Assessment of Medicine Quality in Emerging Markets: The changing face of inferior medicines over time.

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Background

Over the past decade we collected over ten thousand samples of medicines to treat infectious diseases from 28 cities in emerging markets. By analyzing packaging and content we identified fake or 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 ingredients. 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.

Depending on the complexity of the testing method deployed it was possible to identify other flaws in the medicine, notably lack of solubility. As a general rule the more tests applied, the more medicines failed quality control. Quality was assessed with reference to price, location of purchase, regulatory environment and a variety of socioeconomic indicators [1,2].

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

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Administration), performed even better than those just approved by local regulators (this fact is largely explained by the former being western-produced products).

In earlier papers [1] 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” active ingredient as “substandard”. 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; certain techniques are not precise in measurement so 80% is the minimum amount required for a basic pass. All other drugs are considered to be “passing”, that is, they pass the quality test.

The definition we use is different from that of World Health Organization (WHO) which 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 [3], which is hard to prove as an empirical matter. 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 [4].

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 [5]. In contrast, the production and distribution of falsified drugs with no active ingredient requires is a matter requiring better law enforcement and prosecution. It is a significant complication that counterfeiting medicines is not a crime in all countries. [6].

Methods

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.

We prefer to collect samples randomly from a stratified database of all retail outlets in each city. However, this requires detailed information on a census of retail outlets per city, which is usually not available from local governments. Nor can we conduct an exhaustive survey per city given our limited funding. In light of these constraints, for any city in our data, we hired local covert shoppers to procure samples in at least two median income areas of the city. The buyers bought from retail pharmacies, ignoring other possible outlets like kiosks and mobile sellers. In particular, a covert shopper was instructed to visit retail pharmacies in a random walk, claim that an adult family member is suffering from a nasty bacterial infection, and request medicine because a family friend/doctor suggested so. Then the shopper will follow the in-store pharmacist's guidance (if any) to make a purchase. We did not instruct covert shoppers to aim for any particular brand or price range, as doing so could make the pharmacist suspicious of covert shopping and behave differently. Our covert shoppers did not present a prescription to the pharmacist, as most cities we sampled either do not have or do not enforce prescription requirements on antibiotics. In such an environment, presenting a prescription may trigger the pharmacist to suspect that our shoppers are atypical.

As a result of the above approach, the samples are likely to understate the problem of poor-quality drugs, given the expectation and existing evidence that informal vendors sell worse drugs [6].

All medicines were assessed following the Global Pharma Health Fund (GPHF) e.V. Minilab® protocol to identify substandard or falsified medicines [7]. All tests were conducted within 60 days after purchase, following the classification in Bate, Jin and Mathur [1]. 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 with the reference standard. Because of the semi-quantitative nature, it gives a generous pass if approximately 80% of the active ingredient is present. We differentiated falsified and substandard drugs as follows. We classify drugs with zero active ingredient as “falsified” while those with less than 80% active ingredient as “substandard”. All other drugs are considered to be “passing”, that is, they pass the quality test. This also means that the data underestimate the amount of substandard medicines in the marketplace.

To refine our results further, 431 of our samples were tested with high performance liquid chromatography for more accurate assessment of quality (budget constraints precluded wider deployment of more sophisticated techniques). It is important to note that no new medicines were identified as falsified but more samples were identified as substandard, indicating that Minilab results of these samples were therefore false positives, and further that our data underrepresent the true amount of substandard medicines in emerging markets. It is encouraging to note that we did not identify any false negatives from the Minilab procedures.

