison to Figure 5, their contributions are trivial.

Figure 5. Time series of retail insulin exports by percent of global share for first tier Exporters.

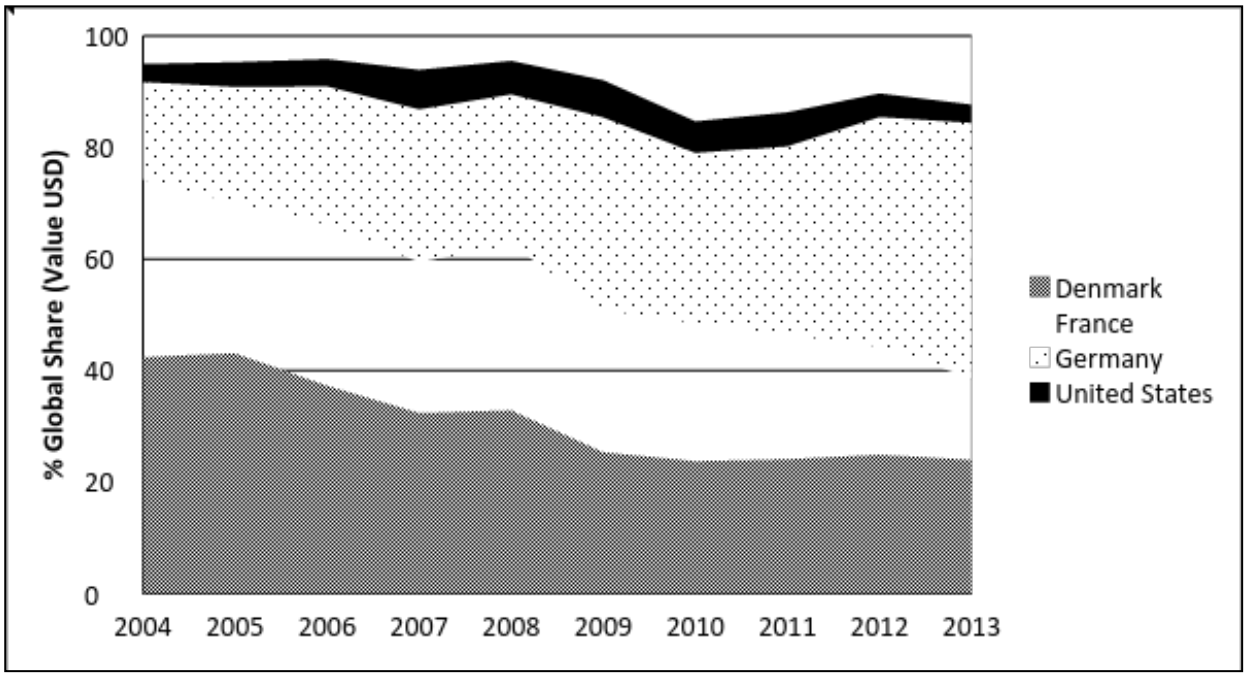


Figure 6. Time series of retail insulin exports by percent of global share for second tier Exporters.

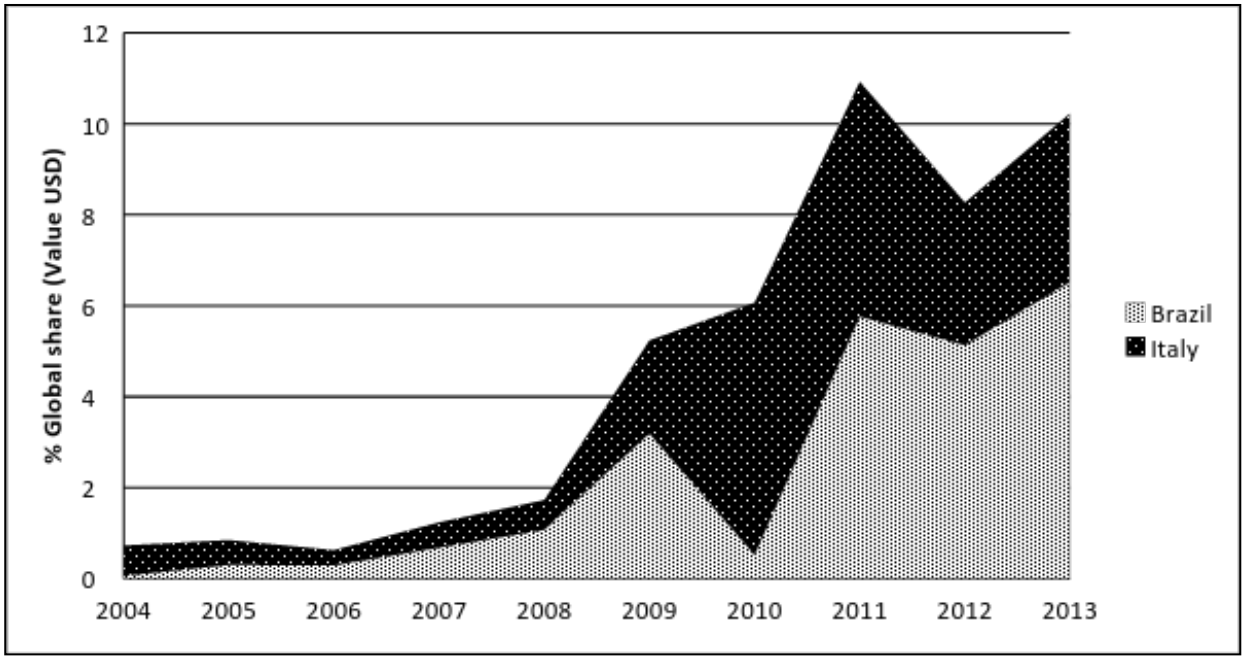
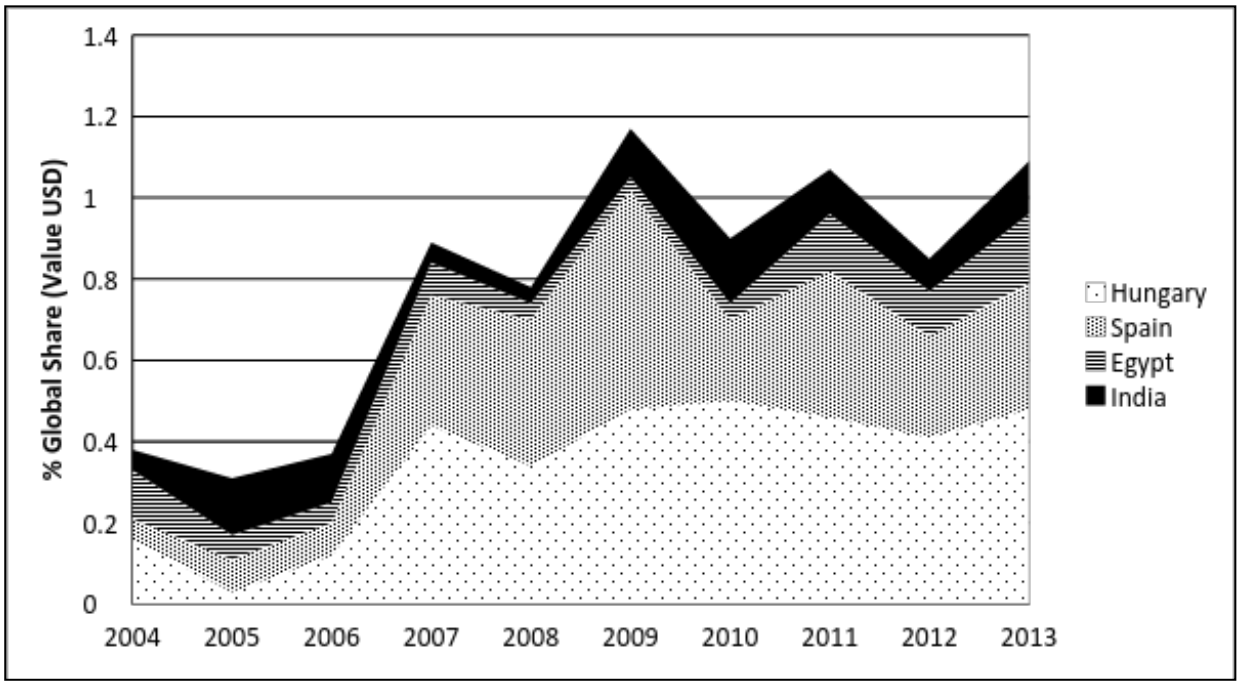


Figure 7. Time series of retail insulin exports by % Global Share for third tier Exporters.



