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Challenges constraining access to insulin in the private-sector market of Delhi, India

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ABSTRACT

Objective: India's majority of patients—including those living with diabetes—seek healthcare in the private sector through out-of-pocket (OOP) payments. We studied access to insulin in the private-sector market of Delhi state, India.

Methods: A modified World Health Organization/Health Action International (WHO/HAI) standard survey to assess insulin availability and prices, and qualitative interviews with insulin retailers (pharmacists) and wholesalers to understand insulin market dynamics.

Results: In 40 pharmacy outlets analysed, mean availability of the human and analogue insulins on the 2013 Delhi essential medicine list was 44.4% and 13.1%, respectively. 82% of pharmacies had domestically manufactured human insulin phials, primarily was made in India under licence to overseas pharmaceutical companies. Analogue insulin was only in cartridge and pen forms that were 4.42 and 5.81 times, respectively, the price of human insulin phials. Domestically manufactured human phial and cartridge insulin (produced for foreign and Indian companies) was less expensive than their imported counterparts. The lowest paid unskilled government worker in Delhi would work about 1.5 and 8.6 days, respectively, to be able to pay OOP for a monthly supply of human phial and analogue cartridge insulin. Interviews suggest that the Delhi insulin market is dominated by a few multinational companies that import and/or license in-country production. Several factors influence insulin uptake by patients, including doctor's prescribing preference. Wholesalers have negative perceptions about domestic insulin manufacturing.

Conclusions: The Delhi insulin market is an oligopoly with limited market competition. Increasing competition from Indian companies is going to require some additional policies, not presently in place. As more Indian companies produce biosimilars, brand substitution policies are needed to be able to benefit from market competition.

Key questions

What is already known about this topic?

- Poor access to insulin is a serious public health concern, given the increasing global diabetes burden, but there is limited local information on this situation in the public and private healthcare sectors in many countries.

What are the new findings?

- The mean availability of insulin in the Delhi private-sector market was far lower than the WHO availability target of 80%; analogue insulin cartridges/pens were 5–9 times more expensive than human insulin phials; and private-sector insulin prices appear unaffordable.
- People with diabetes in Delhi are largely dependent on foreign-made insulins, and only 25% of surveyed pharmacies stocked human (non-analogue) insulin made for, and by, Indian companies; Indian companies are not making analogue insulins for the Delhi market.
- Doctors and patients in India believe that insulin from foreign companies is better and they do not trust Indian companies.
- Manufacturers, some doctors and wholesalers are selling insulin directly to patients, cutting out pharmacies, with the potential implication that pharmacists may choose either to not stock insulin at all or stock mostly more expensive insulins to guarantee some profit.

INTRODUCTION

Insulin is an essential, life-saving medicine needed for persons living with type 1 diabetes and for some with type 2 diabetes. Insulin was first extracted and purified in 1921 from animals and its formulations have evolved.[1] Since the 1980s, recombinant human insulin products have been produced using genetically modified microbes. Over the past decade, recombinantly derived human insulin has been modified as recombinant 'analogue' insulins which are replacing recombinant human insulins in certain markets.[2 3]

Unfortunately, almost 100 years after its first use in humans, insulin is still inaccessible to millions of people with diabetes. With the ever-increasing burden of diabetes, the issue of poor insulin access is becoming a serious public health concern globally as suboptimal treatment results in complications

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Key questions

Recommendations for policy

- The Government of India and pharmacy associations should work with stakeholders to better align the financial incentives of those in the insulin supply chain.
- The Government of India and patient associations could play an important role by framing independent, evidence-based guidelines aimed at prioritising the use of quality-assured and less expensive human insulin whenever possible and when clinically indicated.
- To eliminate the mistrust about Indian insulin, its efficacy and safety must be compared with that of imported products, with results made public and used to effectively communicate value messages to the doctors and procurement agencies.
- The Government of India exerts stronger price controls on domestic than foreign-produced insulin, but it should revisit this practice and support Indian insulin manufacturers in improving their domestic market visibility.

like blindness, amputations and premature death.[2 4–6] In particular, populations in Asia are experiencing an unprecedented increase in diabetes burden, largely driven by economic development, genetic predisposition, nutrition transition and sedentary lifestyle, with young and middle-aged population being disproportionately affected.[7–9]

India has the second largest diabetes burden in the world, and in 2013, there were 65.1 million people (aged 20–79 years) living with diabetes and nearly 32 million were undiagnosed. By 2035, the number of people with diabetes in India will observe an increase of nearly 70%.[10] Such an epidemic translates to an increasing need for antidiabetic medicines, including insulin therapy.

Indian states list some insulin products on their essential medicines lists (EMLs) for free-of-charge provision in the public-sector hospitals. The Delhi EML includes both human and analogue insulin for free provision through public-sector health facilities.[11] In 2010, the Government of India (GOI) launched the National Programme for Prevention and Control of Cancers, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS) to tackle the non-communicable disease burden,[12] but without much success.[13 14] In general, India's central and state governments are underfunded and are able to cover healthcare for only about one-fourth of the population.[15] This forces the majority of the patients—including those living with diabetes—to seek healthcare in the private sector through out-of-pocket (OOP) payments.

Therefore, it would be important to evaluate availability and prices of insulin along with perspectives of various stakeholders in the private sector in India. While other studies on medicine availability, prices and use have been undertaken in Delhi state, India,[16–19] we present this first study specifically studying access to insulin in the private-sector market, not only in India but in any low-income or middle-income country (LMIC). Even in high-income countries, such information may not be available.

METHODS

We employed an exploratory, mixed-methods (quantitative and qualitative) analysis to assess insulin availability, prices and factors influencing market competition, supply and uptake of insulin (market dynamics) in the private-sector market of Delhi state, India.

We used a modified version of World Health Organization/Health Action International (WHO/HAI) methodology. A typical WHO/HAI survey involves data collection on availability and prices of a predefined basket of essential medicines along with additional medicines selected by the investigator.[20] For this study, we surveyed all the insulin products that were available in selected private-sector retail pharmacies. In addition, we conducted in-depth interviews with the private-sector insulin retailers and wholesalers using a semistructured interview guide to study various insulin access issues. In accordance with WHO/HAI standard survey methods, we also undertook an insulin price component analysis.

