

Substandard and falsified anti-tuberculosis drugs: a preliminary field analysis

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SUMMARY

SETTING: Pharmacies in 19 cities in Angola, Brazil, China, Democratic Republic of Congo, Egypt, Ethiopia, Ghana, India ($n = 3$), Kenya, Nigeria, Russia, Rwanda, Thailand, Turkey, Uganda, United Republic of Tanzania and Zambia.

OBJECTIVE: To assess the quality of the two main first-line anti-tuberculosis medicines, isoniazid and rifampicin, procured from private-sector pharmacies, to determine if substandard and falsified medicines are available and if they potentially contribute to drug resistance in cities in low- and middle-income countries.

DESIGN: Local nationals procured 713 treatment packs from a selection of pharmacies in 19 cities. These samples were tested for quality using 1) thin-layer chroma-

tography to analyze levels of active pharmaceutical ingredient (API), and 2) disintegration testing.

RESULTS: Of 713 samples tested, 9.1% failed basic quality testing for requisite levels of API or disintegration. The failure rate was 16.6% in Africa, 10.1% in India, and 3.9% in other middle-income countries.

CONCLUSIONS: Substandard and falsified drugs are readily available in the private marketplace and probably contribute to anti-tuberculosis drug resistance in low- and middle-income countries. This issue warrants further investigation through large-scale studies of drug quality in all markets.

KEY WORDS: MDR-TB; XDR-TB; drug resistance; substandard drugs; malaria

ABOUT A THIRD of the world's population is infected with latent tuberculosis infection (LTBI).¹ Individuals with latent infection have a 10% lifetime risk of developing active TB, although the risk is greater for those whose immunity is impaired, often due to the human immunodeficiency virus (HIV).¹ The World Health Organization (WHO) estimates that there were 8.8 million incident cases of TB and 1.5 million TB deaths in 2010.¹ Most TB-affected populations are concentrated in poorer regions of the world, and fatalities occur disproportionately in Africa.¹

Treatment for TB is long and complicated.² The WHO recommends that new patients with pulmonary TB begin treatment with a daily 2-month intensive phase of isoniazid (INH), rifampicin (RMP), ethambutol and pyrazinamide, followed by a 4-month continuation phase of INH and RMP.³ If treatment is stopped too soon or administered intermittently, or if insufficient anti-tuberculosis drugs are taken as monotherapies, the remaining bacilli can become drug-resistant.⁴ In resource-limited settings, drug resistance arising from poor treatment adherence is compounded by irregular drug supplies, medicines of inferior quality, lax prescription drug laws and weak enforcement of those laws that allows for the ready availability of monotherapies and fixed-dose combinations (FDCs).⁴

Treatment for multidrug-resistant (MDR-) and extensively drug-resistant TB (XDR-TB) is significantly longer and more difficult for patients to complete, taking up to 2 years and requiring patients to ingest large numbers of pills.⁵ MDR/XDR-TB can quickly become fatal, especially if a patient's immune system is compromised.⁶

Available data suggest that antimicrobials and antiparasitics are the two types of pharmaceutical products that are most counterfeited in developing countries.⁷ Substandard and falsified antimalarial drugs have been found to be readily available in low- and middle-income countries.⁸ Little research has been conducted to assess levels of falsified and substandard TB drugs in developing countries outside some research on the degradation of fixed-dosed combination therapies.^{7,9–12} In a pilot study assessing the quality of INH and RMP samples collected from the private sector in two Indian cities, it was found that respectively 12% and 9% of samples failed either thin-layer chromatography (TLC) or a disintegration test, making them substandard.¹³ The present study analyzes the quality of anti-tuberculosis drugs in the private sector in 17 low- and middle-income countries, and explores whether substandard and falsified drugs may be exacerbating the problem of drug resistance.

METHODS

Treatment packs of two first-line anti-tuberculosis drugs ($n = 713$) on the WHO Model List of Essential Medicines,¹⁴ RMP and INH, were collected from 19 cities in 17 low- and middle-income countries. Following the methodology of previous studies, local nationals posing as customers purchased drugs from private sector pharmacies in middle-income areas of each city, selecting pharmacies on first sight during an undirected walk within a single neighbourhood.^{8,15,16} Such an approach is referred to as convenience sampling, with an attempt to reduce bias in the selection of pharmacies from which drugs were procured. The covert shoppers were not informed about the purpose of the collection. As the pharmacists selling the products were taking part in normal business practice, ethical review was not required for the study. All samples were monotherapies purchased without a prescription.

