



RESEARCH ARTICLE

Identifying market risk for substandard and falsified medicines: an analytic framework based on qualitative research in China, Indonesia, Turkey and Romania [version 1; peer review: 4 approved]

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Abstract

Introduction: Substandard and falsified medicines undermine health systems. We sought to unravel the political and economic factors which drive the production of these products, and to explain how they reach patients.

Methods: We conducted in-depth case studies in China, Indonesia, Turkey and Romania. We reviewed academic papers and press reports (n = 840), developing semi-structured questionnaires. We interviewed regulators, policy-makers, pharmaceutical manufacturers, physicians, pharmacists, patients and academics (n=88). We coded data using NVivo software, and developed an analytic framework to assess national risks for substandard and falsified medicines. We tested the framework against cases reported to the World Health Organization, from countries at all income levels.

Results: We found that increasing political commitment to provision of universal health coverage has led to public procurement policies aimed at lowering prices of medical products. In response, legitimate, profit-driven pharmaceutical companies protect their margins by cutting costs, or withdrawing from less profitable markets, while distributors engage in arbitrage. Meanwhile, health providers sometimes protect profits by 'upselling' patients to medicines not covered by insurers. Cost-cutting can undermine quality assurance, leading to substandard or degraded medicines. Other responses contribute to shortages, irrational demand and high prices. All of these provide market opportunities for producers of falsified products; they also push consumers outside of the regular supply chain, providing falsifiers with easy access to customers. The analytic framework capturing these interactions explained cases in most high and middle-income settings; additional factors operate in the poorest countries.

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Conclusions: Most efforts to secure medicine quality currently focus on product regulation. However, our research suggests market mechanisms are key drivers for poor quality medicines, including where political commitments to universal health coverage are under-resourced. We have developed a framework to guide country-specific, system-wide analysis. This can flag risks and pinpoint specific actions to protect medicine quality, and thus health.

Keywords

falsified medicine, substandard medicine, counterfeit medicine, medicine quality, procurement, LMIC,

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Introduction

Substandard and falsified medical products undermine the prospect of achieving effective universal health coverage (UHC)¹. They waste money, fail to cure sick people, and sometimes even kill them. Reviews of *in vitro*, animal, observational and modelling studies conclude that anti-infective medicines that deliver sub-therapeutic doses because of poor formulation or degradation also encourage drug-resistant infections^{2,3}. A 2017 analysis of 1,500 cases of suspect medicines reported to the World Health Organisation Global Surveillance and Monitoring System for substandard and falsified medical products (the WHO GSMS database) showed that they exist in all regions of the world and affect all classes of medicines. Recently published meta-analyses of prevalence studies suggest that between 10 and 20 percent of anti-infective medicines in low- and middle-income countries might be substandard or falsified⁴⁻⁶.

The problem is not new. The WHO outlined factors facilitating the manufacture and trade in poor quality medicines and recommended measures to tackle the problem as early as 1999⁷. Some 18 years later, in 2017, it published a report whose findings and recommendations were remarkably similar. Both reports grouped factors that facilitate the production and circulation of falsified and substandard medicines into three broad areas:

- Access-related: shortages of affordable, accessible, acceptable, quality-assured medicine;
- Governance-related: weak legislation and sanctions, corruption;
- Limited technical capacity: limitations among regulators, investigators, prosecutors, laboratories etc., as well as among producers and throughout the supply chain.

Other reviews have cited similar factors, and have proposed similar response strategies for prevention, detection and response,

underlining, like WHO, the need to strengthen national medicines regulatory agencies⁸.

This begs the question: if both the drivers of poor-quality medicines and the solutions have been known for two decades, why does the problem persist? We hypothesised that previous approaches correctly diagnose the immediate drivers, but did not sufficiently consider the specific political and economic factors which shape the markets for substandard and for falsified medicines, and which may stand in the way of proposed policy responses.

We thus conducted detailed, qualitative case studies in four middle-income countries which are significant producers and consumers of pharmaceuticals. We aimed to identify specific mechanisms through which political, economic and other systemic factors influence the availability of substandard and falsified medicines and vaccines, and the ways in which they enable or obstruct policies aimed at reducing the production, trade and consumption of those products. On the basis of our findings, we further aimed to develop an analytic framework that can be used at the national level to identify policies and practices that create risks for substandard production or degradation of medical products, or that provide opportunities for market entry of falsified products.

Methods

Our team consisted of specialists in epidemiology, criminology, medicine marketing and regulation, economics and public policy. We used WHO's 2017 definitions, adopting "substandard" to refer to medical products that do not meet quality standards, and "falsified" to describe those that deliberately misrepresent identity, composition or source, and excluding patent-related considerations⁹.

Table 1 summarises the steps we took during this two-phase study.

Table 1. Summary of study steps.

Phase 1: Deductive approach
Initial literature review: n ≅ 625
Developed initial working theory using critical interpretative synthesis
Developed a draft coding structure for data analysis in NVivo software
Selected countries for case studies, matching countries to key themes identified in initial literature review, working theory, and staff skills
Phase 2: Grounded theory approach
Country-specific review of literature, court reports, institutional & press reports. n ≅ 215
Conducted 88 semi-structured interviews in four countries
Transcribed interviews, translated them into English
Coded interviews in NVivo software
Iteratively identified common patterns and differences in weekly team meetings; developed draft framework
Presented case study results and Market Risk Framework to informal study advisory panel
Integrated feedback; tested & revised framework against 14 cases from the WHO case reporting database
Finalised framework

Literature review

We began by searching for evidence related to the causes and consequences of substandard and falsified medicines. We searched PubMed, MEDLINE, the WHO Essential Medicines and Health Products Information Portal and Google Scholar using the keywords “counterfeit” (which was, until the 2019 revision, the Medical Subject Heading used for poor quality medicines), “substandard”, “falsified” or “poor quality” in combination with “medicin*”, “medical products” or “pharmaceutical*”. We identified further publications from bibliographies.

We reviewed resulting publications using critical interpretive synthesis—an iterative method designed for analysing heterogeneous qualitative data and developing theory^{10,11}. Early in the process, we developed a coding structure centred on factors that created a market opportunity for poor-quality medicines, as well as factors that motivate, facilitate, or deter their production or trade. We entered this structure into NVivo software v12¹², using it to code further reading and refining it inductively. It reached near-final form before the country case studies were conducted. We provide the final coding structure along with a log of changes to coding during iterative analysis in the study repository (see *Extended data*; 02_Coding_structure.docx¹³).

Choice of countries

We chose to conduct studies in middle-income countries because many, including several with large populations, are now actively pursuing policies designed to achieve or sustain UHC, while at the same time trying to increase domestic capacity for the production of pharmaceuticals. In addition, many are facing a “double burden” of disease, and demand is rising for new treatments for non-communicable diseases, as well as those for neglected and common infectious diseases. Such countries thus provide learning across a wide range of issues; this learning may also be useful to lower income countries that are now considering increasing public financing for health.

In our initial reading, we also identified structural characteristics with potentially significant implications for medicine quality, as described in the Results section below. To the extent possible, we chose to conduct case studies in countries that displayed one of these characteristics. Finally, wishing to search literature and conduct interviews in local languages where possible, we considered the language skills of our research team.

Once countries had been selected for case studies, we searched national institutional websites as well as the internet for sources relating to substandard and falsified medicines in Chinese, Indonesian, Turkish and Romanian.

Field research

We developed question guides based on our literature review, with variations for particular sub-studies (see *Extended data*; 11_Interview_topic_guide.docx¹³). Potential respondents were purposively selected based on their knowledge of the manufacture, regulation, trade, prescription or consumption of medicines; further respondents were suggested by participants. We contacted them electronically and explained the purpose of the

study. Consenting respondents (n=88) were provided with further details in writing in their native language, including around procedures to maintain confidentiality, then interviewed face-to-face or by Skype for between 60 and 90 minutes. Consent to record was sought. Where granted (n= 65) consent was repeated on tape. Where denied (n=14) or technically impractical (n=10), consent to take written notes was sought, and written consent for interview was obtained. Most interviews were conducted in the respondent’s native language; staff of international organisations were interviewed in English.

Data processing, analysis and testing

Recorded interviews were transcribed and translated into English in full or in part by the interviewer. Where no recording was possible, notes were typed in English. Researchers coded their own interviews in a shared NVivo project; the principal investigator (EP) coded a subset of interviews in parallel—differences in coding were discussed in weekly team meetings to develop shared understanding around key concepts. More details of participant recruitment, interviews and data handling, reported following COREQ guidelines¹⁴, is provided in the study repository (see *Reporting guidelines*; 03_COREQ_medicine_quality_study_info_form.docx¹³).

We used a grounded theory approach in developing a coherent framework based on the similarities between country case studies¹⁵. A draft analytic framework was developed and presented to an informal study advisory group in April 2018 (see *Acknowledgements*). It was revised following input from the group.

We then collaborated with colleagues at WHO, asking them to identify cases they considered illustrative of the breadth of reports of substandard and falsified medicines logged in the GSMS database. The selected cases included reports from the Democratic Republic of Congo (×2), Nicaragua, Niger, Pakistan, the United Kingdom, the United States and Venezuela, as well as cross-border and regional cases involving China, France, India, Paraguay, the Middle East and West Africa (×3). We mapped these cases on to the market risk framework, to ascertain the extent to which the factors identified in the framework explained the dynamics of each case.

Ethical approval

The Daily Board of the Medical Ethics Committee of Erasmus University reviewed the study plan and questionnaires and approved the protocol with number MEC-2018-016. National guidelines in all of the concerned countries specify that local ethical approval must be sought for invasive, but not non-invasive research. We discussed the study with officials in the Ministry of Health and/or medicine regulatory authorities (at the provincial level in China and at the national level in other countries) before the start of data collection to ensure that they were fully aware of the aims of our work.

Study funders were consulted over final study design; funders had no role in analysis, manuscript development or decision to submit for publication.

Results

These results bring findings derived from our review of literature and documentation together with data collected in semi-structured interviews. Where no specific reference is given, the finding comes from interview data.

Altogether, we reviewed some 840 papers and documents relating to medicine quality and product falsification in seven languages, and interviewed 88 people. We provide a full downloadable bibliography of all documents reviewed in the study repository (see *Extended data*; 04_Bibliography.ris¹³).