Sampling

Survey facilities

Delhi, also known as the National Capital Territory (NCT) of Delhi, is divided into a total 11 districts. Out of these 11 districts, we randomly selected 8 survey districts. We obtained a list of all the public-sector secondary and tertiary hospitals in each of the eight survey districts from various sources and randomly selected one public-sector hospital in each district as the 'survey anchor'. We surveyed five private-sector retail pharmacies in each of the eight survey districts (n=40 pharmacies). From the survey anchor, in a randomly selected direction, we surveyed the nearest retail pharmacy. From this first pharmacy, and moving in the selected direction, we surveyed four other pharmacies at a walking time of 15, 25, 40 and 45 min, respectively, from the previously surveyed retail pharmacy (see online supplementary appendix webtable 1). When no insulin was available at a particular pharmacy outlet, we surveyed the nearest pharmacy to that outlet to obtain insulin prices. We interviewed the personnel (pharmacists) at these survey retail pharmacies about issues related to insulin access and also asked them about their insulin wholesalers.

Survey medicines

Insulin is available from various sources (animal, recombinant human, analogues), strengths (40, 100 IU/mL) and delivery vehicles (phials, cartridges, pens). For this study, unless stipulated otherwise, we define an insulin 'product' as a unique combination of any particular insulin molecule in terms of its source, dosage strength and delivery option. Because of the potential variety of insulin products available in the Delhi's private sector,

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we chose not to have a predefined list of insulin products as suggested by the WHO/HAI methodology but rather we collected price data for every unique insulin product of any company that was found at a given survey pharmacy.

Data sources and definitions

Data on the prices of all available unique insulin products were collected during January to February 2015. These prices reflect what consumers pay OOP to purchase a given insulin product at the surveyed retail pharmacies. At this time, we also inquired about customer discounts the pharmacists usually offer and about the pharmacy profit margins over their purchasing wholesale prices.

From the product label and packaging, we determined whether the insulin was made in India (domestically manufactured) for either an Indian or foreign company, or if it was 'imported' into India on being manufactured overseas for either an Indian or foreign company. This information on place of manufacture (ie, India or overseas) and company corporate headquarters (Indian or foreign) results in four permutations (table 1). Insulins can be made in India by a company whose corporate headquarters are in India (eg, Biocon, Wockhardt, Ranbaxy, Lupin) or made in India under licence for a foreign company whose corporate headquarters are overseas (eg, made for Novo Nordisk in India by Torrent). Insulins can be manufactured overseas by a 'foreign' company (eg, Novo Nordisk, Eli Lilly and Sanofi) and imported to India or made for an Indian company (eg, made in China for Indian company Lupin) and then imported into the Indian market. See table 1 for this taxonomy of insulin products based on place of manufacturing and the company's corporate headquarters.

To assess supply chain price components such as mark-ups, we obtained the import and wholesale prices (during January to February 2015) of various insulin products found in the facility survey from the Seair Exim Solutions website and insulin wholesalers in Delhi, respectively.[21] We also collected public-sector procurement prices of various insulin products, as available from the governmental and public-sector hospital medicine rate contract/tender documents and colleagues at local universities (see online supplementary appendix webtable 2). These public-sector procurement prices reflect the price at which the Delhi State Government, Municipal Corporation of Delhi and/or Central Government purchased insulin during the years 2013–2015. We converted the public-sector procurement and private-sector consumer unit insulin prices in Indian rupees (Rs) to US dollars (US$) at the January 2015 average daily exchange rate of Rs61.97=US$1.

We identified major insulin wholesalers who supplied insulin to several of the surveyed retail pharmacies in Delhi's private-sector market. We then conducted in-depth qualitative interviews with these experienced wholesalers (n=5) until we achieved response saturation, to explore factors affecting uptake of various insulin products. Prior to these interviews, we explained the purpose of our study and obtained wholesalers' informed consent to take notes or audio record and to conduct thematic analysis using the obtained information and data on the basis of anonymity.

Data analysis

We counted all human and analogue insulins surveyed (including duplicates from different pharmacy outlets) and classified them according to the taxonomy of table 1.

We report insulin availability, on the other hand, as the mean percentage of surveyed pharmacies where a given unique insulin product was available—overall and stratified by insulin type, delivery method, place of manufacture (domestically manufactured or imported) and place of company's corporate headquarters (Indian or foreign). Place of corporate headquarters and place of manufacture were obtained from the product marking and labelling. We also report mean availability for the insulin products we found that are also listed on 2013 Delhi's EML. See online supplementary appendix webtable 3 for the list.

Table 1 Insulin product classification based on where insulin is manufactured and place of corporate headquarters

	Entity for whom insulin is made (by corporate headquarters)	
Place of manufacture	**Indian (eg, Biocon, Wockhardt, Lupin)**	**Foreign (eg, Eli Lilly, Novo Nordisk, Sanofi Aventis)**
India	Domestically manufactured, for Indian company (n=16)	Domestically manufactured, for foreign company (n=87)
	Human insulin=100.0%	Human insulin=100.0%
	Insulin analogues=0.0%	Insulin analogues=0.0%
Overseas	Imported, for Indian company (n=2)	Imported, for foreign company (n=69)
	Human insulin=0.0%	Human insulin=44.9%
	Insulin analogues=100.0%	Insulin analogues=55.1%

Numbers 'n' in parentheses are the number of all products, irrespective of dosage strength and delivery vehicle, found for a particular classification (eg, 87 insulins—including duplicates—made in India for a foreign company).
Percentages are the fraction of products in any classification relegated to human and analogue insulins (eg, all 103 insulins (16+87)—including duplicates—made in India for Indian and foreign companies were human, not analogue insulin).