The purchased drugs were stored at ambient temperature with low humidity and no sunlight until testing. Tests were completed within 40 days of sample collection. The Minilab® (Global Pharma Health Fund, Giessen, Germany) was used to run semi-quantitative TLC on each sample to determine the presence and relative concentration of the active pharmaceutical ingredient (API), and whether it met internationally acceptable standards. In previous studies, TLC testing using the Minilab protocol yielded broadly similar results to high-performance liquid chromatography when used to analyze pharmaceuticals.¹⁷ Laserson et al. showed that TLC is an effective method of detecting substandard anti-tuberculosis drugs.¹⁰ The Minilab protocols award products a 'pass' for TLC if $\geq 80\%$ of the API is present as mentioned on the label.

Disintegration tests were conducted to see if samples disintegrated in water at 37°C in <30 min. Products were labeled 'failures' if they did not pass the most basic requirements of API concentration and solubility. In other words, even products that passed may have been of poor quality.

Each drug brand was checked against the official list of authorized products in the country in which it was procured. Non-registered drugs are not necessarily inferior, but they are illegal, as they are not authorized to be sold in that country. Test results were broken down by registration status once testing was complete to eliminate potential bias. Failing products that contained at least 10% of API were recorded, as, in the absence of data, the authors estimated that these products were likely to contribute to drug resistance.

For the purpose of this study, 'falsified' is defined as drugs that appeared to be deliberately and fraudulently mislabeled with regard to identity. Whereas the term 'counterfeit' has traditionally been used for this purpose, 'falsified' reflects the latest terminology, as 'counterfeit' is now more often used to refer specifically to products that display evidence of trademark infringement.¹⁸ Samples that appeared to be poorly manufactured or degraded were considered substandard.

RESULTS

The Table shows the number of failures by drug type and registration status. Registered drugs were those that were authorized by the relevant drug regulatory authority in the country in which the drug was sold. Overall, 9.1% (65/713) of the drugs sampled failed basic quality control tests. The failure rate was 16.6% in Africa, 10.1% in India and 3.9% in other

Table Drug quality failures by drug type, location and registration status

| Location, drug type | Number of failures | | | |
|--|------------------------------------|--|-------------------------|--|
| | Registered drugs <i>n/N (%)</i> | Non-registered drugs <i>n/N (%)</i> | Total <i>n/N (%)</i> | Drugs with >10% API <i>n/N (%)</i> |
| African cities* | | | | |
| Rifampicin | 4/77 | 13/26 | 17/103 | 13/17 |
| Isoniazid | 3/40 | 7/20 | 10/60 | 6/10 |
| Subtotal | 7/117 (6.0) | 20/46 (43.5) | 27/163 (16.6) | 19/27 (70.4) |
| Indian cities† | | | | |
| Rifampicin | 7/111 | 4/18 | 11/129 | 6/11 |
| Isoniazid | 9/109 | 7/29 | 16/138 | 8/16 |
| Subtotal | 16/220 (7.3) | 11/47 (23.4) | 27/267 (10.1) | 14/27 (51.9) |
| Cities in other middle-income countries‡ | | | | |
| Rifampicin | 1/122 | 4/21 | 5/143 | 1/5 |
| Isoniazid | 1/114 | 5/26 | 6/140 | 2/6 |
| Subtotal | 2/236 (0.8) | 9/47 (19.1) | 11/283 (3.9) | 3/11 (27.3) |
| Total | 25/573 (4.4%) | 40/140 (28.6) | 65/713 (9.1) | 36/65 (55.4) |

*Luanda, Angola; Lubumbashi, Democratic Republic of Congo; Cairo, Egypt; Addis Ababa, Ethiopia; Accra, Ghana; Nairobi, Kenya; Lagos, Nigeria; Kigali, Rwanda; Dar es Salaam, Tanzania; Kampala, Uganda; Lusaka, Zambia.

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API = active pharmaceutical ingredient.

middle-income countries. The failure rate was 28.6% for non-registered products and 4.4% for registered products. However, even registered products exhibited some quality problems in all of the regions studied.