Global overview from literature: contributors to poor quality medicines

Many of the academic research papers we found reported surveys of the prevalence of poor-quality medicines in low income countries⁶. The academic literature also provided many commentaries that summarised existing evidence. Some stressed the importance of market factors¹⁶, and several called for greater political commitment to addressing the threat posed by poor quality medicines^{17–19}. However, few of these provide any detailed analysis of the reasons why that commitment is currently lacking.

Books and institutional reports were more likely to provide information about factors facilitating the circulation of poor-quality medicines, as described in the *Introduction*^{4,5,7,8,20–25}. These documents generally agree on the circumstances commonly associated with poor quality medicines: shortages of affordable, quality-assured medicine; weak legislation and sanctions; under-resourced regulators with poor technical capacity; complex supply chains; and corruption. We used these areas of agreement to inform our coding structure and interview guides.

However, we found no global analyses which described how these factors relate to one another, or to the political and economic landscapes in which they are rooted.

Much of the remainder of the literature fell into two categories: studies of the medicine markets in a particular country or trading area, and investigations of cases in which falsified or substandard medicines reached markets^{26–31}. These provided additional insights about factors likely to affect medicine quality, especially in middle-income markets, and contributed to our choice of country case studies. Salient factors increasing risk included market structures that facilitate arbitrage or parallel trade (to which Romania is subject), very rapid scale-up of health service provision (all study countries), decentralised or otherwise complex government and regulatory structures (Indonesia, China). Protective factors included effective single-payer systems and strong information systems, both present in Turkey.

Country case studies

Table 2 provides key characteristics of the countries selected for case studies.

The particular focus of each country case study influenced the choice of informants approached for interview. China is the largest producer and exporter of active pharmaceutical ingredients (API) in the world; it also has a complex decentralised regulatory structure. We chose to focus on the interaction between international, national and state-level factors influencing quality assurance of Chinese API in Zhejiang province, the country's largest producer and exporter of active ingredients and home to four of the world's top ten producers, according to trade sources³². We thus spoke principally to manufacturers and regulators in Zhejiang.

While health services in Indonesia were decentralised in 2001, the central government committed in 2014 to including all citizens in a single-payer health insurance scheme. Though three-quarters of the population is now covered, the scheme has been in deficit since its inception. We focused our case study on the interaction between the radical changes to health financing and

Table 2. Characteristics of countries studied.

Variable	China	Indonesia	Turkey	Romania
Population 2016 (million)	1,379	261	80	20
World Bank Income classification	Upper middle	Lower middle	Upper middle	Upper middle
Health spending per capita, (US\$ PPP 2015)	779	383	1029	1128
Annualised growth in health spending, 1995–2015 (%)	10.1	5.6	3.1	5.9
public or insured % of health spending (2015)	67	52	83	79
Generics as % of domestic drug consumption, by volume	80	70	56	60
Value of domestic pharma production, 2016 (US\$ billion)	249	3 (2014)	17 (2015)	3
Health financing model (with % covered, 2018)	Social health insurance	Single payer insurance (74%)	Single payer insurance (98%)	Single payer insurance (74%)
Focus of country sub-study	Production of API	Scale up of national insurance	Track and trace	National and regional regulation

API, active pharmaceutical ingredient.

Sources: World Bank and International Health Metrics and Evaluation databases (available through 33,34)

the quality of medicines, speaking to stakeholders across the system.

Turkey undertook a similar transformation in health financing a decade earlier, and has more recently invested in widely praised medicine tracking technology. The Turkish case study paid particular attention to the genesis of this technology, and the factors that facilitated or threatened its implementation; many of the interviewees were directly involved with or impacted by these efforts.

Romania is one of the newest and poorest members of the European Union; out-of-pocket spending on health is close to 40% higher than the EU average³³. Successive governments have promised to reduce medicine prices, but must do this within the EU's single market, while Romanian pharmaceutical companies must comply with EU standards. The Romanian case study included interviewees from across the supply chain, and highlighted the interaction between national and regional goals, regulations and markets.

Table 3 shows the number of interviewees in each country case study.

The particularities of each country focus will be reported separately. The remainder of our results present the common dynamics that we found across these different country case studies, and the analytic framework that arises from them.

Political promises and policies affecting the market for medicines

We found that political promises, and the policies intended to deliver on them, fundamentally shaped the market for medicines in all study countries, with more uniformity on the demand side of the market than on the supply side. Because the Chinese study focused on the API market, we do not include specific

information on the demand side for formulated medicines in China.

Demand for medicines

In all of the study countries, governments have promised to provide virtually all citizens with affordable access to health care. Scaling up service provision to deliver on this promise clearly increases the size of the market for medical products.

The health financing mechanisms that aim to deliver UHC differ in Indonesia, Turkey and Romania, but all include high degrees of public subsidy. This, combined with rising demand, puts pressure on public budgets, and makes cost containment a priority. Procurement policies have thus increasingly focused on bringing down the price of medicines. Other health system measures have reinforced these efforts, as shown in Table 4.

Some of these measures are incomplete or inconsistently implemented. For example, infrequent updating of prices in response to changes in reference prices or exchange rates disrupted markets in Romania and Turkey. In Indonesia, inclusion on the national formulary precedes cost-effectiveness analysis (which is only performed for limited classes of drugs, such as oncology). This reduces the state's bargaining power in auctions.

However, taken together, cost-containment measures have effectively reduced the price paid for many medicines in the study countries³⁵⁻³⁹.

Supply of medicines

China's government includes pharmaceutical industry growth in its national development plan, "Made in China 2025"⁴⁰. In all countries, however, we found many, more general political promises that have implications for the supply of medicines. We group them under the category of "national prosperity"; they encompass areas as diverse as economic wellbeing, environmental health and promotion of religious interests.

Table 3. Number of people interviewed, by country and respondent type.

Interview subject	China	Indonesia	Turkey	Romania	Total
Manufacturers/Pharma industry groups	5	4	2	3	14
Brokers or distributors	5	2	1	4	12
Health care practitioners	-	8	1	5	14
Ministry of Health	-	4	3	2	9
Medicine regulator	7	2	*	1	10
National insurer	-	1	2	1	4
Technical agencies for pharmaceutical policy	2	2	6	3	13
Academic	-	2	1	-	3
Patient, media, civil society	-	6	-	3	9
Total	19	31	16	22	88

Table 4. Policies aimed at containing the cost of medical products.

Measures	Indonesia	Romania	Turkey
Procurement measures			
National formulary	Yes	Yes	Yes
Internal reference pricing	Yes	Limited	Yes
External reference pricing	Yes		Yes
Other pricing policies	Yes	Yes	Yes
Global budgeting	No	No	2010-2012
Restriction to INN generics	Yes	Yes	No
Public auctions/price transparency	Yes	Yes	Yes
Other health system measures			
Clinical guidelines	Limited	Yes	Yes
Health technology assessment	Limited	Yes	Yes

INN, International non-proprietary name.

Sources: Interviews and 7,41,42.

Table 5 details some of the policies we encountered, with their real or potential effect on the supply of medicines. Many of these effects are unintended, but they have very real consequences for companies seeking to supply the medicines market.

While membership of the EU promised prosperity for Romania, for example, compliance with European good manufacturing practice (GMP) regulations pushed the price of domestic medicines up by over 30%, and led to the closure of some companies, according to reports in the financial press⁴³.

Similarly, in China, thousands of factories manufacturing chemicals for the medicine market were closed down as a consequence of policies designed to improve the physical environment. This increased the price of some products, and created severe shortages for others.

“Our company’s sales revenue dropped 4% [in 2017]. In monetary value, we lost 100 million RMB on sales. The most important reason was that many chemical manufacturers were closed down. Now the situation is: we have clients, for example those from India request certain products, but these products are no longer manufactured. So, it’s very frustrating that we have business opportunities, but no products to sell.”

Chemical/pharmaceutical trading company employee, China

The policies affecting the supply side have wide-ranging effects, but the majority that we encountered tend to increase the cost of producing medicines or of importing them in to national markets.

Combined market effect

Most markets are the product of supply and demand. Figure 1 shows schematically how political promises and the policies that operationalize them shape the market for medical products

in the countries we studied. The combined effect of lower prices and higher production costs is to squeeze profit margins for producers and distributors of medicines. And yet most of those companies—domestic and multi-national, innovator and generic, and including the state-owned enterprises in the countries we studied—are profit-oriented and will act to protect their profits.

We thus turn our attention to the actions they take, which we cluster into three areas: cost-cutting, avoidance of loss-making markets and products, and promotion of high-margin products. For each area we describe the action, the results of that action, the steps that are taken to mitigate the risks by medicine regulators and others, and the limitations of mitigating action.

Market response 1: Industry protects margins by cutting costs

Where procurement or other policies make it hard to raise prices, producers and distributors of medicines try to protect margins by cutting costs. They may increase efficiency, seek economies of scale or increase mechanisation. They may also seek cheaper suppliers or skimp on quality assurance procedures.

Q: Is there an effect, where, because of the low offering prices, the components of medicines are compromised?

A: Yes, definitely. Starting with the raw materials. That’s the first thing, manufacturers are going to look for the very cheapest API, they’re going to look for a cheaper supplier. Next is the way they make the medicines available. For example, they might have started with blister packs, but they’ll change those to strips, something cheaper. Basically, they’re looking for ways to make more profit.

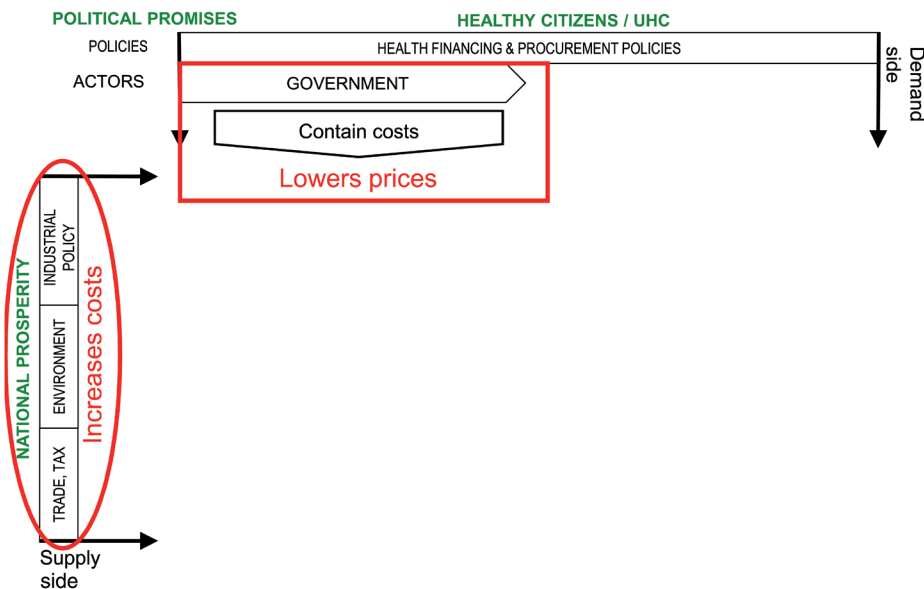
Pharmaceutical manufacturer, Indonesia

An API producer in China confirmed the close link between price and product quality, reporting that controlling a particular impurity at 0.1% or less could increase the price of a

Table 5. Policies affecting medicine supply in study countries, and their effects.