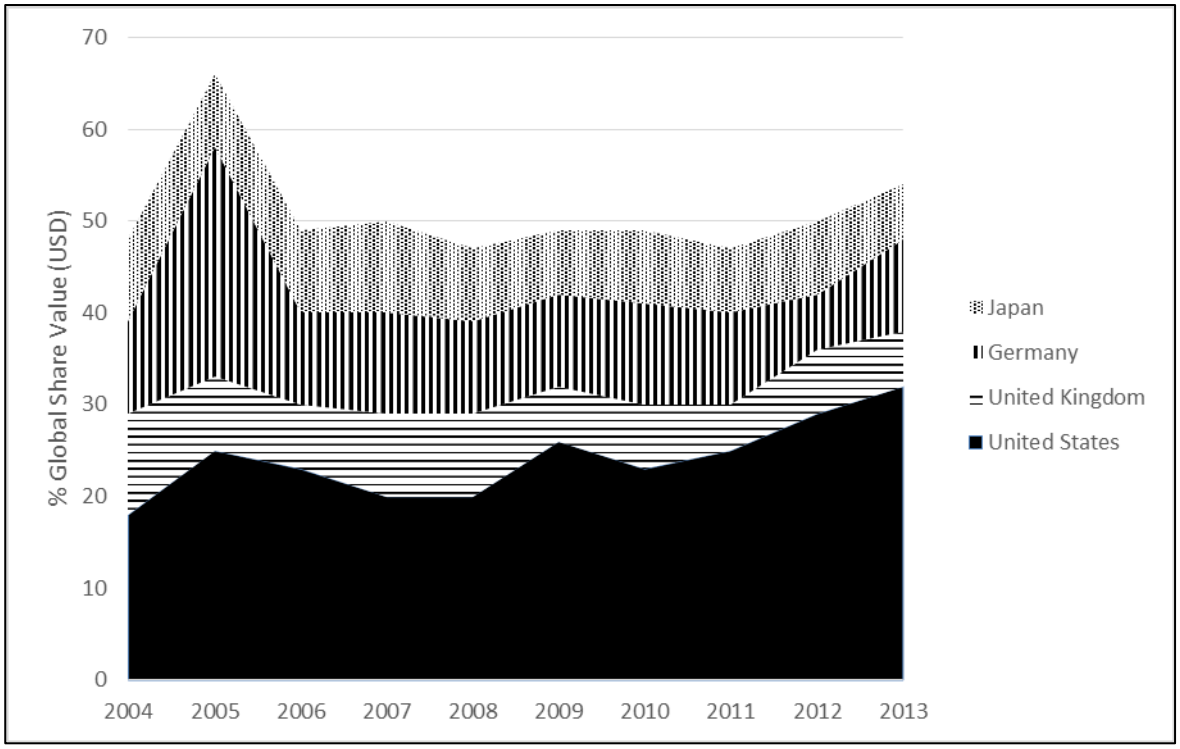
When exports of retail insulin are ranked according to the number of persons with diabetes (Appendix 5), with the exception of Germany and the US, the highest prevalence countries such as India and China are not exporting insulin.

5.3 Imports of Retail Insulin over Time

Appendix 6 contains the ranked list of countries from 2004 – 2013 in terms of their absolute value (constant 2013 dollars) of the respective year's global value of retail insulin imports. Appendix 7 contains the year-specific list of countries ranking terms of their fractional share in the respective year's global value of retail insulin imports. The countries among the top 20 importers make up between 85.2 and 87.2 percent of the global value of retail insulin imports over any given year (2004-2013).

Approximately 50 percent of the global imports of retail insulin between 2004 and 2013 are due solely to the US, UK, Germany, and Japan, with the US being the predominant importer (Figure 8). Among these four countries, their imports (as percentage of global value) are fairly constant over time, except for the US, whose imports of retail insulin have doubled since 2004. We do not know what the consistent spike in imports in 2005 may mean.

Figure 8. Time series of retail insulin imports by percent of global share for top tier Importers.



A second and third tier of importers shows an important and increasing trend (Figures 9 and 10). This includes China (Figure 9), India (Figure 10), as well as Algeria. We infer that, for China and India at least, this reflects their ever-increasing demand for insulin.

Figure 9. Time series of retail insulin imports by percent global share for second tier Importers.

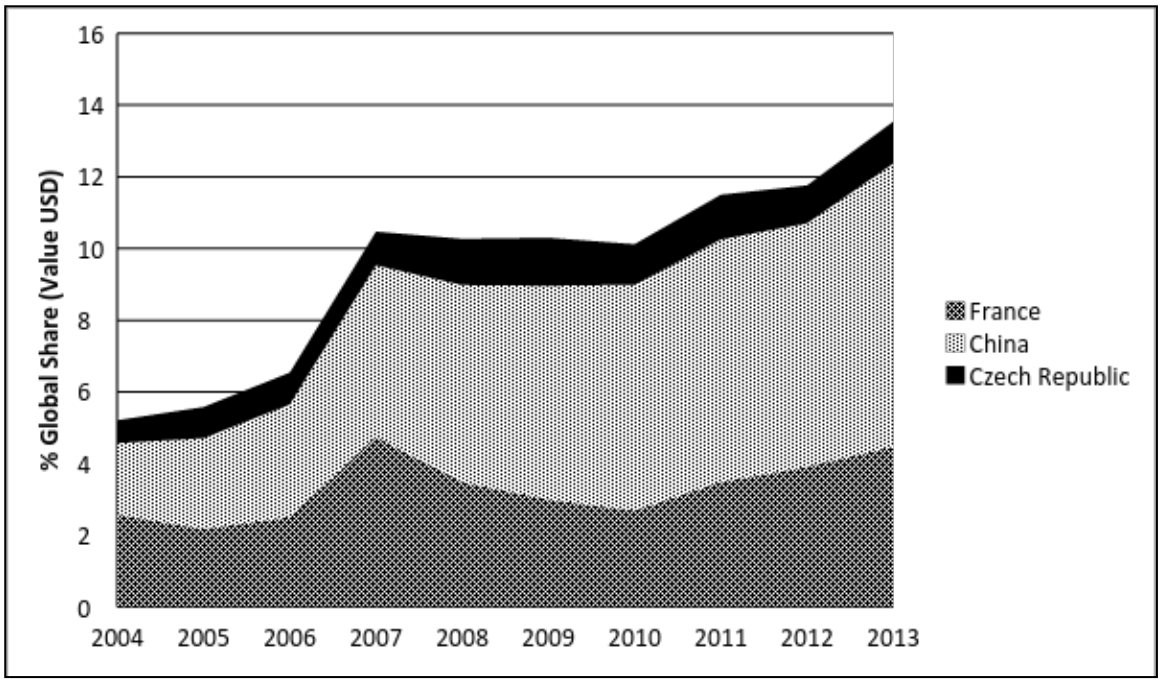
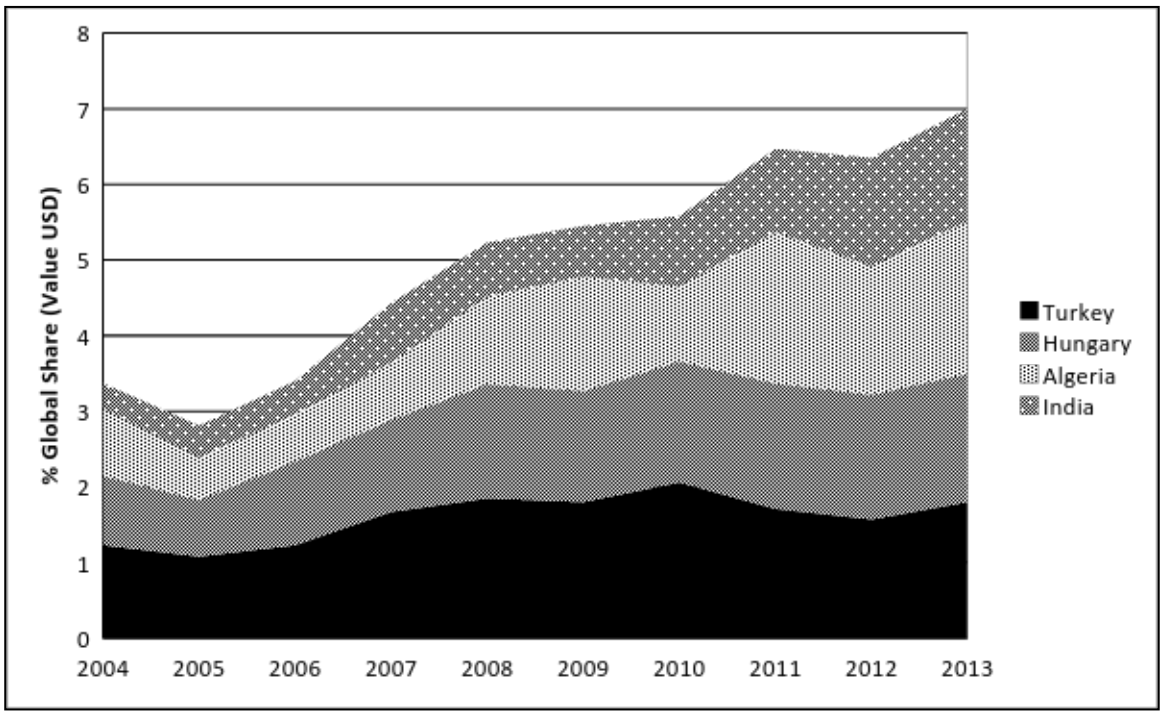


Figure 10. Time series of retail insulin imports by percent of global share third tier Importers.

