Medicine Quality in Emerging Markets: Measuring the problem

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Abstract

The Minilab protocol is an excellent method of identifying falsified medicines, and two per cent (18 out of 899 samples) of our sample of antimicrobial medicines were falsified. However, as the data in this paper show, the Minilab considerably underestimates (by roughly 4.5%) the amount of substandard medicines in the market (totaling roughly 12 per cent in our sample), when measured by high performance liquid chromatography. The underestimation is particularly significant among medicines made by Indian companies. In addition to considerable patient death, substandard antimicrobial medicines are likely to drive drug resistance. Policymakers should redouble efforts to identify and combat such medicines since their presence may be more significant than previously thought.

Background

My research team has undertaken dozens of studies on antimicrobial medicines (beginning with Bate et al 2008), sampling over 10,000 treatment packages from 28 cities in emerging markets since 2007. By analyzing packaging and content we identified falsified medicines, those that are not made by the alleged manufacturer. We also found medicines that were substandard, made by the alleged manufacturer but containing incorrect (usually insufficient) amounts of the active pharmaceutical ingredients (APIs)[1].

We relied on assessing basic quality using the Minilab system. Minilab provides useful estimates of the poorest quality medicines in emerging markets. But Minilab generally only finds the poorest quality medicines (and obvious fakes with zero API). Quality was assessed with reference to price, location of purchase, regulatory environment and a variety of socioeconomic indicators (most recently, Bate et al 2015, Bate et al 2016).

The findings suggested that poverty and illiteracy were correlated with lower quality medicines of both main varieties (fakes and substandards). Fake medicines are priced identically to the real versions they copy, whereas substandards were slightly cheaper. Additionally products registered with local regulators tended to perform much better than products that were unregistered (technically illegal in most jurisdictions). Products registered by stringent regulators (such as the European Medicines Agency and the US Food and Drug Administration), performed even better than those just approved by local regulators (this fact largely explained by the former being western produced products).

In earlier papers (e.g. Bate et al 2015), we differentiated falsified and substandard drugs as follows. We classify drugs with zero active ingredient as "falsified" while those with some but less than "enough"[2] active ingredient as "substandard". All other drugs are considered to be "passing" i.e. they pass the quality test.

The definition I use is different from that of World Health Organization (WHO) which

[1] We also occasionally found degraded medicines, most often crumbling pills. These were found in the poorest locations of Africa and in a couple of instances in India too.

[2] Enough is not always easy to estimate. For most medicines, 95-105% of the correct active ingredient is the ideal amount, but 90-110% is considered acceptable. But certain techniques are not precise in measurement so 80% is the minimum amount required for a basic pass.

defines counterfeit medicines as "medicines that are deliberately and fraudulently mislabeled with respect to identity and/or source". This definition emphasizes the intent to deceive as the primary characteristic of a counterfeit drug (Attaran et al 2012), which as an empirical matter is hard to prove. In light of the difficulty to detect the intent of manufacture, this paper distinguishes substandard and falsified drugs by technical details, notably ingredient content. It is extremely rare for counterfeit medicines to contain the correct active ingredients, so the definition is a reasonable and highly practical proxy (Bate 2012).

Also, targeting falsified and substandard drugs requires different strategies. Substandard drugs arise from the poor production techniques by legitimate manufacturers and therefore can be addressed through better regulations and manufacturing standards (Caudron et al. 2008). In contrast, falsified drugs with zero active ingredient requires arresting criminal activity through better law enforcement and prosecution (Institute of Medicine 2013).

During that time, we have tested some medicines with high performance liquid chromatography (HPLC), which provides far more precise measurement of API. This paper compares the methods and discusses the likely real amount of substandard medicines based on more stringent tests.

Methods

In all samplings, we instructed covert shoppers from the region to randomly walk into pharmacies and claim that a family member needed a specific type of drug (see Bate et al 2008; Bate et al 2015 for more extensive explanations). To mimic real patients as much as possible, the covert shoppers did not present a doctor's prescription and always purchased the pharmacist-suggested choice. Informal drug vendors (bus vendors, mobile carts, etc.) occur in some locations, but to be able to compare across all locations, our shoppers only visited pharmacies with a regular storefront. As a result, the samples are likely to understate the problem of poor-quality drugs, given the expectation and existing evidence that informal vendors sell worse drugs (Institute of Medicine 2013).