Political promise	Country	Policy	Effect
Economic growth	Romania	EU membership	Pharma producers subject to EU standards; single market
Domestic jobs	Indonesia	Minimum 40% domestic components	Threatens Indonesian pharma, which imports >90% API
Healthy environment	China	Reduce polluting industry	Closure of major API producers
Protect religious interests	Indonesia	Halal law, requires halal certification of all medicines	Potential withdrawal of imported products
Fiscal responsibility	Romania, Indonesia	Taxation, incl. clawback tax	Increases tax burden on pharmaceutical firms

Sources: Interviews, and 44–47

**Figure 1. The effect of political promises and policies on medicine markets.**

chemical by 20% or more. Prices of Chinese API vary by destination market; importers in the United States pay approximately three times as much per kilo on aggregate as do importers in Africa⁴⁸.

Risk to product quality: substandard production or degradation

Reducing the quantity of active ingredient to save money will lead directly to a substandard product; buying cheaper API is likely to do the same. Lower-cost excipients may alter the way a pill dissolves or otherwise reduce its bioavailability, and thus its efficacy, and may also increase the risks of degradation.

Choosing cheaper packaging or under-investing in distribution mechanisms, including adequate temperature control, increases the likelihood of degradation⁴⁹. Meanwhile, cutting corners on quality assurance creates risks of mistakes during the production process; this can cost hundreds of lives, for example when

breaches of standard operating procedures lead to chemicals being switched inadvertently⁵⁰.

These effects are represented schematically in [Figure 2](#).

Mitigating actions: inspection, surveillance, prequalification
Cost-cutting should not affect product quality as long as producers observe GMP and distributors adhere to good distribution practice (GDP). In most countries (including all study countries) the medicine regulator periodically inspects factories and supply chains, and issues GMP and GDP certificates.

However, in part because of limited resources, this process is far from water-tight. Political pressure to protect local industry also sometimes obstructs nationally-mandated inspections:

“Sometimes regulation can be difficult. For example, we are not encouraged to impose tough regulation on some

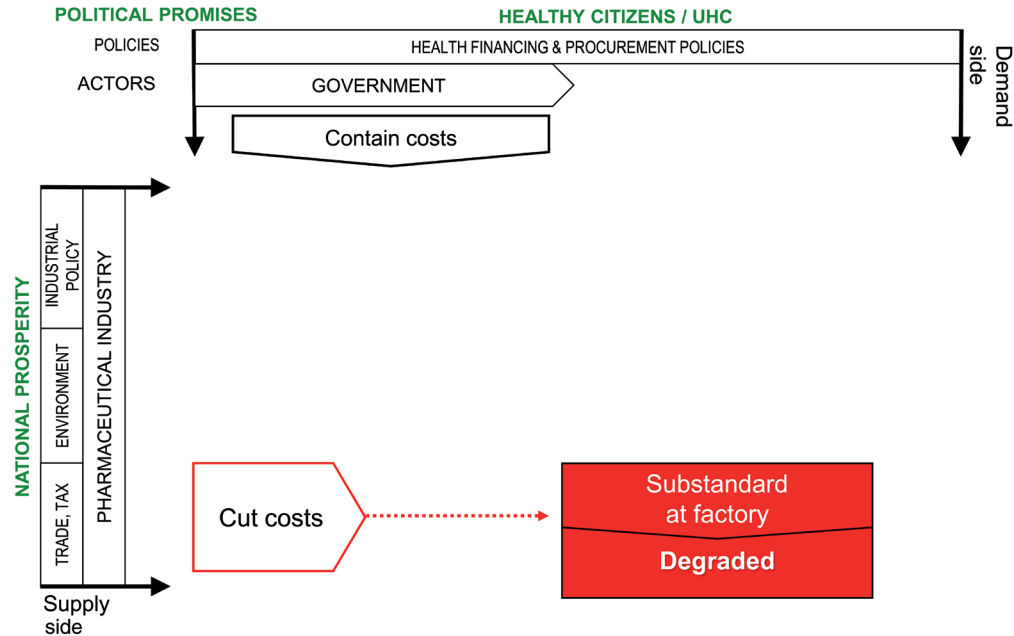


Figure 2. Cost-cutting in defence of profit creates risk for substandard medicines.

enterprises which are highly valued by local governments. Local governments will step in and protect those enterprises.”

Medicine regulator, China

The result of inspections by regulators are not always taken into account by purchasers. In Indonesia, for example, a valid market authorisation is the only indicator of product quality required in public procurement⁴¹. However, market authorisations remain valid for five years, and are not routinely revoked if GMP certification is withdrawn following an inspection, allowing continued procurement of potentially substandard products.

National regulators are not mandated to inspect production or distribution of products for export (although the EU requires exporting country regulators to provide GMP certifications for the API it imports). The onus for quality assurance thus lies with the importer’s regulator, but few countries have the resources to send inspectors to plants in countries from which they buy products, while pre-import GDP inspection is largely absent⁵¹.

A Chinese manufacturer explained how this may lead to a “two-track” system for product quality:

“If the requirement is 0.1% [maximum impurity], a good manufacturer would refine up to 0.07-0.08%.... But some manufacturers would want to save cost and just reach the borderline point. It happens that test result from our clients shows 1.1% and they can’t accept the product. ...What happens next would depend on the status and bargaining power of both sides. If we supply [a top-10 multinational pharmaceutical firm], no doubt the product will be returned and we will have to make new ones for them. If we supply

middle-end customers whose downstream markets are not well regulated, for example the African market – we are not discriminating Africa, but it’s true their state regulations are not so strict – in that case, we may be able to persuade the client to use the product, by offering for example 5% further discount.”

API manufacturer, China

We also found evidence that even the most stringent regulatory authorities take the needs of their domestic industry into account when considering enforcement of GMP, including in other countries. A Chinese manufacturer described the outcome of an inspection of their factory by the United States Food and Drug Administration:

“The USFDA [issued an import prohibition] for all our products at first. But for a few of our products, [we] are the unique producer, and the US often faces shortages of these products, so FDA very soon released the prohibition on these products.”

API manufacturer, China

Importing countries unable to inspect factories in exporting countries may choose to buy products that are quality-assured at source under a WHO-implemented prequalification system⁵². This system currently only covers medicines or vaccines for a few infectious diseases, and some reproductive health products.

Where GMP/GDP inspection at/from source is not an option, regulators may attempt to mitigate the risk of substandard products reaching patients through post-market surveillance. However, we found that in low and middle-income countries

most post-market surveillance is performed using screening tools capable of spotting falsified medicines and incorrect API, but inappropriate for identifying poorly formulated or degraded products⁵³.

Where substandard products are identified, full track-and-trace systems such as that in use in Turkey greatly facilitates rapid recall, minimising public health damage.

Market response 2: Industry protects margins by avoiding unprofitable products or markets

A second response to low margins is to simply avoid products or markets that do not contribute to a company's profits. In the three years after Romania effectively capped prices at the EU minimum while charging producers a claw-back tax, manufacturers withdrew around 2,000 of 6,200 products³⁹. Many of these were lower-priced generic medicines.

"Authorities [explaining supply interruptions] say 'No, no, you've had production problems'. But the truth is that it's very simple to explain the decision not to produce a drug as long as it brings you losses."

Technical agency advisor, Romania

While domestic companies stop manufacturing loss-making products, multi-national firms, whose profit calculus is global, have the option of simply avoiding loss-making markets. They may do this for a single product, by refusing to register it in country, or they may withdraw from a country entirely. One multinational firm shut down their generic production lines in Indonesia after the government introduced new procurement rules to contain medicine costs, citing commercial pressures⁵⁴.

Multinational manufacturers also stay away from low-priced markets to avoid being benchmarked by countries that use external reference pricing to establish domestic prices.

"Innovative medicines do not come...because they know the Turkish market will pull down prices [in other markets], unfortunately. [Manufacturers] do not want to get themselves into something like that."

Academic pharmaceutical market analyst, Turkey

Finally, manufacturers restrict distribution of expensive products to countries with lower prices for fear that profit-seeking brokers will buy them up and resell them in higher-priced markets, thus eroding the manufacturers' profits. Both Turkey and Romania reported this behaviour, although Romania was especially vulnerable because trade regulations allow for the free trade of medicines between EU countries that implement different national medicine pricing policies.

Distributors can reduce costs by distributing only to areas with good infrastructure. In Indonesia, authorities turn a blind eye

when distributors protect margins by withholding products from remote islands, where distribution costs are high:

"Most important for the authorities is that there's no nation-wide stock-out. They just let [a shortage] go for remote regions, because they recognise [the government] auction prices are very low."

Pharmaceutical manufacturer, Indonesia

Interim risk: Shortage of clinically indicated medicines, incentive to buy from unregulated suppliers

The result of all of these actions: shortages of quality-assured, clinically indicated medicines.

"In order to gain political capital, [campaigning politicians] kept saying 'we'll give you the cheapest medicine in Europe.' Wow, how great they are! We'll vote for them! Without thinking that you won't have access [to the medicines]. Because no one brings them anymore, because it's not economically justified anymore, it's not a business anymore. And those that are economically viable leave the country through parallel export. Romanians end up without medicine in one case or the other."