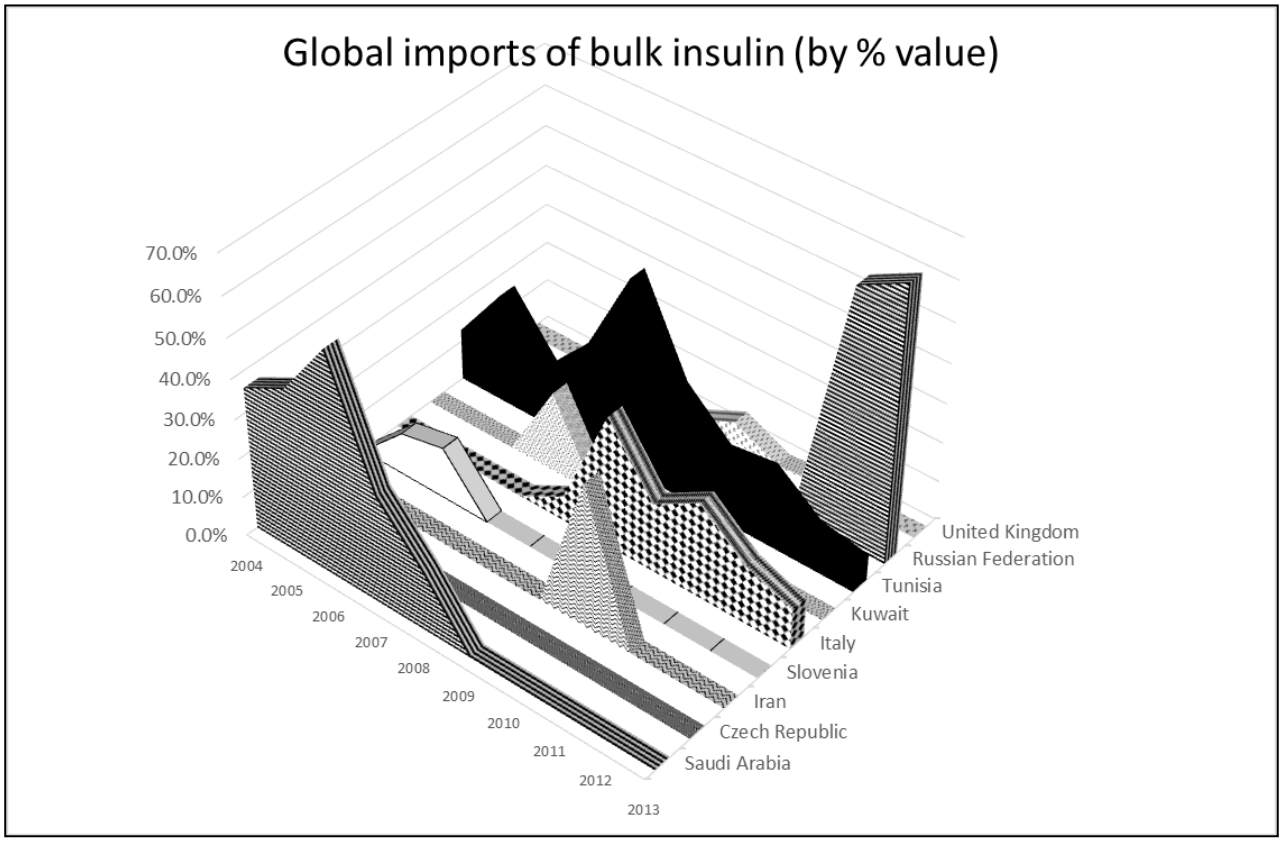


When imports of retail insulin are ranked according to the number of persons with diabetes (Appendix 8), the highest prevalence countries (India and China) are gradually increasing their importation of insulin.

5.4 Imports of Bulk Insulin over Time

In 2004, nine countries imported 65 percent of global bulk insulin by value. We followed these same countries over time, and they individually imported bulk insulin in a sporadic, episodic fashion (Figure 11), quite unlike the much more continuous importation of retail insulin (See Figures 4-6). Indeed, the Russian Federation imported no bulk insulin until 2012 - 2013 when it imported a remarkable 64-69 percent of global bulk insulin by value.

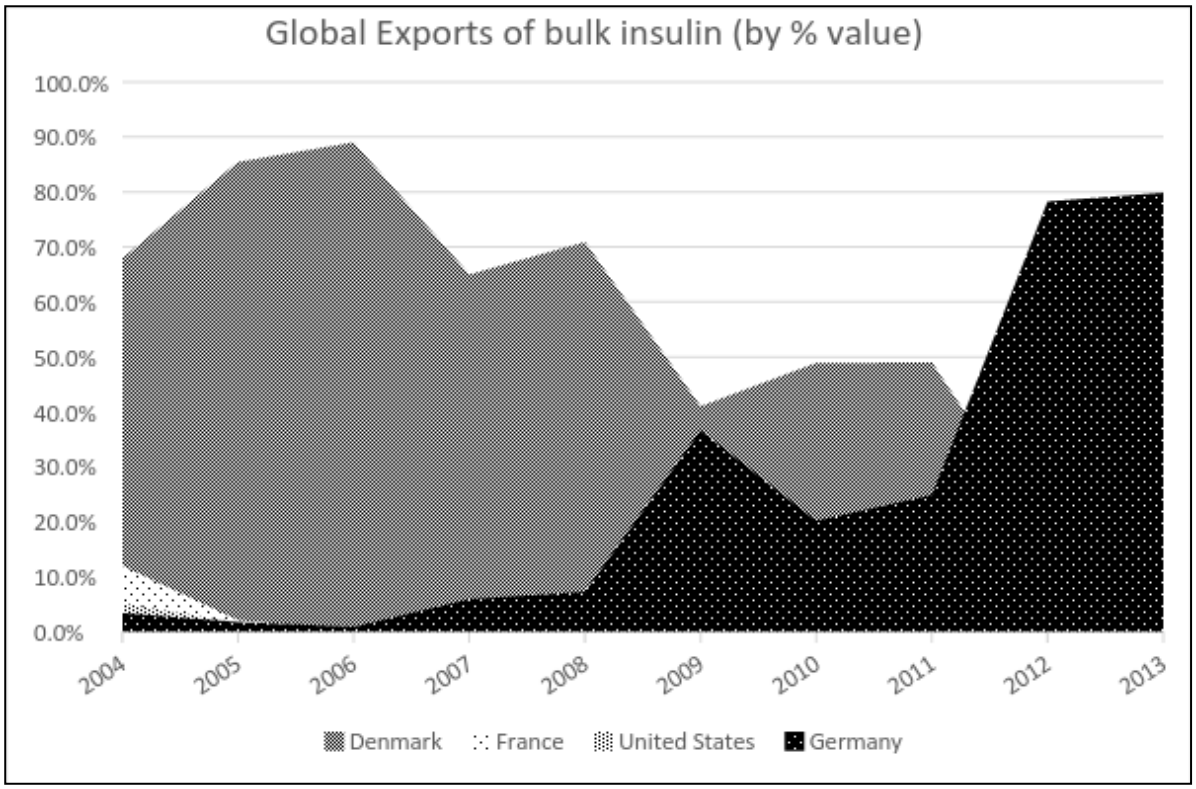
Figure 11. Time series of bulk insulin imports by percent of global share for Importers that import in the aggregate 65 percent or more of global bulk insulin by value.



5.5 Exports of Bulk insulin over Time

In 2004, Denmark exported the vast majority of the world's bulk insulin by value (Figure 12). Danish exports have diminished over time and are being replaced by exports of bulk insulin from Germany, as clearly shown in Figure 12. The US and France exported a trivial fraction in 2004 and continue not to export much insulin in bulk form.

Figure 12. Time series of bulk insulin exports by percent of global share for top tier Importers.