The 28 cities in our sample included 5 cities in India (Chennai, Delhi, Hyderabad, Kolkata and Mumbai) and 12 cities in Africa (Accra, Addis Ababa, Cairo, Dar Es Salaam, Kampala, Kigali, Lagos, Luanda, Lubumbashi, Lusaka, Maputo, and Nairobi).

The remaining 11 cities were in mid-income nations, including Bangkok, Beijing, Istanbul, Moscow, Buenos Aires, Montevideo, Caracas, La Paz, Lima, Asuncion and Sao Paolo.

All medicines were assessed following the Global Pharma Health Fund (GPHF) e.V. Minilab® protocol to identify substandard or falsified medicines (Jahnke et al, 2001). All tests were conducted within 60 days after purchase (starting in October 2007 and ending in February 2016), following the classification in Bate et al (2015), at the Africa Fighting Malaria laboratory in Cambridge UK. The most important test was the semi-quantitative thin-layer chromatography (TLC), which assesses the presence and concentration of active ingredient in a test sample as compared to the reference standard. Because of the semi-quantitative nature, it gives a generous pass if approximately 80% of the active ingredient is present. This also means that the data underestimates the amount of substandard medicines in the marketplace.

To try and get a more accurate figure for quality on the market place 899 samples were tested with high performance liquid chromatography (HPLC) to determine API. These samples were randomly drawn from within the total sample (at the time of collection), and tested in timely fashion. These data are novel and presented here for the first time. This paper compares the subset of 899 samples tested by both techniques to assess whether Minilab misses quality problems, and if so, how much worse medicine quality may be in emerging markets.

Results

The first result of note is that testing with HPLC found no more fake medicines. Since the most obvious characteristics of fake medicine are no API and problems with packaging, this should be of no surprise. The minilab found 18 fake medicines (two percent of the sample) and HPLC confirmed that 18 had zero API. This leaves 881 treatments packs that were not fake. The results of the analysis are below in table 1.

The second key result is that approximately 7.5 per cent of the total non-fake sample fails basic quality with Minilab, which is roughly the same as found across the larger sample of over 10,000 samples tested previously, so it is fair to say that the 881 samples are a reasonably fair reflection of the population from which they are drawn.

Table 1

	Where made	Samples	% of total	Fail Minilab	% Fail Minilab	Fail HPLC	% Fail HPLC	HPLC-Minilab	% HPLC-Minilab
	OECD	287	32.3	1	0.35	3	1.05	2	0.70
	India	344	39.0	33	9.59	59	17.15	26	7.56
	China	189	21.5	22	11.60	30	15.87	8	4.23
	ROW	69	7.8	10	14.50	15	21.74	5	7.24
Total/average		881		66	7.50	107	12.14	39	4.43

There were no identified false positives found by HPLC. The Minilab Protocol found 66 substandard medicines, HPLC found an additional 39 failures (totaling 107 failures 12.14%). Two of the new failures were of medicines made in wealthy nations, one in Belgium and one in USA. But as expected the vast majority of these medicines were well made. What is most striking is that an additional 26 Indian products failed HPLC that passed Minilab. Over 17 per cent of the Indian samples failed HPLC.

The samples made in the rest of the world (ROW) failed more than a fifth of the time (21.74%), but many of these were made in Africa, which from previous analysis African nations have the worst quality medicines (Bate et al 2008; Nayyar et al 2012).

Discussion

It is encouraging that HPLC did not unearth more fake medicine. But it is worrying that almost one in eight medicines sampled was substandard. And given that only 1% of medicines made in wealthy (OECD) nations (and these medicines are usually more expensive), the cheaper medicines that dominate emerging markets fail far too often. It is unknown what impact this has on health in general, but in one paper, scholars estimate that over 120,000 deaths are caused by substandard antimalarial medicine alone (Renschler et al 2015).

Conclusions

The Minilab protocol is an excellent method of identifying falsified medicines. However, as the data in this paper show, it considerably underestimates the amount of substandard medicines in the market, especially among medicines made by Indian companies. In addition to considerable patient death, substandard antimicrobial medicines are likely to drive drug resistance.

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