Results

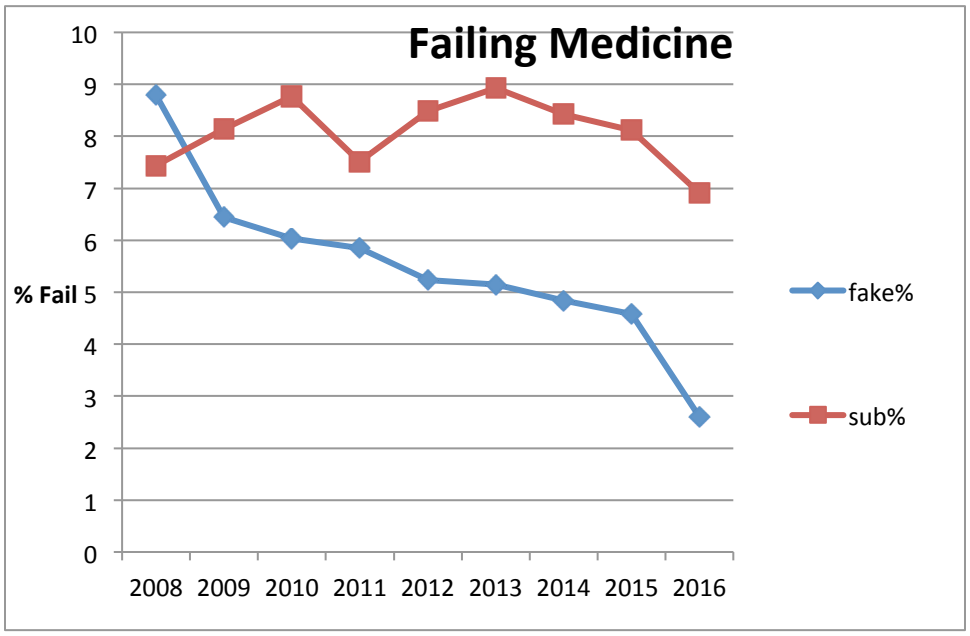
The results in table one shows the summary statistics of all the tests. These findings are presented graphically in figure one.

Over the eight year period, roughly 13.6% of the sample failed quality tests, with 8.1% being substandard and 5.5% fake. There was an improvement over time from 16.23% failing in 2008 to 9.51% in 2016. The most interesting finding is that the percentage of fake drugs falls consistently over time, whereas the failure rates from substandards is more stable, falling very little. It is therefore the fall in fake medicines that accounts for the bulk of the overall decline.

Table 1

Year	Samples	Failing samples	Fail %	Fake	Substandard	Fake %	Substandard %
2008	887	144	16.23	78	66	8.79	7.44
2009	1241	181	14.59	80	101	6.44	8.14
2010	912	135	14.80	55	80	6.03	8.78
2011	1332	178	13.36	78	100	5.86	7.51
2012	2122	291	13.71	111	180	5.23	8.48
2013	874	123	14.07	45	78	5.15	8.92
2014	1199	159	13.26	58	101	4.84	8.42
2015	567	72	12.70	26	46	4.59	8.11
2016	999	95	9.51	26	69	2.60	6.91
	10133	1378	13.60	557	821	5.50	8.10

Figure 1



Discussion

It is a worry for patients in emerging markets that 13.6% of the samples fail basic quality control. Given that more exacting tests would no doubt find more inferior medicines, there can be little doubt that quality is not universally sound. Those suffering from malaria, tuberculosis and serious bacterial infections are at risk that the medicines they take to treat their diseases will not work. There is also the population level risk of accelerated drug resistance due to such medicines.

The decline in poor quality medicines over time is positive and is very largely due to efforts to combat counterfeiting of medicine, samples of which fell from over 9% to under 3% in our surveys. Improvements in understanding about the problem, laws to prevent it, coupled with enforcement, and coordination with international agencies, notably Interpol and the UN Office on Drugs and Crime, have yielded positive results, which show up in the data presented [4][6].

However, the data on substandard medicines show that any efforts against their production and distribution have been ineffectual. Part of the reason is that producers of substandard medicines do not break criminal laws and hence are not treated as seriously by politicians and law enforcement agencies. Even regulators view poor production as a mistake to be rectified, rather than a systematic corner-cutting effort. However, Dinesh Thakur, the whistleblower in the Ranbaxy case, insists that many companies cut corners to save costs; that they do so repeatedly and only stop when caught, prosecuted and sanctioned [8].

Conclusions

A substantial minority of medicines to treat infectious diseases in emerging markets are of suspect quality, at least 13.5% of over 10,000 samples. This is a risk to patients and threatens to accelerate drug resistance. The two main types of inferior medicines are counterfeit or falsified medicines and substandards. As efforts against fake medicines have increased over the past decade, the rate of such products has fallen in our samplings. The international community and domestic regulators must improve efforts against substandards, just as they have against falsified medicines, if quality is to improve further.

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