6. Structure of the Retail Insulin Trading Network

6.1 Number of Import Links and their Value

6.1.1 Number of Import Links per Country

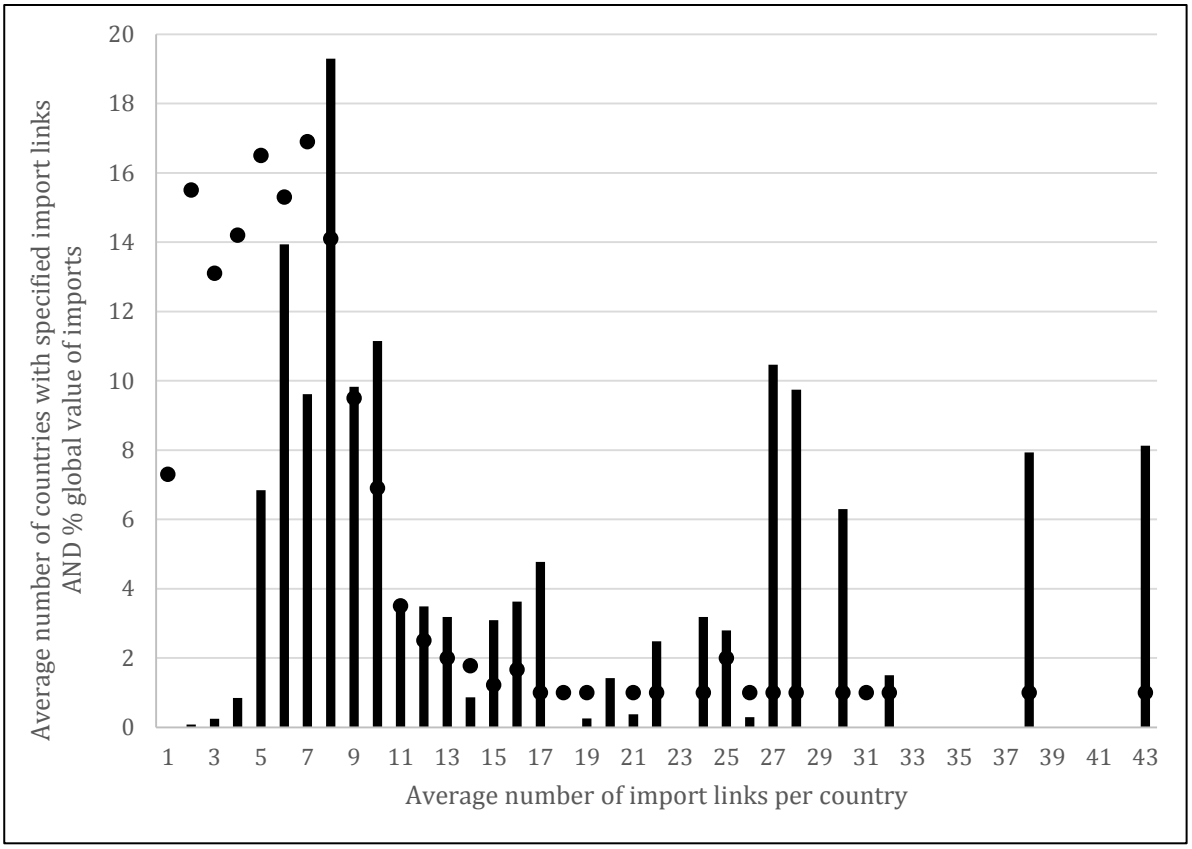
Figure 13 plots on the x axis the average number of import links and plots on the y axis the average number of countries (2004-2013) which have a certain number of import links. Thus, on average between 2004 and 2013, 15 countries (black circles: left Y axis in Figure 13) had only one import link from the rest of the network (x axis in Figure 13), and 17 countries have six import links.

We think it significant that the number of countries who import from between one and seven other countries stay approximately the same until about eight import links are reached. At this point, the average number of importing countries reporting eight or more import links rapidly drops so that only one or two countries import from ten or more countries. We speculate that is may be due to the ever-increasing transaction costs involved in managing multiple imports but it may be an intrinsic property of this particular network given the relatively small number of major exporters of retail insulin.

6.1.2 Value of Import Links

Between 2004 - 2013 about 10-20 percent of all global imports of retail insulin by value (vertical bars: Figure 13 - "average number countries AND average % global value") are relegated to the 13-17 countries that have one to eight import links. Countries with, on average, 25 or more import links (almost invariably Denmark and Germany) contribute an additional eight-10 percent of all imports by value. For example, Germany in 2012 had 42 import links by itself , totaling about 8.1 percent of global retail insulin imports by value.

Figure 13. Average number of countries with specified import links (circles) and percent global value of these import links (vertical bars).



6.2 Number of Export Links and their Value

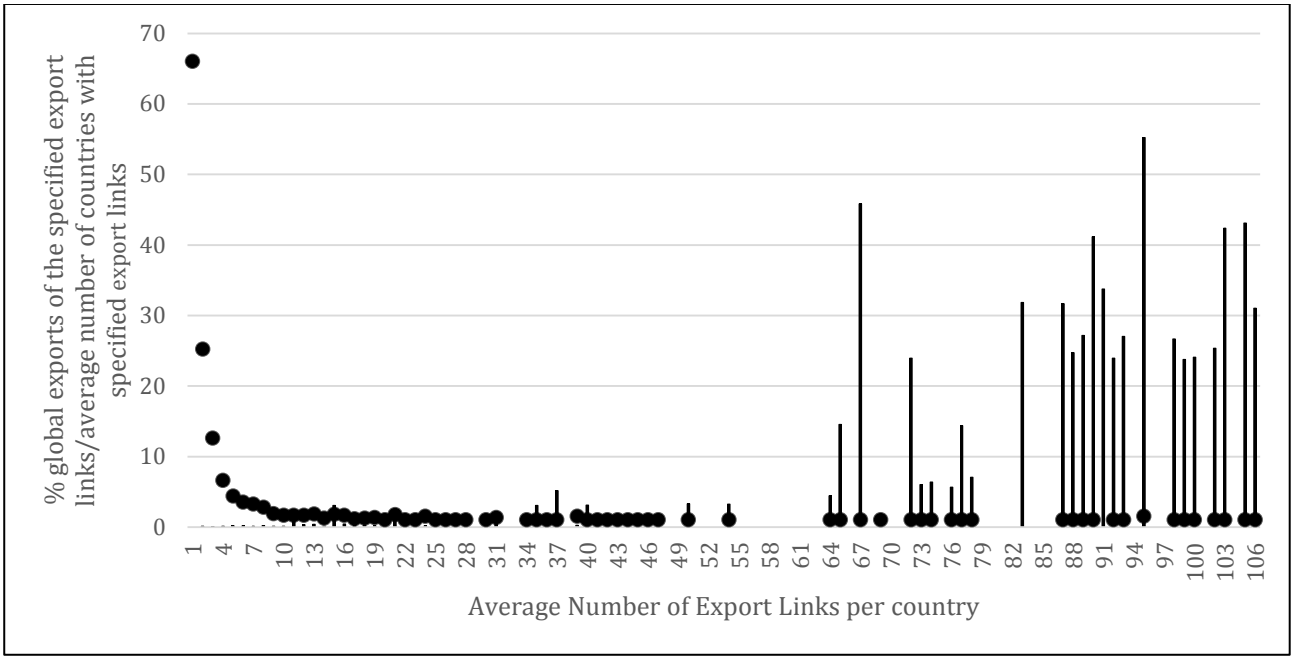
6.2.1 Number of Export Links per Country

On average (over years 2004-2013) there are 66 different countries (black circles, Figure 14) that lack any export links (x axis, Figure 14). This is about 50 percent of the number of countries in the dataset. About 25 countries, on average, have one export link, and about 15 countries have two export links.. The number of countries with ever-increasing export links (x-axis Figure 14) decreases very rapidly so that only a few of countries have 20 export links or more and these are typically the US, Germany, Denmark and France.

6.2.2 Value of Export Links

Averaged over 2004 - 2013 years, the value of all global exports of retail insulin is dominated by the relatively few countries (i.e., France, Germany, Denmark, US) with more than sixty export links (black bars, Figure 14). For example, in 2013 Germany had 67 export links and these links contributed roughly 45 percent of global retail insulin exports by value.

Figure 14. Number of countries with specified export links (circles) and percent global value of these export links (vertical bars) between 2004 – 2013.



7. Impact of Supply Chain Shocks on Retail Insulin Trade

7.1"Vulnerable" countries

We have identified countries that had just one import link for at least one year during 2004-2013 and these are listed in Table 4. Further, no country listed in Table 4 reported having any exports of retail insulin during 2004-2013. Countries whose single importer was Denmark are marked with an asterisk (*).

Countries importing from just one country for just a single year, for example,, Anguilla in 2008, Armenia in 2006 and Burkina Faso in 2008, we define as "vulnerable," – meaning they are more at risk in that year to supply disruptions. It is important to note that there are many countries that have had a single importer for multiple years (e.g., Botswana, Cape Verde, Fiji, Gambia, Mali, Malta, Mauritania, Mozambique, Namibia, and Vanuatu). For seven of the 10 years, Azerbaijan had a single import link (mostly from Denmark) and would be considered "highly vulnerable" to disruptions in insulin supply. The majority of these countries in Table 4 are low- to middle-income economies with no capacity to make insulin.