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We report median prices of unique human and analogue insulin products, adjusted to 10 mL 100 IU/mL. To adjust prices, we calculated the price per IU for a given product and scaled it to our 'internal benchmark' of 10 mL 100 IU/mL insulin pack. We compared the median prices of insulin products by place of manufacture (domestically manufactured or imported). To assess if the price differences were statistically significant (α significance level of 0.05), we conducted non-parametric Wilcoxon rank-sum tests using statistical software SAS V.9.4.

We compared the median consumer prices of the surveyed insulin products to the respective public-sector procurement prices in order to calculate price ratios. To calculate the supply chain mark-ups, we compared the purchase prices of various insulin products at import, wholesale and retail levels. We reported the percentage increase in consumer prices from import to wholesale, wholesale to consumer and import to consumer level.

For the price ratio analysis and the supply chain price component analysis, we matched the insulin products in terms of company's name, molecule description, strength and delivery options (phials, pens, etc) to ensure price comparison of the identical insulin products through the supply chain. Since a given insulin product can be manufactured and imported from more than one country, we also matched the country of manufacture listed on the retail product label to the exporting country on the import database (Seair Exim Solutions).[21] We also conducted an insulin affordability analysis, as per WHO/HAI methodology,[20] where a chronic medicine (insulin) is considered unaffordable if a lowest paid unskilled government worker has to spend over one daily-wage to purchase a month's supply.

RESULTS

Insulin manufacture: taxonomy

All domestically manufactured insulin was human insulin, and most of it (87/103, ie, 84.4% of total products) was made for overseas multinationals. We found no Indian company making analogue insulin domestically, either for themselves or anyone else. Of the 71 insulin products produced outside India and imported, over 99% (69/71) was imported into India on behalf of a foreign multinational. These imported products were approximately equally divided between human and analogue insulins (table 1).

Insulin availability

In the 40 surveyed pharmacies, we found four types of human insulin, each available in 40 and 100 IU/mL strengths, and eight types of insulin analogues, all in 100 IU/mL strength. The mean private-sector availability of those human and analogue insulins that are listed on the 2013 Delhi EML was 44.4% and 13.1%, respectively (table 2).

Table 2 Availability of insulin (any brand or company) in the private-sector market in Delhi state, India (N=40 pharmacy outlets)

Insulin type	Molecule description	Strength (IU/mL)	Per cent availability (number of pharmacy outlets)
Human insulin	Soluble insulin	40*	47.5% (19)
		100	12.5% (5)
	Isophane insulin	40*	25.0% (10)
		100	5.0% (2)
	Biphasic isophane insulin: 30% soluble insulin 70% isophane insulin	40*	67.5% (27)
		100*	37.5% (15)
	Biphasic isophane insulin: 50% soluble insulin 50% isophane insulin	40	20.0% (8)
		100	5.0% (2)
Mean availability of any human insulins listed on 2013 Delhi essential medicine list			44.4%
Analogue insulin	Insulin aspart	100*	12.5% (5)
	Biphasic insulin aspart: 30% insulin aspart and 70% protamine crystallised aspart	100	15.0% (6)
	Biphasic insulin aspart: 50% insulin aspart and 50% protamine crystallised aspart	100	2.5% (1)
	Insulin glargine	100*	25.0% (10)
	Insulin glulisine	100*	5.0% (2)
	Insulin lispro	100*	10.0% (4)
	Insulin lispro biphasic injection: 25% insulin lispro 75% lispro protamine	100	12.5% (5)
	Insulin lispro biphasic injection: 50% insulin lispro 50% lispro protamine	100	12.5% (5)
Mean availability of any analogue insulin listed on 2013 Delhi essential medicine list			13.1%

*Insulins listed on the 2013 Delhi essential medicines list.

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Table 3 presents the availability of human and analogue insulins as a function of the place of manufacturing (ie, domestically manufactured or imported), the delivery options and number of pharmacy outlets where the insulin was found (in parentheses).

Human insulin was found in 40 and 100 IU/mL strengths. Nearly all of the domestically manufactured human insulin unique products were in 40 IU/mL phials (table 3, column 2). We only found imported insulins in 100 IU/mL strength (table 3, column 3).

Slightly more than 80% (82.5%) of pharmacies stocked domestically manufactured human insulin 40 IU or, rarely, 100 IU phials. Most (75%) of this insulin was made in India under licence from foreign companies (primarily Novo Nordisk) (see online supplementary appendix webtables 4 and 5). In contrast, only about one-third (32.5%) of all pharmacy outlets stocked analogue insulin products. All analogue insulins, except for two, were made overseas by a foreign company and imported into the Indian market, and were in cartridge and pen forms only (see tables 1 and 3).

Insulin prices

Consumer prices

Table 4 summarises the median prices of human and analogue insulin products, adjusted to 10 mL 100 IU/mL, identified by place of manufacture as being 'domestically manufactured' and 'imported' (as defined in table 1).

The median consumer prices combined for domestically manufactured and imported human insulin cartridges (US$11.2 | Rs693.3) and pens (US$18.5 | Rs1145.0) were found to be 1.98 and 3.27 times, respectively, the phial prices for human insulin (US$5.6 | Rs350.0; table 4, column 1). Human insulin in phials, wherever made, is less expensive than human insulin cartridges and pens. Among all human insulins, we found those domestically manufactured (by any company, Indian or foreign) were less expensive than their imported counterparts in case of both phial (p=0.001) and cartridge (p=0.0105).

Analogue insulins (all made overseas and imported) were more expensive than human insulins. The median consumer prices of 10 mL 100 IU/mL analogue insulin in cartridge (US$25.0 | Rs1546.7) and pen forms (US $32.8 | Rs2033.0) were 4.42 and 5.81 times, respectively, the phial price of human insulin (table 4, column 1). See online supplementary appendix webtable 6 for price details by company's place of corporate headquarters (Indian or foreign).