Patient advocate, Romania

Both patients and physicians respond to these shortages by stepping outside of the regulated supply chain to acquire the medicines they need. A Romanian doctor, showing researchers vials of magnesium sulphate with no expiry date, carried across the border by a former patient in response to shortages, said:

"What do I know about this vial? When it expires? I tell you, I know for how long I have it and if it turns yellow then for sure it's not good anymore.... What does it do? It saves two lives. Of the mother, and of the baby.... [But] it may be plain water or poison."

Doctor, Romania

Mitigating actions: system-wide planning; market making

Market withdrawal and associated responses are both commercially rational and completely legal; they are responses over which the medicine regulator has very little control. Prevention of shortages of this type requires system-wide planning that accurately forecasts demand, and that incentivises adequate supply, for example by providing guaranteed sales to auction winners.

Strong information systems are a prerequisite for effective planning. Turkey, whose well-resourced medicine regulator operates semi-autonomously under the Ministry of Health, has the most effective information systems of the study countries. These include a Datamatrix system that tracks every transaction involving a medicine in the regulated supply chain, from manufacture to dispensing. The system was implemented in response

to widespread reimbursement fraud, estimated at US\$ one billion⁵⁵, that threatened the government's ability to deliver on its political promise of UHC.

The system imposed significant costs on manufacturers, requiring those that wished to sell in the Turkish reimbursed sector to adapt production lines. Even after internal and external benchmarking lowered prices, manufacturers participated in auctions because of the size and consolidation of the market.

"The customer is king. I pay the money, I determine the conditions. Turkey has such an advantage. [The national insurer] buys more than 80% of the market. They say: "If you are willing to give them under these conditions, then you can give your drugs. Otherwise, I'm sorry, go sell them in another country, don't sell them to me."

Multinational pharmaceutical manufacturer, Turkey

Reimbursement data matched with data from the track and trace system provides an early warning system for low stocks nationally and locally, allowing for rapid procurement as necessary. Well-managed stocks and an adequate benefits package reduce the likelihood that patients will step outside of the regular supply chain in Turkey.

Indonesia also has a single-payer national health insurance, and has attempted through transparent, single-winner auctions to elicit low bids from manufacturers. However, unlike Turkey, Indonesia's insurer reimburses against diagnostic group; it does not collect data on prescriptions or contribute data to the Ministry of Health's demand planning exercise. In 2017, public sector purchases of paracetamol in Indonesia were just 30% of the amount forecast in tender documents, while for iron folate, they exceeded forecasts by over a quarter⁵⁶. Bidders must undertake to deliver volumes set in the tenders. However, there is no concomitant obligation on health providers to purchase those volumes, leaving manufacturers with potentially expensive excess capacity and disincentivising participation in auctions.

Romanian regulators guard against shortages resulting from arbitrage by requiring daily reporting of medicine exports. Given recurring shortages, it is unclear whether these data are analysed³⁸.

Q: "Isn't there a plan in place to prevent shortages [caused by parallel exports or market withdrawal]?"

Respondent 1 laughs uncontrollably.

Respondent 2, laughing: *"If there is such a thing, it obviously serves no purpose."*

National technical agency advisors, Romania

Market response 3: Industry and health service providers promote profitable products

Besides minimising losses, the pharmaceutical industry acts to maximise profitable sales. In all study countries, producers and regulators alike reported that companies actively lobby to

get higher-margin products on to national formularies, as well as to encourage orders for these products from private sector hospitals and others with discretionary buying power.

As countries scale up public financing for health using cost control measures such as reimbursement by diagnostic group, profit margins for private providers of health services also come under pressure. Some seek to maintain income by 'up-selling' patients to medicines that are not covered by national health insurance, for example selling them originator brands rather than giving covered generic alternatives. This reinforces patients' perception that price signals quality, and may contribute to demand for more costly products even when there is no shortage of quality-assured, cost-effective alternatives.

"In my opinion, if a vaccine is more expensive, then automatically it's going to be better quality, and that's that."

Mother of infant, Indonesia

Interim risk: Unmet demand for premium products, incentive to buy from unregulated suppliers

Marketing and prescribing practices that create unmet demand for higher-margin products tend to raise costs to patients. Patients who want, but cannot afford, a premium product that is not covered by insurance may again step out of the regulated supply chain, seeking the desired product over the internet or in informal markets.

Sometimes, health care providers sacrifice due diligence and acquire medicines at a discount, selling them to patients at a premium to maximise profits.

"Freelance" salespeople go from door to door, including to hospitals, offering drugs sometimes at rather low prices... [The buyer] doesn't think about the improbable price, only about the profit.

Pharmaceutical industry association official, Indonesia

Mitigating actions: control of product mix, licensing of outlets, public awareness campaigns

Most countries try to restrict irrational use of medicines using the policies listed in Table 4. Of these, only market authorisation is generally controlled by the medicine regulator. In theory, market authorisation could be granted only to products that have been deemed cost-effective in health technology assessments⁵⁷. This is not universally the case in the study countries, so the procedure does not effectively curb irrational demand.

Regulators try to guard against freelance and cut-price sales and other unethical practice throughout the supply chain by certifying pharmacies and other dispensing outlets. Full track and trace systems, such as that implemented by Turkey, prevent the insertion of falsified medicines into the regulated (but not the unregulated) supply chain.

"There is a "handshake protocol". When you give it to me, you make a sale-notification, but it is still up in the air. If you do not make that sale-notification, and if the system says

when I scan the product: “There is no such thing,” then I’ll tell you: “I cannot buy this, because I cannot sell this.”

Multinational pharmaceutical manufacturer, Turkey

Some countries have launched public awareness campaigns to warn patients of the dangers of buying medicines from unregulated sources. We found little evidence of the effectiveness of these strategies. Rather, the most effective strategy we encountered was that adopted by Turkey, which was to remove the incentive to go outside of the regulated supply chain by ensuring the availability and affordability (in this case through insurance coverage) of quality-assured products.

Risk to product quality: Market opportunity for medicine falsifiers

Commercial strategies to protect profit margins combine to create unmet needs and demand, and to push people to satisfy them outside of the regulated supply chain. Together, this creates a market opportunity for criminals who wish to sell falsified products. These dynamics are represented in Figure 3.

We observed these dynamics in both Romania and Indonesia. In Romania, the main driver was shortages of clinically indicated products due to product withdrawal and arbitrage.

Coming back to your question – why patients buy medicines from the internet – you have to know that the majority of them do this in full knowledge, because the state does not provide them with a treatment in time. They are desperate and take the risk and buy medicines from wherever they can. Desperation pushes them into consciously aggravating their own situation, because is it known that many

of these meds are fakes...And they bought them online, and also, from around the corner of the hospital. The saddest thing is that this trade also takes place next to the oncology institute.

Patient advocate, Romania

In Indonesia, though quality-assured domestic vaccines were available for free, physicians maximised profits by charging patients for expensive imported vaccines. At a time when there was a supply shortage of imported vaccines, some physicians based in private hospitals bought products at cut price from roving salesmen. In 2016, at least 1,500 children were injected with falsified ‘imported vaccines’, containing no active ingredients⁵⁸⁻⁶¹.

Mitigating actions: surveillance, criminal investigation

While full track and trace systems can keep criminally produced products out of the regulated supply chain, they do not operate in informal markets.

As long as a market exists, and the likely profit outweighs the likelihood of getting caught, successfully prosecuted, and sentenced to significant loss of liberty or assets, criminals will sell falsified medicines. In many countries, penalties are slight and investigative mandates unclear. Limitations on the Indonesian regulator’s authority at the time of the 2016 vaccine scandal facilitated the trade of falsified products in a supposedly regulated supply chain.

“Regulation-wise, at that time, we were not allowed to inspect pharmaceutical services in hospitals. The parliament pushed us to know more [about the falsified vaccines].”

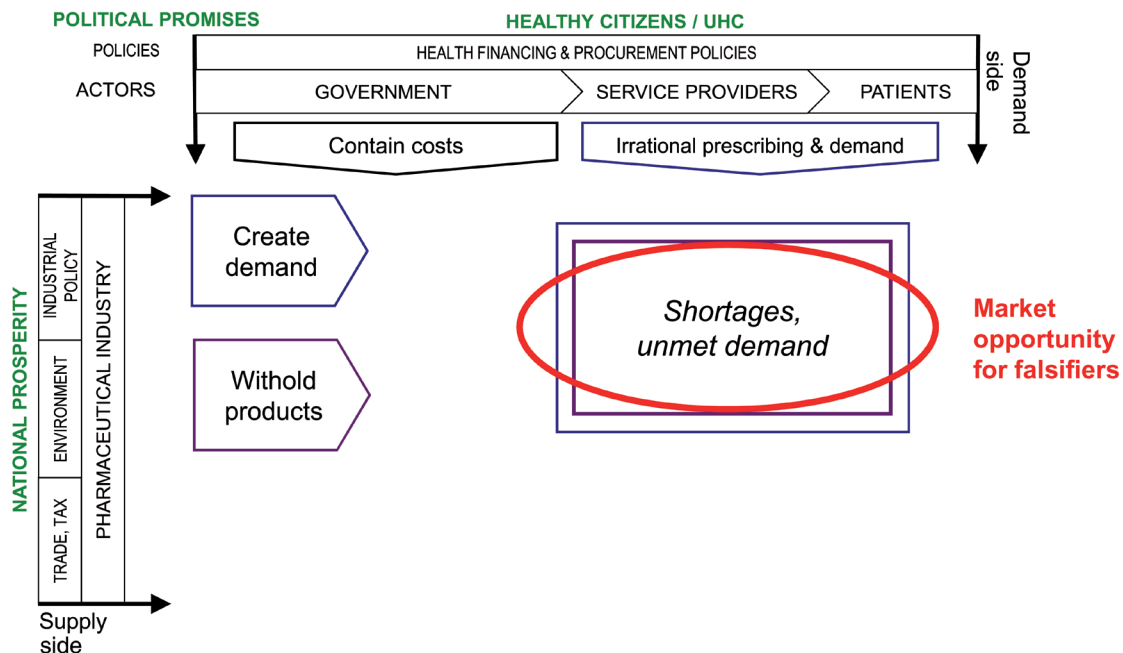


Figure 3. Commercial responses to low margins create market opportunities for medicine falsifiers.

But there was no way we would know about this in the first place. We could not get into those hospitals' systems."

Medicine regulator, Indonesia

Once falsified medicines are in circulation, effective post-market surveillance may interrupt their pathway to patients. Again, however, the reach of regulatory systems in unregulated markets is limited. The high-end products most attractive to falsifiers are also the least likely to be tested, because of the high cost of acquisition and reference standards.