Table 4. List of "vulnerable" countries annually from 2004-2013.

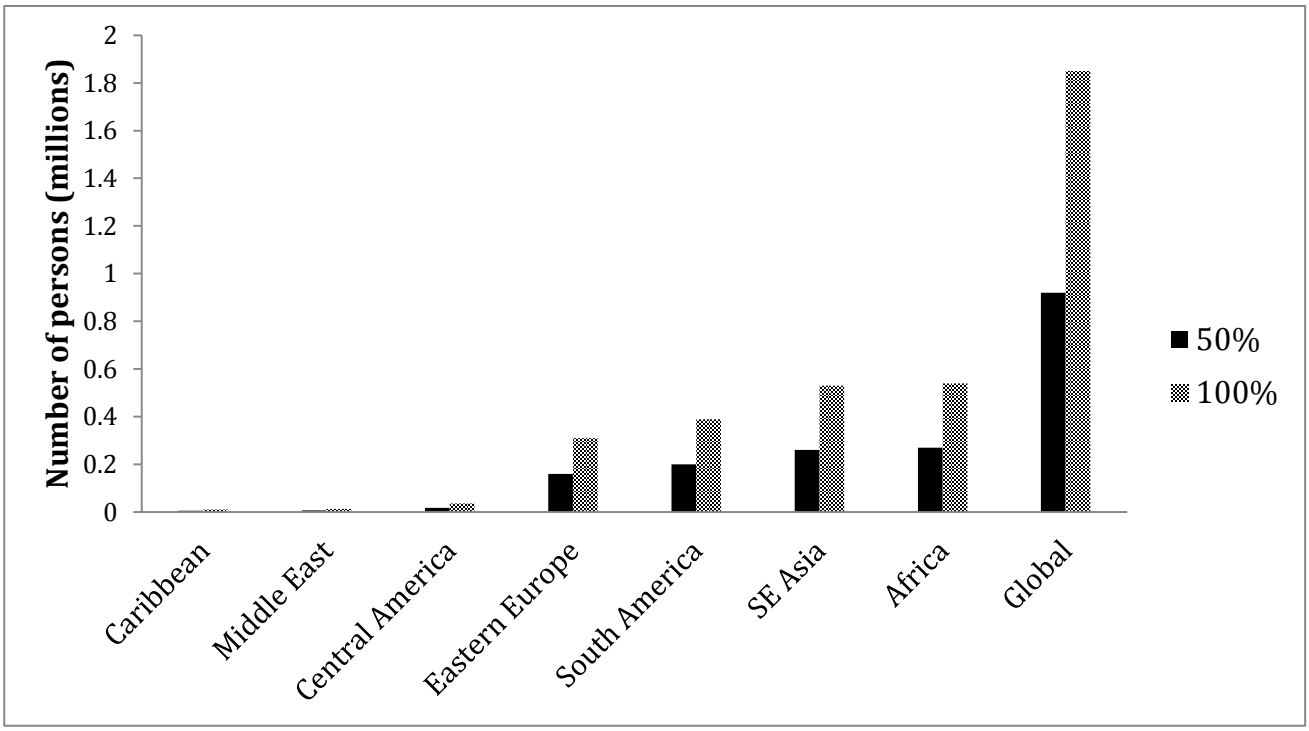
2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Azerbaijan*	Cape Verde	Armenia	Azerbaijan	Anguila	Azerbaijan*	Bhutan	Azerbaijan	Azerbaijan	Cape Verde
Botswana	Cuba*	Azerbaijan*	Belize*	Azerbaijan*	Botswana	Botwsana	Bahamas, The	Botswana	Montserrat
Burundi	Fiji	Bhutan	Burundi	Botswana	Cape Verde	Cape Verde	Botswana	Brunei	Mozambique
Cuba*	Macao*	Botswana	Cape Verde	Burkina Faso	Congo, Rep.	Congo, Rep	Burundi	Burundi	Namibia
Fiji	Madagascar	Burundi	Grenada*	Cape Verde	Djibouti	Gambia	Cape Verde	Cape Verde	
Gambia	Mali	Cambodia	Mali	Congo, Rep.	Gabon	Jordan	Fiji	Fiji	
Iran	Netherlands Antilles	Cape Verde	Malta	Dominica	Jamaica*	Kyrgyz Rep.*	Malaysia	Mali	
Lesotho	Senegal	Comoros	Mozambique*	Dominican Republic	Lesotho	Malaysia	Namibia	Malta	
Mauritania	Swaziland	Sudan	Occupied Pales. Territory	Gambia, The	Malaysia*	Mali	Turks and Caicos Isl.	Namibia	
Mozambique		Gambia	Sri Lanka	Guinea	Malta	Mauritania	Vanuatu	Palau	
New Caledonia		Grenada*	St. Lucia	Libya	Mauritania	Namibia	Zambia	Panama	
Sri Lanka*		Malta	Sudan	Malaysia	Namibia	Syrian		Togo	
Swaziland		Mozambique	Tunisia*	Namibia	Occ.Pal.Terr	Tonga		Turks and Caicos Isl.	
Uganda*		Namibia	Vanuatu	Seychelles	Rwanda	Vanuatu		Zambia	
		Netherlands Antilles	Yemen	St. Lucia	Sri Lanka				
		Occ.Pal.Terr		Tunisia*	Syrian Arab Republic*				
		Sri Lanka		Zambia	Togo				
		Swaziland			Tunisia*				
		Tunisia			Vanuatu				
		Vanuatu			Yemen				

7.2. Potential Impact of Supply Disruptions from Denmark

To illustrate the potential impact of supply disruptions from Denmark, we applied the simple model as described in Section 5.2.4 to a proposed situation where Denmark's exports in 2012 were either completely stopped or cut in half (Figure 15). In 2012, Denmark exported to four countries in Eastern Europe (Hungary, Czech Republic, Russian Federation, Ukraine), about 27 countries in Africa, 12 countries in Southeast Asia (including China, India Australia and some Pacific Islands), eight countries in South America, 20 countries in Eastern Europe, six countries in Central America, five countries in the Middle East and five countries in the Caribbean.

With regard to the 100 percent export "shutoff" scenario, if there was complete disruption in exports in 2012 from Denmark, in 2012, there would be in total approximately one million persons not receiving insulin in Africa and Southeast Asia. To put this into context, Mexico has approximately seven million people living with diabetes. (26) One can see that the size of Denmark's contribution to the Caribbean, Central American and Middle Eastern markets is small compared to other regions, primarily we expect this to be a function of the number of countries in the region. Globally, number of people who would not receive insulin in these two scenarios ranges from about 920,000 to nearly two million.

Figure 15. Number of persons (millions) capable of being treated with "missing" 2012 exports of retail insulin from Denmark



8. Estimations of the Unit Cost of Imported Retail and Bulk Insulin

The global aggregated unit price for retail and bulk insulins was estimated from the data in Table 5 and is summarised as "global bulk" and "global retail" unit price ($/ 10 ml). Several points are noteworthy. First, each year, the total global value of retail insulin is about two orders of magnitude greater than the total global bulk insulin value. By weight, retail insulin is about 50 times that of bulk insulin. Second, a crude estimate of the price of 10gm(ml) of imported **retail** insulin is with a very narrow range, between about 3.1- 3.8 U.S. dollars per 10 gm/10ml. Global bulk unit price is one –half to one-third the price of retail, except for the sudden spike in 2012 and 2013

Table 5. Global bulk and retail insulin imports by value and weight (2004-2013) and estimates of global unit price.

	TOTAL IMPORTS					
Year	TOTAL GLOBAL BULK VALUE*1000 USD	TOTAL GLOBAL BULK WEIGHT (KG)	TOTAL GLOBAL RETAIL VALUE*1000 USD	TOTAL GLOBAL RETAIL WEIGHT (KG)	GLOBAL BULK UNIT PRICE	GLOBAL RETAIL UNIT PRICE
2004	65694	332678	3598155	11345624	1.97	3.17
2005	52785	212895	4706876	13575299	2.47	3.46
2006	77532	874288	5086224	14899998	0.88	3.41
2007	71557	647018	5884621	16369616	1.10	3.59
2008	34874	275481	6652888	18226674	1.26	3.65
2009	35364	283221	7411649	20290098	1.24	3.65
2010	56035	538404	7839550	22573477	1.04	3.47
2011	72562	615086	8918487	23444158	1.11	3.8
2012	135131	296760	9275157	27008877	4.55	3.43
2013	126067	259066	10529043	28710835	4.86	3.66

The second, "country-specific" method of calculation shows similar qualitative trends in unit price of both bulk and retail insulin (Figures 16-18) as do the global estimates (Table 5). The particular spike in median price of bulk insulin in 2011 (Figures 16 and 18) can be explained by the extraordinary high price ($2609/10 ml) paid for by the US for imported bulk insulin. We think this might be a numerical error in the database. Without this value, the median unit bulk price would be $2.51/10 ml.