We estimate that the lowest paid unskilled government worker in Delhi will have to work 1.5 and 8.6 days,

Table 3 Availability of insulin by type, delivery device and place of manufacture in surveyed retail pharmacies in Delhi state (n=40 pharmacy outlets)

	Place of manufacturing		
	Combined (domestically manufactured plus imported) (1)	Domestically manufactured insulin (2)	Foreign insulin (3)
Insulin type and delivery device	Percentage availability (number of pharmacy outlets)		
Human insulin (all molecules)	90.0 (36)	82.5 (33)	37.5 (15)
Phial(IU/mL)			
40	77.5 (31)	77.5 (31)	0.0 (0)
100	15.0 (6)	2.5 (1)	12.5 (5)
Cartridge (IU/mL)			
40	2.5 (1)	2.5 (1)	0.0 (0)
100	25.0 (9)	5.0 (2)	22.5 (9)
Pen (IU/mL)			
40	0.0 (0)	0.0 (0)	0.0 (0)
100	22.5 (4)	0.0 (0)	10.0 (4)
Analogue insulin (all molecules)	32.5 (13)	0.0 (0)	32.5 (13)
Phial (IU/mL)			
40	0.0 (0)	0.0 (0)	0.0 (0)
100	0.0 (0)	0.0 (0)	0.0 (0)
Cartridge (IU/mL)			
40	0.0 (0)	0.0 (0)	0.0 (0)
100	17.5 (7)	0.0 (0)	17.5 (7)
Pen (IU/mL)			
40	0.0 (0)	0.0 (0)	0.0 (0)
100	22.5 (9)	0.0 (0)	22.5 (9)

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Table 4 Median consumer prices (US dollars) of insulin, by place of manufacture and combined

	Combined (domestically manufactured plus imported) (1)	Domestically manufactured insulin (2)	Imported insulin products (3)	p Value
Human insulin				
Phial	US$5.6 (n=106)	US$5.6 (n=98)	US$5.6 (n=8)	0.0011*†
Cartridge	US$11.2 (n=24)	US$8.5 (n=5)	US$11.4 (n=19)	0.0105*
Pen	US$18.5 (n=4)	‡	US$18.5 (n=4)	–
Analogue insulin				
Phial	‡	‡	‡	–
Cartridge	US$25.0 (n=19)	‡	US$25.0 (n=19)	–
Pen	US$32.8 (n=21)	‡	US$32.8 (n=21)	–

The prices of all survey insulin products with variable pack sizes (millilitres) and strength were adjusted to 10 mL 100 IU/mL pack for purpose of comparisons.
n refers to the number of insulin prices available to calculate median insulin consumer price.
*Statistically significant at α significance level of 0.05.
†While the medians in comparison are same, the distribution is different with lower prices in domestically manufactured insulin group. This is because the Wilcoxon rank-sum test ranks all of the observations from both groups and then sums the ranks from one of the groups which is compared with the expected rank sum. Although uncommon, it is possible for groups to have different rank sums and yet have equal or nearly equal medians.
‡No insulin product in the respective delivery option was found in the facility survey, and therefore p value was not calculated.

respectively, to be able to pay OOP for monthly private-sector supply of human insulin (phial) and insulin analogue (cartridge). Furthermore, our estimated per capita annual private-sector cost of insulin ranged from over 1 to about 6.5 times India's per capita health spending in the public and private sectors (see online supplementary appendix webtable 7).

Consumer prices compared with public-sector procurement prices

On average, private-sector consumers are paying 2.62 times the price that the government pays to purchase a given insulin, regardless of insulin type or place of manufacture (table 5, column 4).

Insulin prices: supply chain mark-ups

Figure 1 summarises the supply chain price mark-ups for imported insulin products from import to wholesale and retail (consumer) levels, with human and analogue insulins viewed side-by-side as three sets of figures.

For all human insulin products, median consumer prices were 43.8% higher than the import prices of identical products (figure 1: human insulin 3). The overall import to consumer mark-up was highest (58.5%) for Mixtard 30 HM (Novo Nordisk) made in Denmark and was lowest (36.4%) for Huminsulin N (Lilly) made in Egypt (figure 1: human insulin 3). The median import to wholesale (figure 1: human insulin 1) and wholesale to retail (consumer) mark-ups (figure 1: human insulin 2) were 16.8% and 19.3%, respectively.

For all analogue insulins, the median import to consumer price mark-up (figure 1: analogue insulin 3) was 42.1%, ranging from 16.5% (Humalog Mix 25 (Eli Lilly)) to 128.6% (Basugine (Lupin)). Significantly, Basugine (Lupin) was actually made in China for Lupin and had the highest import to wholesale mark-up (figure 1: analogue insulin 2: 74.7%) yet the actual consumer price for Basugine was lower than that of other analogues (US$26.4 | Rs1638.3 vs US$25.0 | Rs1546.8) of the same strength and delivery vehicle (see online supplementary appendix webtable 8 for details).

Qualitative results

Market dynamics: private-sector insulin market

Of the 40 interviewed pharmacists, 60% offered discounts on insulin products (mean discount: 7%, up to 10% for insulin analogue). Pharmacists reported that doctors prescribed the recombinant human insulin by brand name, that patients trusted foreign company products and did not want to substitute with products made for Indian companies, and this is why the pharmacists "…stocked those (foreign) brands which were in demand [meaning prescribed]". There exists a C-D-MR (company-doctor-medical representative) triangle "…which is now operating to directly deliver insulin to patients and is replacing the pharmacists' role and financial incentives".

> I do not want to stock insulin anymore as doctors are directly selling free samples at discounts on print price. Patient are losing trust in pharmacists as they think we sell more expensive than doctors. A Delhi pharmacist

Several major themes emerged from our five in-depth interviews with insulin wholesalers. These themes were: the Delhi insulin market in India is dominated by a few multinational companies; three main factors influence insulin uptake; and wholesalers have negative perceptions about domestic insulin manufacturing.

Delhi insulin market dominated by a few multinational (foreign) corporations

Wholesalers' views on market shares were based on their own and on their competitors' business experiences.