The higher failure rate in Africa may be explained by the fact that fewer products are registered in Africa; consequently, more failures are caused by the greater number of illicit products on the market. Africa also has the highest percentage of failing products with non-trivial amounts of API (70.4%), compared to 51.9% in India and 27.3% in other middle-income countries. These products are most likely to be degraded or poorly manufactured (substandard) rather than falsified.

Of the 25 properly registered 'failures', 11 (44%) appeared to be falsified, as they either contained no API or had suspect packaging. Of the non-registered product failures, 7/40 (17.5%) appeared to be falsified. This figure is conservative, as other products with low levels of API (but >0%) may also have been falsified. As dissolution testing was not conducted in this study, these figures may in fact underestimate the problem, particularly for RMP, which often exhibits solubility problems when poorly manufactured.¹⁹

DISCUSSION

It is not always possible to discern why a drug fails quality control. None of the 'failures' had too much API. In addition to poorly formulated drugs, some of the under-dosed products may have been properly manufactured but lost API due to degradation in poor storage conditions.

Although it is impossible to be certain, it is likely that 44% of the properly registered 'failures' were falsified, as they contained no active ingredient or had suspect packaging. While product packaging was visually inspected for correctness, comparison with reference samples was not always feasible, as attempts to collect such samples from manufacturers were unsuccessful—some manufacturers will only share information with large customers and regulators. An additional 17.5% of non-registered 'failures' appeared to be falsified for the same reasons, and others with low levels of API may also have been falsified. These products can cause physical harm to patients and economic damage to the companies whose products they imitate. Even if they contain no active ingredient, they can cause increased resistance to the other drugs with which they are taken in combination.

Most of the 'failures' were not properly registered. By and large, even poor quality, non-registered products were made by legitimate manufacturers—which were often licensed in at least one country. Medicines produced by legitimate manufacturers with insufficient API or improper solubility constituted a proportionately larger share of drug failures than falsified samples. While these drugs may work in some cases,

the insufficient API dose may prevent patients' chances of cure and contribute to drug resistance.

These results are limited to the private sector and did not include samples procured from National TB Programs. While TB is typically viewed as a public health issue, Wells et al. showed that large numbers of patients seek treatment for TB in the private sector.²⁰ Moreover, if drug resistance spreads as a result of poor quality anti-tuberculosis drugs in the private sector, both public and private sector patients will suffer.

There is a need for the WHO to conduct larger studies to determine the full extent of the availability of substandard and counterfeit anti-tuberculosis drugs and to provide clear, consistent and useful definitions of each of the above terms. Seear et al.'s definition for counterfeit drugs includes only those drugs with 0% API,²¹ which is too narrow, as some counterfeit manufacturers fake versions of drugs through a 'second shift' at what are otherwise legitimate manufacturing sites, with some—but intentionally insufficient—levels of API.²²

Lessons from the malaria community

The malaria community started paying attention to the dangers of falsified and substandard drugs in the 1990s, and the TB community needs to catch up. Substandard or falsified antimalarial drugs may indirectly cause the death of a child within 48 h of disease onset.²³ However, this tragic fact means that strains of malaria have less time and fewer opportunities to develop resistance. As TB is less acutely fatal than malaria, patients taking under-dosed anti-tuberculosis drugs may temporarily feel better, but if the drug does not eliminate the bacilli, resistance may develop. This may also extend the required treatment time, increasing both the cost of treatment and the risk of developing resistance.

In 2011, physicians in Mumbai made headlines when they reported multiple cases of TB for which they could identify no successful medicinal treatment.²⁴ As the drugs used to treat MDR/XDR-TB are more expensive and less effective than the first-line drugs,²⁵ it is vital to preserve the efficacy of first-line treatment. We also need new anti-tuberculosis drugs that will reduce treatment duration and provide alternative treatments for patients with drug-resistant TB. A significantly shortened treatment regimen would reduce the risk of developing drug resistance.²⁶

The Government of India pays close attention to ensuring that low-cost anti-tuberculosis drugs can be accessed by the poor, both in India and throughout the developing world. This is indeed important; treatment interruptions due to the inability to pay for drugs may be as damaging as providing patients with under-dosed drugs, and may equally contribute to drug resistance. These two problems are not antagonistic to each other; they must be tackled simultaneously with

all means available. Expanding access to anti-tuberculosis drugs without addressing quality concerns could create a massive drug resistance crisis. Increasing resistance will cause a small increase in patient deaths in the short term, but will be extremely deadly and costly to patients, and increase costs and complications for health providers alike in the long run.