Table 6 summarises the responses to market pressures that we encountered in study countries, and their effects.

Market risk framework for substandard and falsified medical products

Figure 4 brings all the elements discussed together into a single framework, which we dub the "Market risk framework" for assessing the likelihood that substandard and falsified medicines will reach a nation's patients.

Figure 5, meanwhile, adds information which illustrates the points at which action by national medicine regulators may mitigate risk.

A narrated video walking through the framework is available in the study repository (see *Extended data*; 01_Pisani_et_al_medicine_quality_market_risk_framework.mov) and on [Vimeo](#).

In the study repository, we provide versions of the framework describing the specific factors that create risks for substandard and falsified medicines in our study countries, fully annotated with data from the studies (see *Extended data*; 05_China, 06_Indonesia, 07_Romania and 08_Turkey¹³).

Testing the framework

We tested the framework against cases selected by colleagues at WHO from the GSMS database, as described in the methods section.

To illustrate the results from countries at different income levels, we provide brief annotated versions of the framework

Table 6. Response to pressure on profits in study countries, and their potential effects on medicine quality.

Goal	Action	Interim risk	Potential risk to product quality	Preventative action by medicine regulator	Preventative action by others
Reduce production costs	Use cheaper API		Higher impurities	Domestic production: GMP inspection Imports: only authorise prequalified products	
	Use cheaper excipients		Higher impurities, less bioavailability		
	Use cheaper packaging		Degradation		
	Use less API		Sub-therapeutic dose		
	Bypass quality assurance		Production errors		
Reduce distribution costs	Under-invest in control of temperature/humidity		Degradation	GDP inspection. (For imports, only possible after arrival)	
	Limit geographical reach	Localised shortages	Market opportunity for falsifiers, including in health facilities		
Avoid loss-making products	Cease production	Shortages	Market opportunity for falsifiers, including in health facilities		Fair pricing
Avoid loss-making markets	Withdraw from market				
	Fail to register in market				
	Limit distribution				
Seek profitable markets	Arbitrage	Shortages in source market	Market opportunity for falsifiers including in health facilities		Fair pricing
Maximize profits from patients	Aggressive market entry	Irrational demand for high priced product	Market opportunity for falsifiers, especially targeting patients	Consider HTA in granting market authorisation	National formulary, HTA
	Aggressive marketing				Clinical guidelines
	Up-sell to off-plan products				Comprehensive insurance coverage

API, active pharmaceutical ingredient; GMP, good manufacturing practice; GDP, good distribution practice; HTA, health technology assessment.

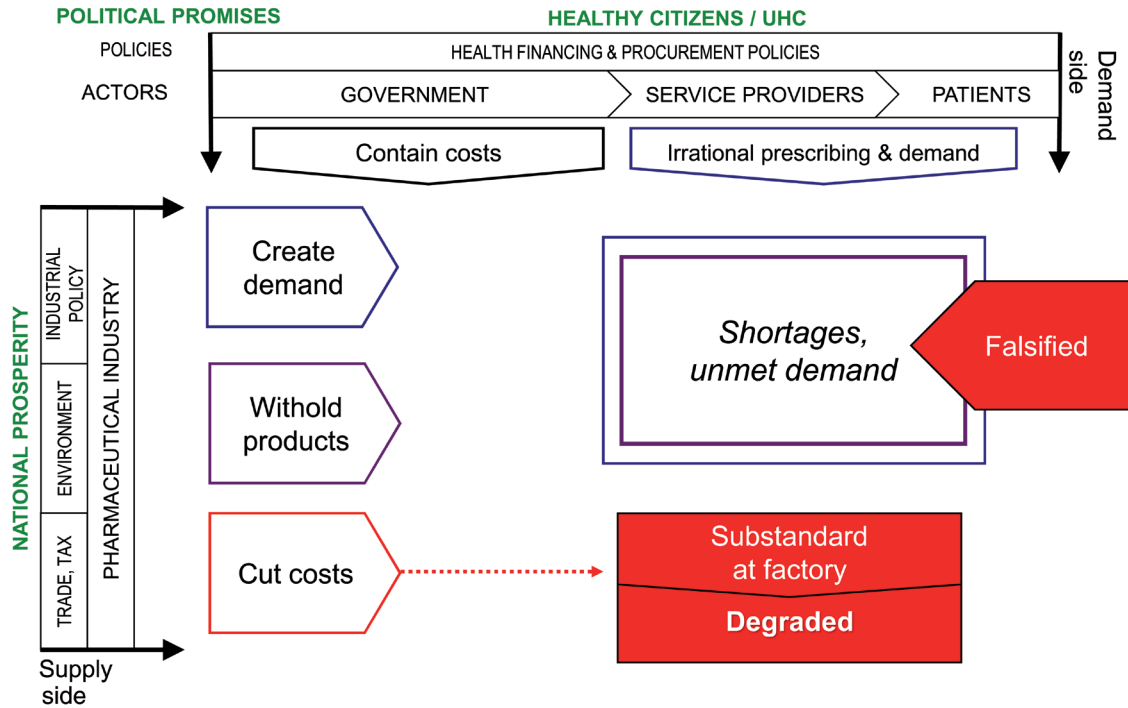


Figure 4. Identifying substandard and falsified medical products: a market risk framework.

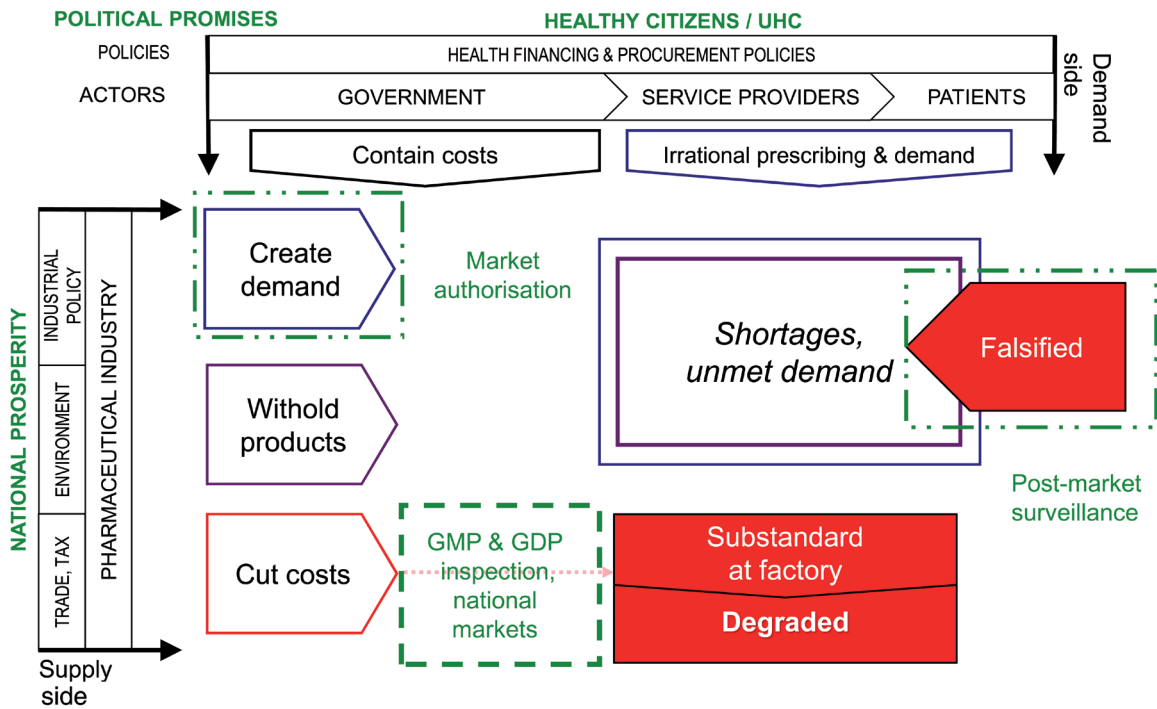


Figure 5. Actions by national medicine regulators mitigating market risk.

for GSMS cases with data in the public domain from the United States, Pakistan, and Democratic Republic of Congo. These can be found in the study repository (see *Extended data*; 09_WHO_database_case_studies.docx¹³).

Overall, we found that the framework developed in middle-income countries with aspirations to achieve UHC explained most of the factors driving the falsification of medicines in countries of all income levels, as well as the production and import of substandard medicines in lower income countries. However, some additional factors emerged in low income countries:

- Substandard production is sometimes simply the result of limited technical capacity among producers;
- Where most spending on medicine is out of pocket, people buy in informal markets for convenience and affordability, even when there are no shortages;
- In heavily aid-dependent countries, procurement practices of donors can undermine national efforts to build sustainable markets and systems.

In addition, the framework, which focuses on national drivers and deterrents, does not adequately capture the potential for cross-border exchange of information in guiding GMP inspection and post-market surveillance.

Discussion

Substandard and falsified medicines have increasingly been identified as a neglected challenge to global health^{62,63}. Efforts have been made to describe the causes of poor-quality medicines, and to identify appropriate responses to the threat they pose^{4,7,8,22}. However, none has provided a comprehensive, evidence-based framework which simultaneously:

- Elucidates the system-wide policies that incentivise and facilitate the production, trade and consumption of poor quality medical products;
- Differentiates those that drive substandard production and degradation from those that create opportunities for falsification;
- Maps specific regulatory responses on to specific pathways, highlighting the likely effects of different investments and policy choices.

By comparing detailed case studies in four countries, and testing the results against recorded cases in other countries, our work has provided a framework which disentangles the many factors previously grouped under broad headings such as "limited access to quality medicines", "poor governance" and "restricted technical capacity". We provide granularity to help guide national plans to prevent, detect and respond to substandard and falsified medical products.

The study shares the limitations common to qualitative research regarding subjects involving illegal or unethical behaviour. While we worked hard to include a wide range of participants

and to stress that data would be anonymised, some potential respondents declined interview while others, particularly from government institutions, gave normative responses. However, we were able to capture a wide range of opinions and experience, including detailed descriptions of unethical practices, giving us confidence that our results are sufficiently comprehensive.

The four middle-income countries studied shared characteristics that are not reflective of all nations; when we tested the framework against cases reported in other countries, we identified refinements which may be necessary in adapting the framework for lower income settings.