Nevertheless, the data suggest a slow decrease in the unit price of retail insulin that is being imported into the top 30 importing countries and tracks the global crude (Table 5) estimate, qualitatively, and quantitatively.

Figure 16. Time series of median unit bulk insulin price (USD/10ml) exported to the top 20 global importers (with 75th/25th percentiles).

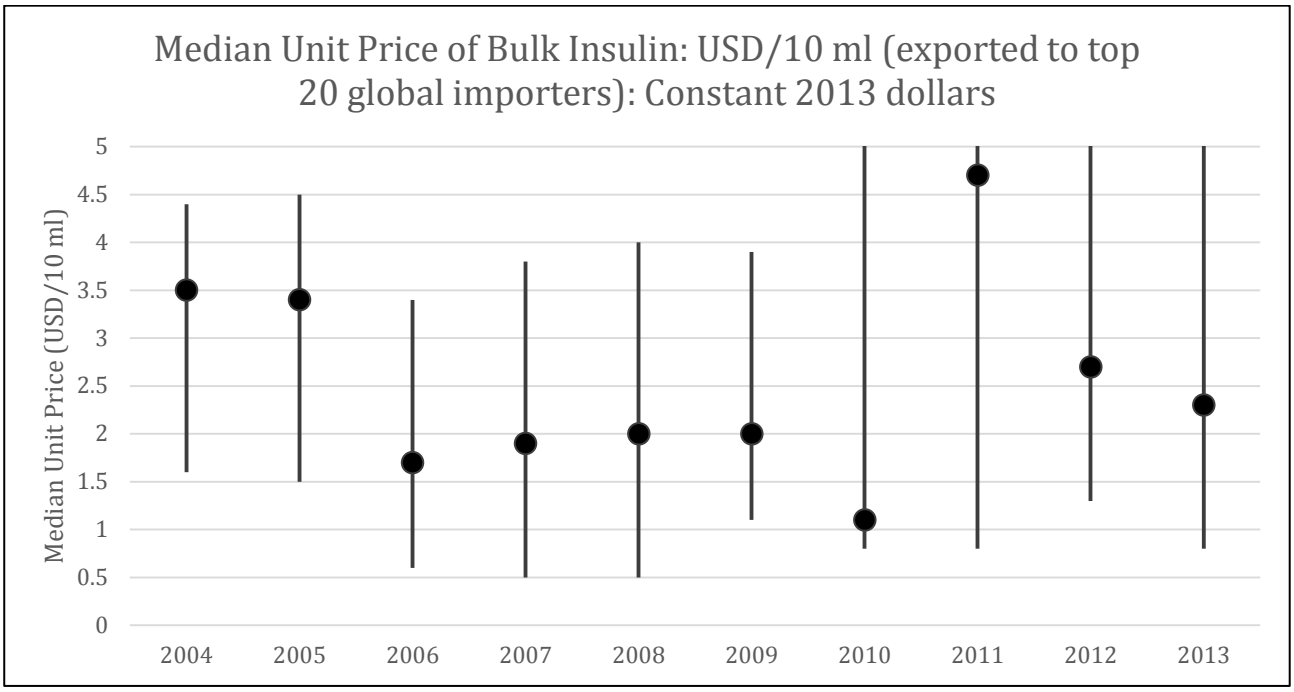


Figure 17. Time series of median unit retail insulin price (USD/10 ml) exported to top 30 global importers (with 75th/25th percentiles).

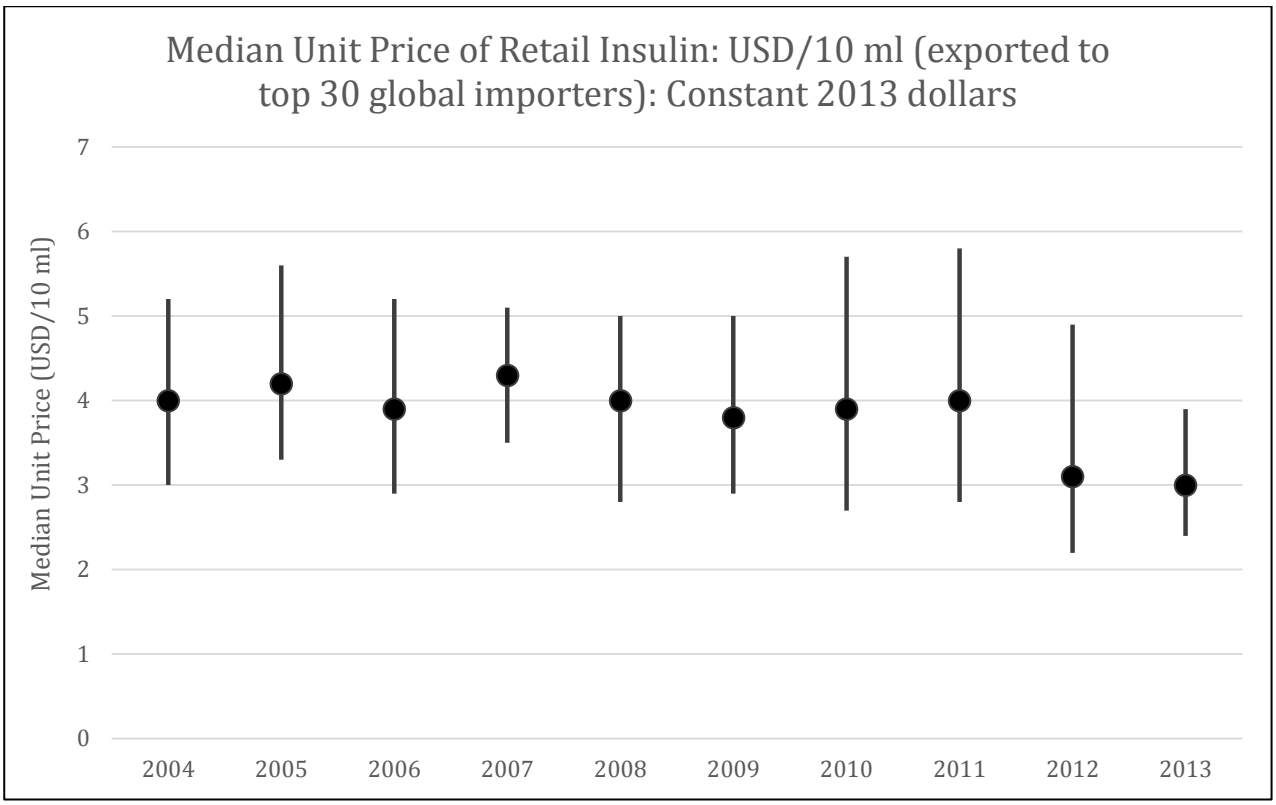
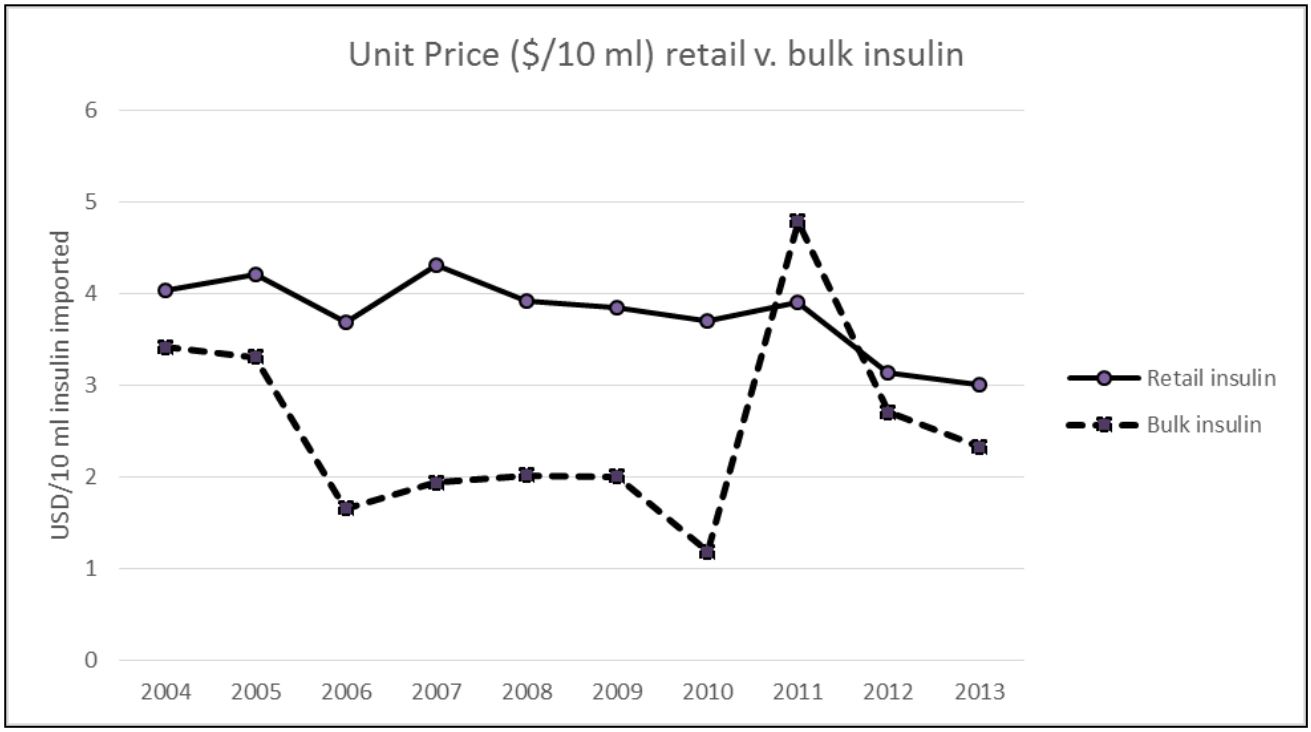