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Table 5 Comparison of private-sector consumer prices of insulin to the public-sector procurement prices in Delhi state, India (adjusted to cost to 10 mL 100 IU/mL)

Insulin type	Strength (IU/mL) (1)	Median consumer price (US$) per 10 mL 100 IU/mL insulin (2)	Public-sector procurement price (US$) per 10 mL 100 IU/mL insulin (3)	Price ratio: consumer price/ public-sector procurement price* (4)
Human insulin				
Soluble insulin	40	5.7 (n=26)	2.4	2.39
	100	11.2 (n=5)	2.4	2.62
Isophane insulin	40	5.7 (n=13)	2.4	2.39
	100	11.2 (n=3)	2.4	2.62
Biphasic isophane insulin: 30% soluble insulin 70% isophane insulin	40	5.7 (n=49)	2.4	2.36
	100	11.2 (n=26)	2.4	3.63
Biphasic isophane insulin: 50% soluble insulin 50% isophane insulin	40	5.7 (n=10)	2.1	2.72
	100	11.7 (n=2)	2.1	5.65
Analogue insulin				
Insulin lispro	100	25.3 (n=4)	14.8	1.60
Insulin lispro biphasic injection: 25% insulin lispro 75% lispro protamine	100	25.0 (n=5)	4.7	5.32
Median (minimum, maximum)				2.62 (1.60, 5.65)

*A positive integer price ratio of 'x' would mean that the consumer prices were 'x' times higher than the procurement prices. This analysis includes only those survey insulin products for which respective public-sector (Delhi Government, Municipal Corporation of Delhi and/or Central Government) insulin procurement prices were available. 'n' refers to the number of insulin prices available to calculate median insulin consumer price. See online supplementary appendix webtable 2 for details on public-sector insulin procurement prices.

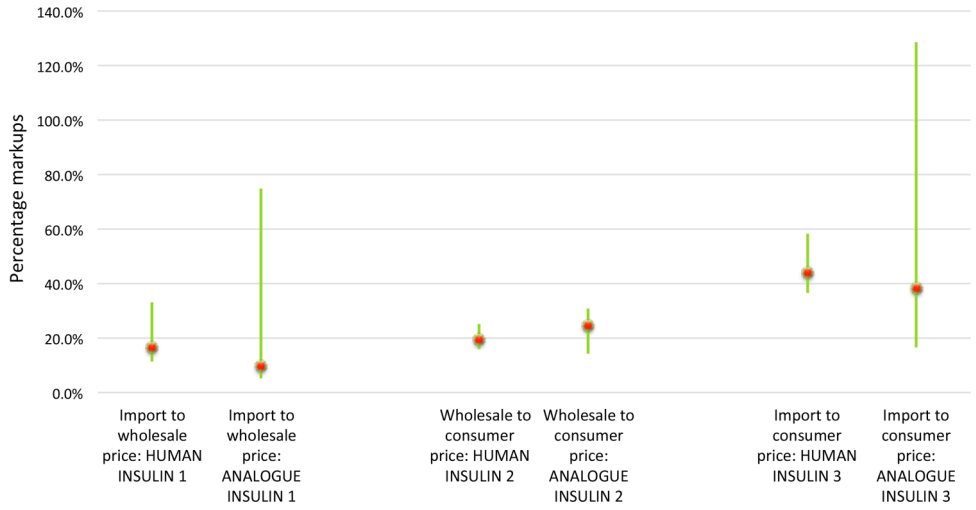


Figure 1 Price components (mark-ups) of imported insulin products found in the private-sector market in Delhi state, India. Median (red), minimum and maximum (green) mark-ups are shown.

The interviewees acknowledged the fact that the Indian insulin market (compared with other medicines) is oligopolistic with relatively few supplier companies. They reported that the Delhi insulin market (by volume) was dominated primarily by the three foreign companies Novo Nordisk, Eli Lilly and Sanofi Aventis. Indian companies like Biocon, Lupin, Wockhardt and Ranbaxy Laboratories do mainly supply recombinant human insulin products but their market shares (by volume) are small and are diminishing. This is consistent with the insulin availability results from our facility survey.

Decisions by wholesalers as to which insulins to stock are driven almost entirely by profit and business considerations. Foreign companies (eg, Novo Nordisk, Eli

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Lilly) which primarily deal in insulin products prefer wholesalers with stronger insulin-specific business potential and market coverage (region and client base), while Indian companies (eg, Ranbaxy, Wockhardt) with a more diverse medicine product portfolio would prefer wholesalers who can sell other products alongside insulin.

> We look for demand in market, look at profit margins and then we decide accordingly. That's all…there is nothing more to it! Wholesaler A

Notably of the five wholesalers we interviewed, only one supplied insulin products made by one or more of the Indian companies (ie, Lupin, Biocon, Ranbaxy and/or Wockhardt) in addition to those from one of the major foreign companies. Another wholesaler who now supplies only Novo Nordisk's products said that he used to supply insulin from an Indian company (ie, USV) but he could not keep up profits due to low demand of insulin from that company.

> I used to supply USV insulin but now I don't. They could not capture the market shares and one needs sales volume to be in business. I cannot comment on their manufacturing capacity. If their demand [increases], I will be happy to supply USV or other Indian insulins as long as I make profits. Wholesaler B

Three main factors influence insulin uptake

Product marketing and branding

The foreign companies target patients' insulin initiation in order to secure long-term market volumes. Once prescribed their first insulin product, patients with diabetes rarely switch to other insulin products due to the associated potential risk of clinical complications, and relatively more frequent doctor visits needed for check-ups and tests like glycated haemoglobin monitoring. To realise this strategy, the major multinationals leverage their larger (relative to Indian companies) doctor base, driven by marketing and financial interests, to prescribe the companies' insulin products especially at initiation phase.

> Their [dominating companies'] market strategy is… patients do not want to switch insulin products as there are so many clinical complications associated with insulin use. Now when a patient gets diagnosed (and needs insulin), he/she is given the (multinational) insulin. The patient feels better and wants to continue with the same insulin and not convert [switch] to other [product/brand]…Wholesaler C

During our facility survey, several pharmacists asserted that they only stocked insulin products made by foreign companies because those were the ones in demand (prescribed). Further, a wholesaler testified that the insulin market is region-specific as the doctors in one area prescribe a given range of products which may have to do with the companies' marketing strategies.