Our results did, however, prove robust across a wide range of settings. They suggest that when the incentives driving demand for affordable, cost-effective medical products are aligned with the rewards for producing and distributing those products at assured quality, substandard medicines will be rare, and there will be little opportunity to profit from the sale of falsified products. However, it is currently hard to align production incentives with rewards, because the forces shaping demand are largely determined by national governments aspiring to maximise access to affordable care, while suppliers are motivated by profit, often calculated globally.

Much of the current discourse about medicine quality focuses on strengthening the capacity of national regulatory agencies to oversee the production or import of medicine products, and their distribution. Certainly, well-resourced national medicine regulators are critical in assuring product quality. However, our analysis shows that many policies far beyond the reach of the medicine regulator contribute to shaping the market for medicines, sometimes incentivising the production or import and sale of substandard or falsified products.

We find that unless quality is explicitly included in pricing and procurement policies, downward price pressures can actively incentivise the production of substandard medicines and facilitate degradation. No country can hope to achieve sustainable, effective UHC without quality-assured generic products, yet low-profit-margin generic products are especially vulnerable to corner-cutting in response to price pressures.

A key safeguard is thus to ensure that prices cover quality production and distribution, as well as fair profit. This is an unpalatable message. "Fair profit" is hard to determine, since manufacturers rarely disclose real costs^{64,65}. Further, profit is often conflated with profiteering in discussions of pharmaceutical pricing, while the fear that innovator producers hope to undermine public confidence in generic products discourages discourse around quality assurance for low-cost products. Meanwhile, large exporters of generic products often respond to calls for more quality assurance by accusing more expensive producers of covert protectionism⁶⁶⁻⁶⁹.

A further safeguard against substandard production is close regulation of manufacturing practice. We find evidence, however, that a political commitment to the promotion of domestic manufacturing may put pressure on regulators to lower standards

for GMP or product quality inspection. This is worrisome in a climate of increasing economic nationalism in many middle-income countries, including those needing to find new sources for medicines previously supplied by the Global Fund for AIDS, TB and Malaria⁷⁰.

The current global system concentrates the burden for quality-assurance on medicine regulators in over 190 consuming countries, rather than in a handful of major exporting nations. Adequate quality assurance of products made for export would increase efficiency in a globalised pharmaceutical market. This is a political rather than a technical challenge, but models exist in other sectors, such as aviation⁷¹. More cost-effective, streamlined regulation could eat into fees that national regulators now earn for often duplicative authorisation procedures, but it would cut costs for quality manufacturers, reducing the risk of product withdrawal and shortages.

Product shortages, as well as the quest for affordability or profit, can push patients and health care providers out of the regulated supply chain, creating opportunities for falsifiers. As the Turkish case study demonstrates, the existence of a consolidated market in which both patients and producers are relatively well protected against excessive price pressures is an effective protection against this risk. Market-based solutions such as this appear more effective than attempts to tackle falsification primarily through product regulation¹⁶.

Conclusion

As The Lancet Commission on Essential Medicines observed, UHC cannot be achieved with poor quality pharmaceuticals¹. We thus conclude that organisations and governments aiming to ensure UHC must consider the potential impacts of procurement rules as well as industrial, environmental and trade policies on the quality of medicines, and support and implement systemic approaches that provide fair reward for the production and distribution of quality-assured, cost-effective therapies.

There is considerable scope to validate the market risk framework in different country settings, and to use it in combination with well-designed quantitative surveys to better understand the scale of the problem and to address the locally-specific drivers of vulnerabilities to poor quality medical products at the systemic as well as the national level⁷². Distinguishing between risk factors for substandard medications and falsified products can also guide choices about post market surveillance equipment⁵³.

The framework also functions as diagnostic tool to identify market and regulatory failures that have incentivised or facilitated a specific case of falsification/substandard production. We encourage its adaptation to local circumstances, and its use in ensuring that the call for greater “access to medicines” reliably means “access to medicines that work”.

Data availability

Underlying data

The interviews that underlie this study discuss sensitive and at times illegal behaviours. During our informed consent procedure, we assured participants of anonymity. We are unable to comply with that commitment if we make the recordings of the

interviews available. We believe there is an unacceptably high risk of disclosure in sharing full transcripts, and believe fully redacted manuscripts may be of limited value.

Our detailed coding structure is published in the study repository. Researchers from universities and accredited public-interest research institutions are welcome to request specific coding queries. Please contact the Medical Ethics Committee of Erasmus University (metc@erasmusmc.nl), giving your name, institution, and the purpose for which you will use the data, and citing study number MEC-2018-016. Please copy your request to the Erasmus Data Service Centre (edsc@eur.nl) and to the corresponding author of this paper. If the ethics committee raises no objection, the research team will run the query as requested, redact the results only to the extent necessary to ensure anonymity, and pass the results on to fellow researchers, for the stated use only.

Extended data

Harvard Dataverse: Supporting data for: Identifying market risk for substandard and falsified medicines: an analytic framework based on qualitative research in China, Indonesia, Turkey and Romania. <https://doi.org/10.7910/DVN/0GGI9D>¹³.

This project contains the following extended data:

- 01_Pisani_et_al_Medicine_quality_market_risk_framework.mov
- 02_Coding_structure.docx
- 04_Bibliography.ris
- 05_China_case_study.docx
- 06_Indonesia_case_study.docx
- 07_Romania_case_study.docx
- 08_Turkey_case_study.docx
- 09_WHO_database_case_studies.docx
- 10_Medicine_quality_in_Indonesia.mov
- 11_Interview_topic_guide.docx

Reporting guidelines

Harvard Dataverse: COREQ checklist for article “Identifying market risk for substandard and falsified medicines: an analytic framework based on qualitative research in China, Indonesia, Turkey and Romania”. <https://doi.org/10.7910/DVN/0GGI9D>¹³.

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Authors' contributions

All authors contributed actively to analysis, interpretation and the development of the framework, and provided improvements to the draft manuscript. In addition:

EP designed the study, led the analysis and wrote the first draft of the manuscript.

AN expanded the literature search and conducted the Romanian case study.

AH conducted the Indonesian case study.

KP conducted the Turkish case study.

JYX conducted the Chinese case study.

MK contributed to the analytic methodology

References

- Wirtz VJ, Hogerzeil HV, Gray AL, *et al.*: **Essential medicines for universal health coverage.** *Lancet.* 2017; **389**(10067): 403–476.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Review on Antimicrobial Resistance: **Safe, Secure and Controlled: Managing the Supply Chain of Antimicrobials.** London: AMR Review; 2015.
[Reference Source](#)
- Pisani E: **Antimicrobial resistance: What does medicine quality have to do with it?** London: Antimicrobial Review; 2015.
[Reference Source](#)
- World Health Organization: **WHO Global Surveillance and Monitoring System for substandard and falsified medical products.** Geneva: WHO; Report No.: WHO/EMP/RHT/2017.01. 2017.
[Reference Source](#)
- World Health Organization: **A study on the public health and socioeconomic impact of substandard and falsified medical products.** Geneva: WHO; Report No.: WHO/EMP/RHT/2017.02. 2017.
[Reference Source](#)
- Ozawa S, Evans DR, Bessias S, *et al.*: **Prevalence and Estimated Economic Burden of Substandard and Falsified Medicines in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis.** *JAMA Netw Open.* 2018; **1**(4): e181662.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- World Health Organization: **Counterfeit Drugs. Guidelines for the development of measures to combat counterfeit drugs.** Geneva; Report No.: WHO/QSM/99.1. 1999.
[Reference Source](#)
- Buckley GJB, Gostin LO: **Countering the Problem of Falsified and Substandard Drugs.** committee on understanding the global public health implications of substandard, falsified, and counterfeit medical products. Washington, D.C: National Academies Press: Institute of Medicine of the National Academies; 2013.
[PubMed Abstract](#) | [Publisher Full Text](#)
- World Health Organization: **Member State mechanism on substandard/spurious/falsely-labelled/falsified/ counterfeit medical products.** Report by the Director-General. WHO; 2017.
[Reference Source](#)
- Dixon-Woods M, Cavers D, Agarwal S, *et al.*: **Conducting a critical interpretive synthesis of the literature on access to healthcare by vulnerable groups.** *BMC Med Res Methodol.* 2006; **6**: 35.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Barnett-Page E, Thomas J: **Methods for the synthesis of qualitative research: a critical review.** *BMC Med Res Methodol.* 2009; **9**: 59.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- NVivo: QSR International; 2018.
[Reference Source](#)
- Pisani E, Nistor AL, Hasnida A, *et al.*: **Supporting data for: Identifying market risk for substandard and falsified medicines: an analytic framework based on qualitative research in China, Indonesia, Turkey and Romania.** Harvard Dataverse, V2. 2019.
<http://www.doi.org/10.7910/DVN/0GGI9D>
- Tong A, Sainsbury P, Craig J: **Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups.** *Int J Qual Health Care.* 2007; **19**(6): 349–357.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Glaser BG, Strauss AL, Strutzel E: **The Discovery of Grounded Theory; Strategies for Qualitative Research.** *Nurs Res.* 1968; **17**(4): 364.
[Publisher Full Text](#)
- 't Hoen E, Pascual F: **Viewpoint: Counterfeit medicines and substandard medicines: Different problems requiring different solutions.** *J Public Health Policy.* 2015; **36**(4): 384–389.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Attaran A, Barry D, Basheer S, *et al.*: **How to achieve international action on falsified and substandard medicines.** *BMJ.* 2012; **345**: e7381.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Mackey TK: **Global health diplomacy and the governance of counterfeit medicines: a mapping exercise of institutional approaches.** *J Health Dipl.* 2013; **1**.
[Reference Source](#)
- Newton PN, Taberner P, Dwivedi P, *et al.*: **Falsified medicines in Africa: all talk, no action.** *Lancet Glob Health.* 2014; **2**(9): e509–e510.
[PubMed Abstract](#) | [Publisher Full Text](#)
- United Nations Interregional and Criminal and Justice Research Institute: **Organised Crime Strategies in the Production and Trade of Counterfeit Medicines.** Turin: UNICRI; 2013.
[Reference Source](#)
- Council of Europe: **Counterfeit medicines and similar crimes: Fact Sheet.** Council of Europe; 2012.
[Reference Source](#)
- Seiter A: **A Practical Approach to Pharmaceutical Policy.** World Bank; 2010.
[Publisher Full Text](#)
- Przyśwa E: **Counterfeit medicines and criminal organisations.** IRCAM; 2013.
[Reference Source](#)
- Newton PN, Fernandez FM, Green MD, *et al.*: **Counterfeit and substandard anti-infectives in developing countries.** *Antimicrobial Resistance in Developing Countries.* Springer; 2010; 413–443.
[Publisher Full Text](#)
- Bate R: **Making a killing: the deadly implications of the counterfeit drug trade.** Washington, D.C.: Blue Ridge Summit, PA: AEI Press; Distributed to the trade by National Book Network; 2008.
[Reference Source](#)
- Binagwaho A, Bate R, Gasana M, *et al.*: **Combatting substandard and falsified medicines: a view from Rwanda.** *PLoS Med.* 2013; **10**(7): e1001476.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Antignac M, Diop BI, Macquart de Terline D, *et al.*: **Fighting fake medicines: First quality evaluation of cardiac drugs in Africa.** *Int J Cardiol.* 2017; **243**: 523–528.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Nayyar GM, Breman JG, Newton PN, *et al.*: **Poor-quality antimalarial drugs in southeast Asia and sub-Saharan Africa.** *Lancet Infect Dis.* 2012; **12**(6): 488–496.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Newton PN, Green MD, Mildenhall DC, *et al.*: **Poor quality vital anti-malarials in Africa - an urgent neglected public health priority.** *Malar J.* 2011; **10**: 352.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Rupasinghe YN: **Politics, pills and procurement: the challenges of ensuring**