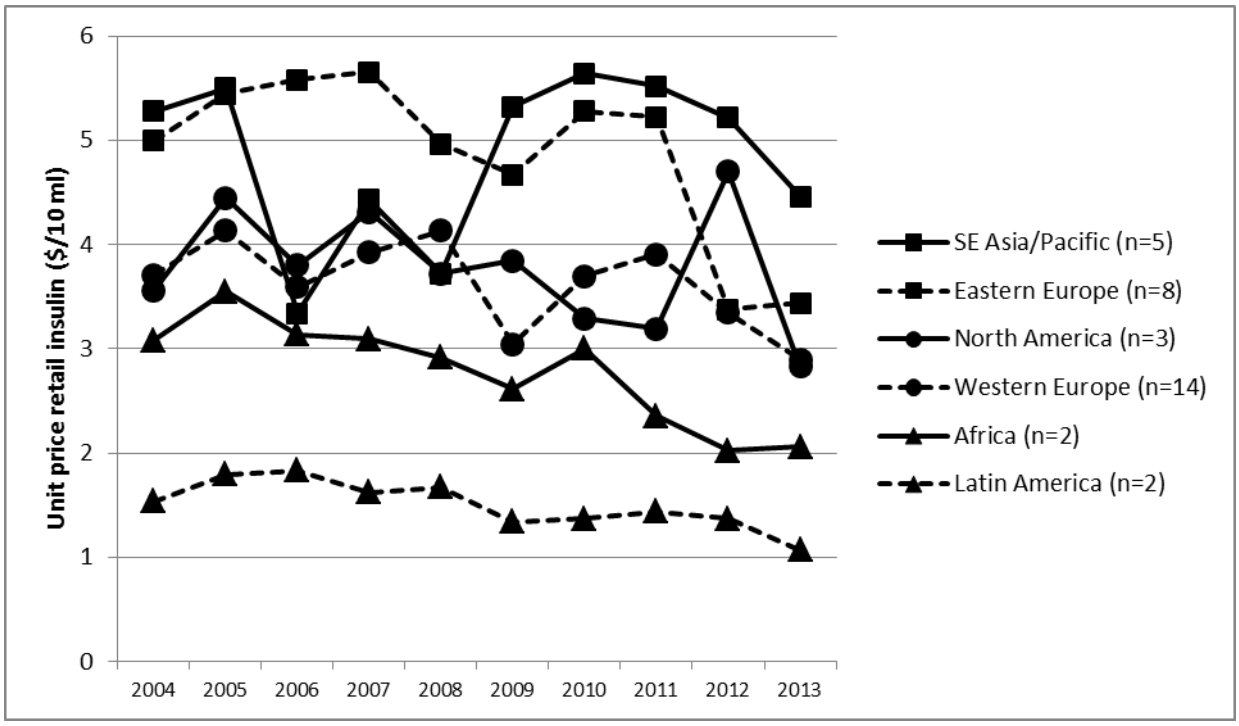
Figure 18. Time series comparison of median unit price (USD/ 10 ml) of bulk and retail insulin



We further disaggregated these 30 top importing countries by region and included four additional countries; Brazil and Argentina as representing Latin America, Mexico as the third NAFTA country, and India as the additional country in Southeast Asia/ Pacific region.

The time series of median retail insulin unit price is shown in Figure 19 for various geographic regions. Note that the number is small for Latin America and the median unit price is at least one-third that of the other regions. Roughly the lowest unit retail insulin prices are in Africa and Latin America, and those with the highest unit prices are in Southeast Asia/Pacific and Eastern Europe. Generally North America and Western Europe lie in between. The variation in Southeast Asia /Pacific is almost entirely due to India whose import prices for retail insulin are very high, averaging $53.9/10 ml [median $30.15] overall years (See Annex 1).

Figure 19. Time series of median unit retail insulin price (USD/10ml) in different geographic regions.



9. Discussion

Germany, Denmark, France, and to a lesser extent, the US are the critical components of the global insulin trade. Indeed, 84.6 to 95.8 percent of global retail insulin by value is exported by these four countries. (Appendix 3, 4 and Figure 5). US contributes relatively little towards global exports of retail insulin by value. Brazil and Italy have been increasing their export share (by value) over time. India, Spain, Hungary and Egypt are the third tier exporters, although their contributions are small compared to the US and Europe.

Similarly, the global trade in imported insulins is dominated by high-income countries. Approximately 50 percent of the global imports of retail insulin between 2004 and 2013 were due solely to the US, UK, Germany, and Japan, with the US being the predominant importer. The imports of retail insulin (by value) into the US have doubled since 2004.

The insulin trade network created by trading partners may have an additional property as there appears to be a limit to the number of import links into any given country. After eight import links are reached by a country, the average number of import links rapidly drops. Only one to two countries import from 10 or more countries. This is likely to due to the high transactional costs needed to manage eight or more tenders and/or procurement procedures. We note that some small countries and islands are particularly vulnerable to disruptions in supply of retail insulin (e.g.,

Azerbaijan, Botswana, Cape Verde, Fiji, Gambia, Mali, Malta, Mauritania, Mozambique, Namibia, and Vanuatu).

10. Conclusions

In developing a response to the issue of access to insulin, it is crucial to understand its global need. Only a few companies dominate the market so the question, without large scale manufacturing/export from India or China or any other emerging economy, is whether the three main multinational companies can meet the global demand for insulin. Providing any answer is complex, not least because of paucity of data, and this document only partially provides an answer. Clearly, many small economies are highly vulnerable to disruptions in supply of insulin as they rely on a single source.

Moreover, insulin needs in each country will be different and that will depend, in large part, on the number of diagnosed and undiagnosed persons. In Nicaragua it was found that in comparison to global estimates, the number of people with diabetes 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. (29) In the UK with approximately 750,000 adults living with type 2 diabetes not diagnosed, this is equal to 16.5 percent of the total number estimated to have diabetes in 2013. (30)

Although not analysed in this report, a number of questions present themselves for a further research agenda.

- Are imports of retail insulin (by weight) to countries that have no local production capacity (e.g., most of Africa) enough to supply what we think is the in-country need?

This is a first-order question but given the uncertainties in estimating the number of persons with diabetes this is a significant issue. (31) We note that different biomarkers and definitions for diabetes can provide different estimates of population prevalence of diabetes, and differentially identify people without previous diagnosis as having diabetes. Using an HbA_{1c}-based definition alone in health surveys will not identify a substantial proportion of previously undiagnosed people who would be considered as having diabetes using a glucose-based test. (32)

- What is the difference between the unit price of imported insulin into a country and the retail selling price?
- What are the factors (e.g., number of persons living with diabetes in importing country, volume of insulin imported, gross national income) that impact the unit price of imported retail insulin?

In different countries the average price of insulin to the public sector varied from US$ 4.10 in Mozambique in 2003 to US$ 8.40 in Kyrgyzstan in 2009. (2-4) Some countries benefitted from a differential pricing scheme developed by one of the leading insulin manufacturers. Different duties, taxes, and mark-ups increase the cost of insulin impacting affordability to the health system and individual. The financial burden of insulin to the health system is of concern to all countries. Affordability to the individual is dependent on the types of insulin purchased, mark-ups within the system, if insulin was available in the public sector, etc., but most importantly whether or not people with diabetes have to pay for their insulin or if the cost is covered by the health system.

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.