> Yes it [demand/prescribing] depends on area. For instance, [in] Safdarjung area…you may find relatively more utilization of Lantus. It all depends on company-doctor ties and their marketing strategies. Now-a-days marketing is not like earlier when a medical representative used to visit the doctor with a product information brochure, now there are many financial ties. Wholesaler D

Furthermore, as per wholesaler and pharmacist interviews, foreign companies apparently are also selling insulin directly to the patients either through doctors (a clear conflict of interest) or directly from the company's marketing personnel. On further inquiry, we learnt that patients are sometimes able to get cheaper prices than in retail pharmacy outlets if insulin is purchased directly from the doctors. The wholesalers' and retailers' margins are removed and companies pay commissions to doctors or marketing personnel. Some providers/doctors, however, may even be charging maximum retail prices to the patients when possible.

> My sales are being affected, because companies are selling directly to the patients…The doctors provide phone numbers of company (marketing) personnel who deliver medicines at their homes. Now why should we be in business or deal in medicines (insulin)! Wholesaler D

Doctor prescribing

Wholesalers mentioned that insulin market shares, perhaps like any other medicine, are largely driven by what doctors are prescribing. Therefore, we sought wholesalers' views on the possibility that doctors could be increasing their prescribing of some high priced (possibly unaffordable) analogue insulins. Wholesalers believed that the doctors assess which insulin is to be prescribed based on three aspects: clinical impact, patient's buying capacity and their own financial interests. Wholesalers acknowledged that human insulin is cheaper than analogues but doctors are increasingly prescribing analogues because foreign companies rarely market recombinant human insulin. Wholesalers believed that the Indian companies which produce recombinant human insulin products do not market these products well. Moreover, if two products with similar clinical effect are available, some wholesalers question why a doctor would prescribe a less expensive insulin to someone who can afford the expensive insulin.

> …companies make hype that analogues are better… Doctors will get personalized services for prescribing analogues. Also doctor sees if patient can afford, then why not prescribe analogues. But even when a patient is unable to afford analogues, even then some doctors prescribe analogues for personal reasons and preferences. Wholesaler A

Furthermore, some companies have 'bundling arrangements' with the doctors, which allow doctors to offer patients with an extra insulin supply on a certain

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purchase threshold. Sometimes there are special rebate schemes by companies; doctors and pharmacists who sell more, get more rebates. This is how companies have been able to capture a bigger patient pool to initiate treatment with their insulin.

> Doctors are even able to avail that injection to patients at 1 + 1 scheme. We do not have such margins. I sold a patient 15 injections, who later complained…as I did not give him 5 extra injections which a doctor could offer him. We do not get free samples like doctors. I asked the patient to show me what doctor gave him and in return promised to pay back his money on my sales return. I noticed that he got free 5 samples which had imprinted on them "free samples not for sale." Wholesaler D

It would also be hard to alter the prescribing behaviour of doctors who have been prescribing a given (eg, expensive, foreign) product for a long time.

> …a good doctor who sees over 50 patients daily and has been prescribing 'Human Mixtard' [human insulin by Novo Nordisk]. Now if a marketing rep goes and ask him to start prescribing other human insulin, the doctor will not entertain him. Wholesaler C

Patient's buying capacity and perception

In the private-sector market, the uptake of insulin products also depends on the patient's purchasing capacity. These products are primarily paid for OOP and therefore doctors may tend to assess the purchasing capacity of the patients while prescribing. The wholesalers noted the prevailing socioeconomic variations and mentioned that a doctor with high visiting fee would perceive the patient to have a higher purchasing capacity and would therefore prescribe more expensive analogue products.

> …it [prescribing] also depends on the kind of doctor one visit: whether a patient goes to a private-sector doctor who charges a visiting fee of Rs. 1,500 or who charges Rs. 100. The doctor charging Rs. 1,500 will prescribe better and expensive products as he perceives these patients to be able to afford the insulin that offers better quality of life. There is a lot of variation based on buying capacity in India. The Rs. 100 doctor will not prescribe insulin costing higher than Human Mixtard and Human Actrapid. Wholesaler C

However, wholesalers noted that if doctors prescribing a cheaper recombinant human insulin to poor patients also tell them that analogues are better, then the patients would try to arrange the money for the expensive (analogue insulin) products.

> …if a doctor thinks that patient is poor, the doctor may prescribe a cheaper, human insulin. However if doctor… tell[s]…that analogues are expensive but better choice insulins…patient will anyhow find money to buy analogue and therefore analogues sales are increasing. But there are doctors who care about the patients more and also some patients cannot at all afford analogues, and therefore human insulin is still being sold. Wholesaler A

Insulin uptake is also influenced by patient's perception of quality for a given product. The wholesalers pointed out that public-sector procurement officials in Central Government Health Scheme (CGHS) often purchase expensive analogue insulin even if they can buy fewer quantities given the budget constraints, as these officials have more trust in foreign companies.[22] One of the wholesalers suggested studies to compare quality of Indian and foreign insulin to inform patients' and doctors' perception.

> It [an Indian human insulin product] was being available by CGHS services to government employees. These employees used to sell the product in market and purchase Novo Nordisk's [product]. It's about patient trust and patients prefer [an] international company! These international [meaning foreign] companies position their brand well. Wholesaler D

Wholesalers' have negative perceptions about domestic insulin manufacturing

The wholesalers raised several concerns which if resolved, according to them, could help improve the market share of Indian companies. First, wholesalers pointed out that Indian companies are really not making their own insulin but are importing insulin crystals from European countries for reformulation and repackaging.

Second, the wholesalers said that the Indian insulin products are not innovative, but are the 'same old molecules…' as the foreign companies. This—according to wholesalers—fails to convince doctors to prescribe Indian products. It would be unlikely to have doctors change their prescribing behaviour unless a marketing company comes up with some sort of improved clinical or economic benefits.