- drug quality in Bihar.** Harvard University. 2018.
[Reference Source](#)
31. Newton PN, Fernández FM, Plançon A, *et al.*: **A collaborative epidemiological investigation into the criminal fake artesunate trade in South East Asia.** Reidenberg M, editor. *PLoS Med.* 2008; 5(2): e32.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 32. MENET: **Chinese companies account for six of the world's top ten API manufacturers, 2017.** In: MENET.com. 2017; [cited 2 Apr 2018].
[Reference Source](#)
 33. World Bank: **Health, Nutrition and Population Data and Statistics.** 2018; [cited 19 Jul 2018].
[Reference Source](#)
 34. Institute for Health Metrics and Evaluation: **Financing Global Health 2017: Funding Universal Health Coverage and the Unfinished HIV/AIDS Agenda.** Seattle: IHME; 2018.
[Reference Source](#)
 35. TNP2K: **Reviews of implementation of pharmaceutical policy at healthcare facilities under Jaminan Kesehatan Nasional.** 2017.
[Reference Source](#)
 36. Britton K, Koseki S, Dutta A: **Expanding Markets while Improving Health in Indonesia: The Private Health Sector Market in the JKN Era.** Health Policy Plus Project; 2018; 69.
[Reference Source](#)
 37. Anggriani Y, Ibrahim MIM, Suryawati S, *et al.*: **The impact of Indonesian generic medicine pricing policy on medicine prices.** *J Generic Med.* 2014; 10(3-4): 219-229.
[Reference Source](#)
 38. Mixich V, Mardale S, Ștefan V, *et al.*: **Radiografia Exportului Paralel de Medicamente din Romania. Focus pe Medicamentele Oncologice.** Bucharest: Observatorul Român de Sănătate; 2018; 1-33.
[Reference Source](#)
 39. QuintilesIMS: **IMS Market Prognosis 2017-2021.** Europe - Romania. 2017.
 40. National Manufacturing Strategy Advisory Committee: **Made in China 2025: Key Area Technology Roadmap, 2015.** Beijing: Government of China; 2015.
[Reference Source](#)
 41. Ursu I, Rabovskaja V: **Financial Sustainability and Coverage Effectiveness of the Indonesian Health Insurance System The role of benefit package design and pharmaceutical policy.** GTZ; 2017.
[Reference Source](#)
 42. Wasir R, Irawati S, Makady A, *et al.*: **Use of medicine pricing and reimbursement policies for universal health coverage in Indonesia.** *PLoS One.* 2019; 14(2): e0212328.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 43. David I: **Prețul mediu al unei cutii de medicamente s-a dublat în ultimii șapte ani | Ziarul Financiar.** 2012; Accessed 26 Jul 2018.
[Reference Source](#)
 44. Puscaciu V, Puscaciu FD, Puscaciu RM: **Claw-back Tax - a Fang of Romanian Health System, or a Moral Duty?** *EIRP Proc.* 2016; 11.
[Reference Source](#)
 45. Radu P, Chiriac N, Pravat M: **Romanian Claw-Back Taxation: From A Financial Solution to A Challenge for Patients Access to Drugs.** *Value Health.* 2016; 19: A502.
[Publisher Full Text](#)
 46. PharmaBoardroom: **The Indonesian Halal Law: A Headache for Pharma.** 2017; [cited 1 Aug 2018].
[Reference Source](#)
 47. Pugatch M, Torstensson D, Laufer M: **The Next Frontier in Ensuring the Quality of Medicines: Maintaining international Quality and safety standards in the Manufacturing and supply of active Pharmaceutical ingredient.** Pugatch Consilium; 2015.
[Reference Source](#)
 48. cn-ferment: **Average export price for Chinese API, 2017.** In: cn-Ferment. 2018.
[Reference Source](#)
 49. Van Assche K, Nebot Giralt A, Caudron JM, *et al.*: **Pharmaceutical quality assurance of local private distributors: a secondary analysis in 13 low-income and middle-income countries.** *BMJ Glob Health.* 2018; 3(3): e000771.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 50. World Health Organization: **Deadly medicines contamination in Pakistan.** WHO; 2013.
[Reference Source](#)
 51. Caudron JM, Ford N, Henkens M, *et al.*: **Substandard medicines in resource-poor settings: a problem that can no longer be ignored.** *Trop Med Int Health.* 2008; 13(8): 1062-1072.
[PubMed Abstract](#) | [Publisher Full Text](#)
 52. 't Hoen EFM, Hogerzeil HV, Quick JD, *et al.*: **A quiet revolution in global public health: The World Health Organization's Prequalification of Medicines Programme.** *J Public Health Policy.* 2014; 35(2): 137-161.
[PubMed Abstract](#) | [Publisher Full Text](#)
 53. Vickers S, Bernier M, Zambrycki S, *et al.*: **Field detection devices for screening the quality of medicines: a systematic review.** *BMJ Glob Health.* 2018; 3(4): e000725.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 54. Sandoz: **Sandoz Company Presentation.** Business presented at; 2017.
[Reference Source](#)
 55. **Cold Chain IQ Benchmarking Report 2014.** Cold Chain IQ; 2014.
[Reference Source](#)
 56. Sosialine E: **Reformasi Kebijakan Ketersediaan Obat Melalui Pengadaan Obat Berdasarkan Katalog Elektronik oleh Pemerintah dan Swasta.** Jakarta. 2018.
[Reference Source](#)
 57. Naci H, Cylus J, Vandoros S, *et al.*: **Raising the bar for market authorisation of new drugs.** *BMJ.* 2012; 345: e4261.
[PubMed Abstract](#) | [Publisher Full Text](#)
 58. Direktori Putusan Mahkamah Agung Indonesia: **Putusan Nomor 1508/Pid. Sus/2018/PN Bks.** Pengadilan Negeri Bekasi; 2016; 102.
 59. The Jakarta Post: **Bekasi court hands down sentences to distributors of fake vaccines.** City - The Jakarta Post. Indonesia; 2017; Accessed 27 Mar 2019.
[Reference Source](#)
 60. Ministry of Health of Indonesia: **Kemenkes Himbau Fasilitas Kesehatan Beli Vaksin Melalui Produsen/Distributor Resmi.** In: Kementerian Kesehatan Republik Indonesia. 2016; [cited 27 Mar 2019].
[Reference Source](#)
 61. Ministry of Health of Indonesia: **Kemenkes Jamin Ketersediaan Vaksin Program untuk Pelaksanaan Vaksinasi Wajib Ulang.** In: Kementerian Kesehatan Republik Indonesia. 2016; [cited 27 Mar 2019].
[Reference Source](#)
 62. Nayyar GML, Breman JG, Mackey TK, *et al.*: **Falsified and Substandard Drugs: Stopping the Pandemic.** *Am J Trop Med Hyg.* 2019; tpm180981.
[PubMed Abstract](#) | [Publisher Full Text](#)
 63. The Lancet Respiratory Medicine: **Fake medicines: fighting on all fronts.** *Lancet Respir Med.* 2018; 6(5): 315.
[PubMed Abstract](#) | [Publisher Full Text](#)
 64. World Health Organization: **Fair Pricing Forum: 2017 Meeting Report.** 2017.
[Reference Source](#)
 65. Hill A, Khoo S, Fortunak J, *et al.*: **Minimum costs for producing hepatitis C direct-acting antivirals for use in large-scale treatment access programs in developing countries.** *Clin Infect Dis.* 2014; 58(7): 928-936.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 66. TWN Info Service on Health Issues: **WHO: Socio-economic impact study of SSFFC medicines is "propaganda", says South.** Third World Network; 2015.
[Reference Source](#)
 67. Oxfam: **High-Priced Medicines and Lack of Needs-Driven Innovation: A global crisis that fuels inequality.** Oxford: Oxfam; 2017.
[Publisher Full Text](#)
 68. Attaran A, Bate R, Mathur A, *et al.*: **Drug quality and global trade.** *Am Enterp Inst Ideas India.* 2015.
[Reference Source](#)
 69. Das S: **India-led BRICS opposes UN arm's move on model drug law.** *Economic Times.* New Delhi; 2014; Accessed 21 Apr 2015.
[Reference Source](#)
 70. Preston C, Valdez ML, Bond K: **Strengthening medical product regulation in low- and middle-income countries.** *PLoS Med.* 2012; 9(10): e1001327.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 71. Havel BF, Sanchez GS: **The International Law Regime for Aviation Safety and Security.** The principles and practice of international aviation law. Cambridge: Cambridge University Press; 2014; 173-216.
[Publisher Full Text](#)
 72. Newton PN, Lee SJ, Goodman C, *et al.*: **Guidelines for field surveys of the quality of medicines: a proposal.** *PLoS Med.* 2009; 6(3): e52.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

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Prashant Yadav

Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA

Summary

This paper attempts to investigate political and economic factors which drive the demand and supply of sub-standard and falsified (SF) medicines. Using a grounded theory approach, the authors try to develop a market risk framework for SF medicines. The main issue addressed by this paper is of significant policy relevance and impact. It is the first paper (to the best of my knowledge) which uses a demand/supply and market risk framework to study this problem.