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12. Annexes

Annex 1. Conversion of insulin weight to liquid volume

Total weight (imports) converted to total International Units of retail insulin as follows:

1. Total weight of retail insulin re- calculated as number of 10 gram units.

2. We assume density of insulin to be 1gram/milliliter.

3. Ten grams (ml) of retail insulin contains 100 International Units (IU).

4. From the total IU's, the number of persons treatable can be estimated by assuming each person's daily requirement of insulin is 40 International Units per day or (365*40 IU person-yr).

Annex 2. “r” codes

R codes:

```
> library(igraph)
> world2004<- read.csv(file.choose())
> attach(world2004)
> fix(world2004)

> world2004<-world2004[1:643,]
> myedgelist <-
cbind(as.character(world2004$Exporting.to.Reporter),as.character(world2004$ReporterName))
> g <- graph.edgelist(myedgelist,directed=TRUE)
> E(g)$Value <- world2004$TradeValue.in.1000.USD
>
#Total number of countries in the database/network
> vcount(g)

#Total number of trade links/edges in the trade network
> ecount(g)

#List of exporter-only countries
> V(g)$name[degree(g, mode="in")<1]

#List of importer-only countries
> V(g)$name[degree(g, mode="out")<1]

#Countries ranked on basis of number of incoming trade links/edges or partners they import
from
> d.in <- degree(g,mode="in")
> d.in[order(d.in,decreasing=T)]

#Countries ranked on basis of number of outgoing trade links/edges or partners they export
to
> d.out <- degree(g,mode="out")
> d.out[order(d.out,decreasing=T)]

#Countries ranked on basis of number of total (import plus export trade partners)
> d.tot <- degree(g,mode="total")
> d.tot[order(d.tot,decreasing=T)]

#Countries ranked on basis of number of total import dollar value
> st.in <- graph.strength(g,mode="in",weights=E(g)$Value)
> st.in[order(st.in,decreasing=T)]

#Countries ranked on basis of number of total export value
> st.out <- graph.strength(g,mode="out",weights=E(g)$Value)
> st.out[order(st.out,decreasing=T)]

#Countries ranked on basis of number of total import plus export value
> st.out <- graph.strength(g,mode="total",weights=E(g)$Value)
> st.out[order(st.out,decreasing=T)]


# Codes to generate Excel spreadsheet with information on country-specific percentage
import share

#Assign working directory/folder where excel file will be exported
>setwd("C:/Users/Sk/Desktop/Diabetes/Insulin time series again")
```

```
#After loading the "xlxs" package in R, assign trade value to each edge
> E(g)$Value <- tmp$TradeValue.in.1000.USD

#Add all in-degree edge values (import value in dollars) for each country
> st.in<-graph.strength(g,mode="in",weights=E(g)$Value)

#Sum the total import value of all countries to get the denominator to calculate percentage
> totalimp<-sum(st.in)

#Get the percentage for each country by dividing the country's import value by the
total/global sum of all import values
> imp_percentage<-(st.in/totalimp)*100

#Create a table with country, import value, and percent of total/global import value
> table_imp<-cbind(st.in,imp_percentage)

#Sort the table in decreasing order of import value
>table_imp<-table_imp[order(-st.in),]

#Exports the table to EXCEL
>write.xlsx(table_imp, file = "ImportValueRank.xlsx",sheetName = "TestSheet")
```

Similarly, codes to generate Excel spreadsheet with information on country-specific percentage export share

```
>E(g)$Value <- tmp$TradeValue.in.1000.USD
>st.out<-graph.strength(g,mode="out",weights=E(g)$Value)
>total_exp<-sum(st.out)
>exp_percentage<-(st.out/total_exp)*100
>table_exp<-cbind(st.out,exp_percentage)
>table_exp<-table_exp[,order(-st.out),]
>write.xlsx(table_exp, file = "ExportValueRank.xlsx",sheetName = "TestSheet")

#Merge import and export tables
>import_export <- merge(table_imp, table_exp, by=0)
>write.xlsx(import_export, file = "Country_Import_Export.xlsx",sheetName = "TestSheet")
```

#Codes for generate excel sheet with information on import (in-degree) and export (out-degree) frequency

```
> d.in <- degree(g,mode="in")
> orderedbyIn<-d.in[order(d.in,decreasing=T)]
> freq<-table(orderedbyIn)
> freq

> write.xlsx(x = freq, file = "import2 link frequency 2004.xlsx", sheetName = "world2004importfreq",
row.names = FALSE)
> d.out <- degree(g,mode="out")
> orderedbyOut<-d.out[order(d.out,decreasing=T)]
> freq<-table(orderedbyOut)
> freq

> write.xlsx(x = freq, file = "export2 link frequency 2004.xlsx", sheetName = "world2004exportfreq",
row.names = FALSE)

> d.tot <- degree(g,mode="total")
> orderedbytot<-d.tot[order(d.tot,decreasing=T)]
> freq<-table(orderedbytot)
> freq
> write.xlsx(x = freq, file = "total(imp+exp2 link frequency 2004.xlsx", sheetName =
"world2004trade(import+exportfreq)", row.names = FALSE)
```

#Codes to generate excel sheet with information on country-specific in-degree (number of exporters), out-degree (number of countries exporting to), in-strength (import value) and out-strength (export strength)

```
> setwd("C:/Users/Sk/Desktop/Diabetes/Insulin time series again")
>table<-cbind(d.in,st.in, d.out,st.out)
>write.xlsx(table,file="2004Merged.xlsx", sheetName = "exportReported")
```

Codes to plot the insulin trade network maps

```
library(xlsx)

library(igraph)

library(plotrix)


#Read in import/export data

tmp <- read.csv("2012insulin.csv",header=T)

tmp<-tmp[1:786,]


#Create network

myedgelist <- cbind(as.character(tmp$Exporting.to.Reporter),as.character(tmp$ReporterName))

g <- graph.edgelist(myedgelist,directed=TRUE)


#Read in datasheet I made for import/export value for each country

impexp<-read.csv("pie_chart_data.csv",header=T)


#Creates list to use in pie charts

imp_exp=list()


for(i in 1:141){

  imp_exp[[i]]=c(impexp[i,1], impexp[i,2])

}


#Read in number of diabetics for each country

diabatt<-read.xlsx("diabatt.xlsx",header=T, sheetName="TestSheet")

diabattribute <- diabatt[1:141,]
```

```
#Assign number of diabetes as a country attribute
people<-diabattribute$People
V(g)$diabetes<-people

#Assign trade value as an edge attribute
E(g)$Value <- tmp$TradeValue.in.1000.USD

#Multiple each edge attribute (trade value) by 1000 and take log.
logum<-log(E(g)$Value*1000)

#Rescale the log values to all be between 0 and 1.
#Assign a gray scale color to each value and color each edge accordingly.
Ecol <- gray(rescale(logum, c(1, 0)))
E(g)$color<-Ecol

#Make the edge width the square root of the value divided by 50.
E(g)$width<-sqrt(E(g)$Value)/50

#Make the vertex size proportional to number of diabetics by taking log.
V(g)$size=log(V(g)$diabetes)

#Set vertex label size
V(g)$label.cex = 1.35

#Read in coordinates of vertices.
coords<-read.xlsx("coordsin.xlsx", header=F,sheetName="TestSheet")
coords <- as.matrix(coords[1:141,])

#Plot the network and output it.
png(file="insulinplotDraft_forAbhi.png",width=1700,height=1350)
plot(g, layout=coords, edge.arrow.size=1, vertex.label.font=3, vertex.shape="pie", vertex.pie=imp_exp,
vertex.pie.color=list(heat.colors(2)),asp=0, rescale=T, xlim=c(-0.86,0.86), ylim=c(-0.9,0.9))
dev.off()
```

```
#Open interactive plot.
id1<-tkplot(g)

#Get coordinates from the plot to use later in regular plotting function.
sample_coords<-tkplot.getcoords(id1)

#Save coordinates to Excel file.
write.xlsx(sample_coords, file = "SampleCoordsForPlot.xlsx", sheetName = "TestSheet")
```

Links to Annexes 3 - 8

See website for Annexes

Annex 3. Top 30 exporters of retail insulin (by 2013 constant US dollar value) for years 2004 - 2013

Annex 4. Top 30 exporters of retail insulin (by percentage dollar value share) for years 2004 - 2013

Annex 5. Export of retail insulin (by dollar value) amongst the top 30 countries with highest number of people with diabetes: 2004 – 2013

Annex 6. Top 30 importers of insulin (by 2013 constant US dollar value) for years 2004 – 2013

Annex 7. Top 30 importers of insulin (by percentage dollar value share) for years 2004 – 2013

Annex 8. Import of retail insulin (by percentage dollar value) amongst the top 30 countries with highest number of people with diabetes: 2004 – 2013