> …Indian companies are providing the same molecules as the multinational [meaning foreign] companies. If Indian companies could provide better (self-researched) molecules, then doctors might think of prescribing their products. Wholesaler C

Third, the wholesalers acknowledged that it is difficult to manufacture insulin unlike 'small (chemical) molecules' and felt that the GOI needs to support the Indian companies. Wholesalers asserted that it would be important to evaluate Indian companies' insulin manufacturing costs and have the GOI assure them of enough profit margin to sustain manufacturing over the longer term. Wholesalers indicated that Indian companies may not be doing well in the insulin market because of the price capping by India's National Pharmaceutical Pricing Authority (NPPA); the price caps are higher for foreign, imported human insulin products than domestically manufactured Indian company products and these caps do not include the analogue insulins.[23–25]

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> In India, things are improving. Better hospitals are coming up…Pharmaceutical industry is growing at a rapid pace. However in case of insulin…Some Indian companies like Ranbaxy make insulin but their promotion strategies are not good enough. It's mainly marketing, the key to survival. They also have to say at what prices are they being able to manufacture. Also a company should be able to explain/convince a doctor why its product is better. Wholesaler D

> Indian companies will not produce [enough insulin] until there is price capping as they cannot make profits. Only few companies have been able to sustain because of their relatively larger volumes. Wholesaler A

Finally, the wholesalers repeatedly reported that Indian companies are not marketing their products efficiently enough to gain larger market volume shares which is important for sustained production. They believed that several Indian insulin manufacturing companies also manufacture various other generic 'small molecule' pharmaceutical products—unlike international companies like Novo Nordisk which focus primarily on insulin—and therefore Indian companies' marketing efforts are diluted.

> Indian companies are not marketing their [insulin] products aggressively. Because they do not have enough margins. They are on the market but they do not try to sell it at large volumes…They are not much attentive/interested towards insulin. They have other [generic pharmaceutical] products. Furthermore insulin is not easy (is relatively expensive) to manufacture and market. The more you produce cheaper it is, but for that sales volume should be higher. Wholesaler D

DISCUSSION

To the best of our knowledge, this is the first study to analyse the private-sector availability, prices and access issues for insulin not only in India but any LMIC. The literature tells us that the global availability of insulin is suboptimal. In the private sector, only two countries—that is, Lebanon (2013) and Kwazulu-Natal State, South Africa (2001)—out of 15 countries had insulin availability of over 80%. The mean overall availability in the private sector was 39% (range Kyrgyzstan 0% to Kwazulu-Natal State, South Africa 95%).[2] In our Delhi survey, we found the mean private-sector availability of recombinant human and analogue insulins listed on the Delhi's EML (44.4% and 13.1%, respectively) was far lower than the WHO availability target of 80%.[26] In India, previous WHO/HAI surveys have consistently reported lower availability of essential medicines in the public sector compared with the private sector.[16 17] For this reason, we would expect the public-sector insulin availability to be even lower than what we found in the private sector.

India, along with other emerging markets,[3] is observing a transition in usage from recombinant human to recombinant analogue insulins (and from phials to cartridges and pens). This is likely due to multinational marketing and branding forces, doctors' prescribing behaviour, supply chain incentives, and the increasing per capita income of patients. The WHO Model EML recommends only recombinant human insulin but the Delhi state EML also lists analogue insulin products. This is despite the fact that the 18th WHO Expert Committee on the Selection and Use of Essential Medicine concluded that "insulin analogues currently offer no significant clinical advantage over recombinant human insulin and there is still concern about possible long-term adverse effects".[27]

The inclusion of analogue insulin on the Delhi EML is, in part, driving the transition to increased uptake of analogue insulin.[11] This has major cost implications for insulin therapy in India as analogue insulin cartridges/pens, in our survey, were 5–9 times more costly than human insulin phials. As cautionary tale, the annual expenditure of the UK's National Health System (NHS) on insulin increased by 130%, and cost 50 million euros for a purported few extra benefits every year due to unnecessarily increased uptake of analogue insulin.[28]

Moreover, in the Delhi context, insulin prices appear unaffordable. While patients with diabetes are expected to have higher health expenditure due to comorbidities like hypertension and neuropathies, the annual per patient insulin cost can be up to six times India's per capita health spending (see online supplementary appendix webtable 7). We note that affordability of insulin in the private sector depends both on the type of insulin used and on various supply chain factors.[2] Interestingly, we found that consumers paid an extra 16–128% over the insulin import prices which could be attributed to the taxes, supply chain margins, mark-ups and other costs (figure 1).

This work has revealed complex relationships among components of the Delhi healthcare system in terms of insulin access. Persons with diabetes in Delhi are largely dependent on insulin products manufactured and marketed by foreign companies, notwithstanding the fact that Indian domestic manufacturers have been selling their own branded insulin for the past 8–10 years.[29 30] Some Indian companies, such as Biocon and Wockhardt, with considerable production capacity, have lower prices and have also started to export insulin.[30]

We identified one insulin glargine cartridge product (Basugine) imported from China (made by Gen and Lee Pharma) for the Indian company Lupin. This supports our supposition (see also table 3 and online supplementary appendix webtable 4) that Indian companies perhaps cannot, or will not, make/market analogue insulins for the Delhi (Indian) market. Further, the import to wholesale mark-up and the overall mark-ups for this Basugine product were the highest among any product we found, regardless of formulation or delivery vehicle (see online supplementary appendix webtable 8). It may be that the Chinese can make

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Basugine cartridges more cost-effectively than Lupin can make it for themselves. Further, there are price caps mainly on domestically manufactured (but not imported) insulin products.[23–25] We speculate that Basugine, made in China for Lupin, is being imported at near-marginal cost but is being sold in India with a very high mark-up to take advantage of the possibly bigger difference between imported/Chinese production cost and the 'allowed' price cap selling price for imported products.