Below I point out a few areas in the paper where I would have liked to see greater depth in analysis or clearer exposition of what this analysis tells us with a reasonable degree of confidence, and what parts remains less clear.

Comments

- The key hypothesis is that SF medicines are largely the result of market responses to demand for lower prices/cost containment, industrial policy and environmental control pressures. There may be other underlying root causes for the prevalence of SF. This is where the authors' use of grounded theory methodology (and the sampling approach used) falls a little short. The manuscript does not provide much detail (there is some discussion on p13) on how they looked for cases/instances that do not fit the main reasons they have identified, what they found, and did they attempt to look at filling gaps in initial data collected to clarify uncertainties. This would have allowed them to add more depth/density and allow a reader to fully understand which parts of their grounded theory to have stronger confidence in, and which parts to have lesser confidence in. They delve into this a little bit in the discussion section, but it would have been better to see a clearer and more elaborate exposition of the negative cases in the main section which discusses the market risk framework.
- All the countries included in the sample have a high degree of health insurance coverage or some form of pooling. To what extent would the findings of this study apply to out of pocket markets without any price controls? Posing this question would help bring out the external validity scope of this paper more clearly. It will also more clearly highlight other factors that lead to SF.

- It will be useful for the authors to look at Boswell-Dean (2019)¹ which shows that price controls in India may have led to higher quality in the out-of-pocket medicines market.
- The drivers for sub-standard and falsified medicines are often very different and the framework developed by the authors and Figures 3, 4 and 5 clearly demonstrate that. It may be useful to categorize them more explicitly in Table 6.
- Shortages (due to different reasons) are identified as the primary driver for falsified medicines. While this may be true for the 4 middle income countries studied, in many other markets, falsified medicines are supplied to out-of-pocket paying patients even when the “genuine” product is in abundant supply (although is priced higher). This sometimes makes the distinction between the underlying reasons for sub-standard and falsified a little murky. Also, see Bate *et al.* (2011)² for some discussion regarding this.
- While unclear if it applies widely due to the nature of the study sample, it is worth exploring if a possible market response would be to differentiate drug quality according to the consumption sub-market as in Bate *et al.* (2016)³.
- While I understand purposive sampling based on market characteristics, using API market in one country (China) and finished products in the other countries is not a very good comparison strategy for building grounded theory. Cost containment from political pressures only directly effects finished product producers. The effect of cost containment on finished product translates into a much lower price effect on APIs (depending on the type of medicine only a small fraction of the cost is API cost). Also, there is limited evidence that finished product producers pass-on their price decrease pressures to API suppliers. Economics of API manufacturing is also much more volume and fixed cost dependent so its better to make larger quantities and supply them at marginal cost to other “non-consumption” markets.

References

1. Boswell Dean E: Who Benefits from Pharmaceutical Price Controls? Evidence from India – CGD Working Paper 509. *Center for Global Development*. 2019. [Reference Source](#)
2. Bate R, Jin G, Mathur A: Does Price Reveal Poor-Quality Drugs? Evidence from 17 Countries. 2011. [Publisher Full Text](#)
3. Bate R, Jin G, Mathur A, Attaran A: Poor Quality Drugs and Global Trade: A Pilot Study. 2014. [Publisher Full Text](#)

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pharmaceutical and health product supply chains.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 14 May 2019

<https://doi.org/10.21956/wellcomeopenres.16629.r35340>

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Helen Lambert 

Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK

This is an impressive contribution to a particularly difficult-to-research issue in global health. While the problem of substandard and falsified medicines and its potentially adverse health consequences is well recognised, research has tended to focus on documenting the scale of the problem and enumerating the contributory factors. This paper uses empirical case studies and review of secondary literature to develop a 'market risk' analytic framework for use in mapping the political and economic system dimensions of the problem in specific country settings. The framework is built on a literature review followed by comparative analysis of qualitative interviews with relevant informants and stakeholders in four diverse middle-income countries.

This is a complex issue influenced by a range of interwoven factors, many of which are highly technical or difficult to grasp for non-specialist readers (ranging from Good Manufacturing Practice and regulatory standards to diverse market structures, the effects of differing insurance systems and international trade arrangements). Given this, the authors do a good job in general of highlighting the key dimensions at play without losing the reader in technical detail. Occasionally a little further explication would be helpful, for example in elucidating the role of arbitrage or the practice of auctions through which (it appears) governments select a supplier for a required pharmaceutical product.

The study design is generally sound and the use of semi-structured interviews is particularly appropriate for gathering material on sensitive topics such as this. The authors could perhaps have made fuller use of the substantial review of academic papers and press reports that they conducted by using an established scoping review framework and by providing further details of the critical interpretive synthesis conducted (these results are not included). The development of a coding framework based solely on the secondary literature and its subsequent deployment for coding and analysis of the interview data is somewhat unusual. Analysis of the qualitative case study material could have been enriched by combining the use of this coding scheme with a more inductive approach, to allow development of unexpected themes emerging from the interview data. A fully grounded theory approach would also have included testing the authors' hypothesis against divergent/deviant examples. However, the more structured approach utilised here does serve the authors' purpose of framework development effectively,

by focusing on the specific political and economic dimensions that may heighten risk for creating markets for substandard or falsified medicines. Importantly, the authors identify different influences operating for these two types of inferior product. The figures provide clear and useful diagrammatic characterisations of the processes described, such as the effect of cost-cutting on the risk of substandard medicines.

The conclusions are generally sound though broader statements could be better evidenced, such as the framing assumption of the paper that downward pressures on prices are exerted by political promises to deliver Universal Health Care. Only the implementation of such promises through legislation, regulation or other government actions to reduce costs of medicines rather than the 'promises' themselves are really relevant to this assertion; and since many governments are focusing efforts toward UHC primarily on expanding health insurance coverage, some further discussion of the potential implications of different health insurance arrangements on risks relating to medicine quality would have been helpful.

Nonetheless, overall this is a sophisticated and impressive analysis that provides an original conceptualisation that helps to clarify a rather murky field. It provides a potentially useful framework for further country-specific analyses to disaggregate the various contributory factors that may influence susceptibility for low quality and falsified medicines to appear in the market. Moreover, it rightly shifts focus from product regulation, where efforts have mostly concentrated to date, to causal market mechanisms; and it usefully pinpoints the need to differentiate the economic forces likely to result in the appearance of substandard medicines from those that increase risk of falsified medicines being manufactured and marketed.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Social science (anthropology) and global health; antibiotics and antimicrobial resistance; treatment-seeking behaviour; qualitative and interdisciplinary research.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 13 May 2019

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Charles Clift

Centre on Global Health Security, Chatham House, London, UK

This is an interesting study of the drivers of substandard and falsified medicines which develops a market risk framework based on four country case studies.

While the study identifies a number of factors that contribute to the problem, the methodology is not entirely satisfactory. The choice of countries is somewhat eclectic - it is not quite clear why they were chosen over others. The focus of the case studies is different in each case as is the occupational distribution of the interviewees.

The paper would have benefited from a more systematic analysis of the health systems and pharmaceutical policies in each of the countries. The details on p.5-6 are quite cursory. This applies also to the case studies themselves in the extended dataset.

With regards to the central conclusion that "increasing political commitment to provision of universal health coverage has led to public procurement policies aimed at lowering prices of medical products" I am not sure that it is supported by the data. Public procurement has long sought to minimize prices, often without due regard to medicines quality. UHC, to the extent that it involves greater public funding of health services and a reduction in the number of patients buying their own medicines, could actually improve the prospects for reducing reliance on falsified and substandard medicines. The fault lies in defective procurement policies that do not properly factor in quality criteria and the reluctance of governments to provide adequate financing. Where there is a substantial generic industry, as the report points out, there is also political pressure not to enforce strict regulation.

In that context, the report refers to the need to allow "fair profit" to ensure that quality standards are maintained, but how to achieve that raises a lot of issues that are not pursued in any depth.

On specific points:

- The comment about the WHO prequalification programme on p.9 rather understates its importance as the reference makes clear. It also covers diagnostics.
- On p.15 the list of additional factors in low income countries really needs referencing.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: My qualification relates to work carried out some time ago on the definition of counterfeit medicines and I have worked extensively on projects related to access to medicines in LMICs

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 23 April 2019

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**Delia Grace**

International Livestock Research Institute (ILRI), Nairobi, Kenya

Specific questions

- The authors have not made the interview data available. However, the explanation for this is fully satisfactory.

Overall

- There is great concern but little understanding about the prevalence, drivers and impacts of sub-standard drugs. This paper is timely. It develops a framework, which while not necessarily definitive, is useful. It gives insight into the issue of fake drugs by seeking to understand the drivers for undesired behaviours leading to poor outcomes.

Introduction

- Although there are pragmatic reasons for lumping “substandard” and “falsified” drugs and although this is current WHO terminology, combining the two categories can be mis-leading as they have very different drivers and hence different solutions.
- It is going too far to say that solutions for poor quality medicines in LMICs are known. There is an argument that the solutions proposed, largely drawn from historical experiences in HICs, are inappropriate and unworkable in the context of LMICs.

Methodology

- The choice of countries requires more explanation. How many countries fitted the criteria chosen by the researcher?

- The number of participants per country is rather small, but probably adequate for this time of qualitative study.
- Ethical approval for non-invasive research is rather a grey area. They should refer to national guidelines that say local ethical approval is not needed for non-invasive research. Most countries where we work require local ethical approval.

Results and Discussion

- It would be useful to have information on the size of the un-regulated drug sector in these countries.
- The results capture very much the “received wisdom”. It would be interesting to have perspectives of some of the “un-approved stakeholders” e.g. the people who buy drugs on line or sellers of illegal products.
- The paper very well documents the un-intended consequences of well-intended goals. They should be more cautious in suggesting preventative actions as it is very likely these preventative actions will have their own set of un-intended consequences.
- The application to low income countries was perfunctory and a more in-depth analysis is warranted.

Generally, very well written and error free.

“begs the question” does not mean “asks the question”.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

No

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Veterinary public health epidemiology with research interests in veterinary drug use by qualified and non-qualified personnel and informal veterinary drug markets.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