CONCLUSIONS

In this preliminary analysis, 9.1% (65/713) of the INH and RMP samples tested failed quality control tests. Approximately half of these failing products (36/65, 55.4%), or 5% of the total, had API > 0%, making them likely to contribute to drug resistance.

The TB community needs to pay greater attention to preventing the proliferation of falsified and substandard anti-tuberculosis drugs. Governments—especially those with high TB burdens—should improve the regulators' capacity to remove drug manufacturers that repeatedly fail quality control testing from government tenders, and they should use law enforcement mechanisms, such as Interpol's Medical Product Counterfeiting and Pharmaceutical Crime Unit, to disrupt the illicit trade in falsified drugs. Curbing the manufacture and availability of falsified and substandard anti-tuberculosis drugs is necessary both to protect the public health and to safeguard the efficacy of existing drugs—above all the cheap, effective first-line drugs.

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R É S U M É

CONTEXTE : Pharmacies dans 19 villes en Angola, Brésil, Chine, République Démocratique du Congo, Egypte, Ethiopie, Ghana, Inde ($n = 3$), Kenya, Nigéria, Russie, Ruanda, Thaïlande, Turquie, Ouganda, République Unie de Tanzanie et Zambie.

OBJECTIF : Evaluer la qualité de l'isoniazide et de la rifampicine, médicaments antituberculeux de première ligne, provenant de pharmacies du secteur privé afin de déterminer dans quelle mesure des médicaments de moindre qualité et falsifiés sont disponibles et pourraient contribuer à la résistance aux médicaments dans des villes de pays à revenus faibles ou moyens.

SCHÉMA : Des ressortissants locaux ont procuré 713 ensembles de traitement provenant d'une sélection de pharmacies de 19 villes. Ces échantillons ont été testés pour

leur qualité au moyen de 1) chromatographie en couche fine afin d'analyser les niveaux d'ingrédients pharmaceutiques actifs (API) ; et 2) tests de désintégration.

RÉSULTATS : Sur 713 échantillons testés, 9,1% ont échoué dans les tests élémentaires de qualité pour les niveaux requis d'API ou de désintégration. Le taux d'échec est de 16,6% en Afrique, de 10,1% en Inde et de 3,9% dans d'autres pays à revenus moyens.

CONCLUSIONS : Des médicaments de qualité insuffisante et falsifiés sont facilement disponibles sur le marché privé et contribuent probablement à la résistance aux médicaments antituberculeux dans les pays à revenus faibles ou moyens. Ce problème justifie des investigations complémentaires au moyen d'études à large échelle concernant la qualité des médicaments sur tous les marchés.

R E S U M E N

MARCO DE REFERENCIA: Las farmacias en 19 ciudades de Angola, Brasil, China, la República Democrática del Congo, Egipto, Etiopía, Ghana, India ($n = 3$), Kenia, Nigeria, Rusia, Ruanda, Tailandia, Turquía, Uganda, la República Unida de Tanzania y Zambia.

OBJETIVO: Evaluar la calidad de los medicamentos anti-tuberculosos de primera línea (isoniazida y rifampicina) dispensados en las farmacias del sector privado, con el fin de verificar si existen productos farmacéuticos falsificados o de mala calidad que puedan contribuir a la aparición de farmacorresistencia en las ciudades de los países con medianos y bajos ingresos.

MÉTODO: Los profesionales locales de un grupo escogido de farmacias en 19 ciudades procuraron 713 paquetes de tratamiento. Se evaluó la calidad de estas muestras mediante las siguientes pruebas analíticas: 1) la

cromatografía de capa delgada a fin de analizar la concentración de principio activo (API) y 2) la prueba de desintegración.

RESULTADOS: De las 713 muestras examinadas, el 9,1% no aprobó las pruebas básicas de calidad en materia de API ni de desintegración. La tasa de fracaso fue 16,6% en África, 10,1% en India y 3,9% en los demás países de medianos ingresos.

CONCLUSIÓN: Existen en el mercado privado medicamentos falsificados y de mala calidad, que probablemente contribuyen a la aparición de tuberculosis farmacorresistente en los países de bajos y medianos ingresos. Se justifican nuevas investigaciones sobre este problema, mediante estudios en gran escala de la calidad de los medicamentos en todos los mercados.