The GOI NPPA exerts stronger price control over domestic insulin prices.[23–25] Such variable price capping allows foreign companies to support their intensive marketing activities, that is, offering some free samples or newer delivery devices (like pens) to patients and convincing doctors to prescribe foreign products especially at the initiation phase. In the face of this variable price capping, if domestic Indian insulin manufacturers are not marketing their insulins to their own populations, this is a public health failure. It has been 13 years (2003) since Wockhardt became the fourth company in the world after Eli Lilly, Novo Nordisk and Sanofi Aventis to develop, manufacture and market insulin.[29]

Today, however, the belief that increasing market competition in India would improve access to insulin is not necessarily true. In Delhi state (India), the low market penetration of the insulins made by Indian manufacturers for the Indian market affects profits earned by various stakeholders (wholesalers, retailers, prescribers) in the supply chain to such an extent that these stakeholders apparently are choosing to supply imported/foreign insulin products. Indian companies are producing some insulin molecules on the Delhi EML but these products were rarely stocked in pharmacies (see online supplementary appendix webtables 3 and 4).

The implications of 'direct manufacturer/doctor/wholesaler to patient' supply are important. One wholesaler even admitted that they sold directly to patients. Most pharmacists and wholesalers reported that such direct supply is impacting their profits but it also indirectly impacts the public's health by putting patient access and availability at risk. That foreign companies are trying to directly influence patient behaviour is just a more extreme variant of their attempted influence on prescribers. At least in the USA, they appear to be directly impacting doctor prescribing patterns. US doctors who receive payments from the pharmaceutical and medical device industry do indeed tend to prescribe drugs differently than their colleagues who do not. The more money they receive, on average, the more brand name medications they prescribe.[31] We cannot say for sure whether this is happening with regard to insulin in India but Indian doctors often do engage in exploitative practices with the motive of earning profits.[32]

It appears that doctors in Delhi (India) believe that insulin from foreign companies is better and they do not trust Indian companies.[33] From our study, this may be an indictment of a weak Indian medicine regulatory agency as well as a statement about the profit motive of dispensing doctors when faced with the marketing power of multinationals selling expensive analogues. All this, of course, exacerbates the public health risk with regard to access and availability of quality-assured, domestic insulins.

CONCLUSION

Increasing competition from Indian manufacturing companies is going to require some additional policies that domestic companies/manufacturers and/or the government are currently not providing. The Delhi insulin market is an oligopoly, and such limited market competition has implications for suppliers' incentives to meet patients' need and for insulin prices and usage in lower income countries.

India should promote domestic Indian manufacturers of quality-assured insulins at lower prices than the multinationals. To eliminate the existing mistrust about the quality of domestic-manufactured Indian insulin, the efficacy and safety of domestically produced insulins must be compared with that of imported products and these data must be made publically available. Whatever the evidence, it should further be used to effectively communicate value messages, regarding assured quality, clinical outcome and potential cost saving, to the doctors and procurement agencies. The GOI must at least revisit their price controls to support Indian insulin manufacturers in order to improve their market shares and visibility, whose efforts are not only in line with India's 'Make in India'[34] programme but have a potential to meet the unmet global insulin need.[2 4 5 35] Domestic Indian manufacturers of quality-assured insulin need improved marketing strategies and incentives to increase market shares within India.

The Delhi EML has listed analogue insulins as essential medicine. Several consensus guidelines from India's doctor associations have recommended premixed insulin analogues as a preferred initiation option.[36 37] Perhaps this preference of premixed insulin to human insulin in India also reflects acceptance by the patients. All this is notwithstanding the 18th WHO Expert Committee recommendations regarding treatment initiation with human insulin.[27]

Third, 'direct company/doctor/wholesaler to patient' supply cuts out the pharmacies and will have implications for availability as pharmacists may choose to not stock insulin at all (or at least the less expensive products) as their profit motive will have evaporated. It may well be that profit incentives are better interventions than education to improve retail pharmacy services in Asia.[38] Both the GOI and pharmacy associations impacted by this practice should work with stakeholders (including patients) to better align the financial incentives of those in the insulin supply chain.

Even in the highly urbanised and relatively medicalised state (Delhi) in India, there are barriers to insulin access.

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The results of our analysis of the insulin access situation in India's national capital region (Delhi state) may not be representative of other states in India; however, we provide a reference point and methodology for future studies to be conducted in India and other LMICs.

In India, especially in the rural areas, there are delays in diagnosis and insulin initiation among patients with type 1 and 2 diabetes. The reasons for these delays include lack of advanced laboratories and other diagnostic facilities in the public sector, high cost associated with private-sector diagnostics, low confidence among primary doctors about their ability to initiate insulin therapy, poor availability of specialists and endocrinologists as well as insulin storage/refrigeration facilities in rural areas.[39 40] Whenever possible, future studies should consider evaluating these factors that influence access to insulin therapy.

The GOI and Indian patient associations could play an important role by framing independent, evidence-based guidelines aimed at prioritising the use of quality-assured and less expensive human insulin whenever possible and when clinically indicated. We could not identify any guidelines authorising Indian pharmacists to substitute the prescribed brands with less expensive, interchangeable insulin products, whether analogue or human. To be fair, large-scale and repeated substitution of insulins will make it difficult to obtain information on long-term safety risks. Nonetheless, from a socioeconomic and public health viewpoint, one could view insulin postmarketing studies sponsored by one or more of the three multinational companies as primarily marketing exercises.[41]

As more Indian companies—like Biocon and Wockhardt—produce biosimilars,[42 43] it is imperative to have policies allowing brand substitution to be able to benefit from market competition. In short, a better understanding is needed of the economic incentives and dis-incentives with regard to insulin use and availability among insulin manufacturers, public and private healthcare sectors and patients with diabetes in order to improve access to appropriate insulin therapy in India.

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Contributors AS conceived the study. AS and WAK designed the research methodology and planned the field survey. AS conducted the survey and data collection. AS and WAK conducted data analysis and the literature review. AS wrote the first draft of the paper. AS and WAK interpreted the results, revised and edited subsequent versions of the manuscript to its final stages, and approved the final manuscript.

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