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COUNTERFEIT PHARMACEUTICALS AND METHODS TO TEST THEM

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Pharmaceutical counterfeiting is a global threat that can kill patients, contributes to the rise of drug resistance, and increases citizens' mistrust of health systems. To monitor drug quality, governments and health programs must invest in regulations, technologies, and infrastructure, including anti-counterfeiting measures, specialised analytical facilities run by experienced staff, and portable technologies for screening medicines in the field.

The United Nations Office on Drugs and Crime has identified pharmaceutical counterfeiting as a global threat[1]. Although health professionals assume that they are prescribing good-quality medications, and patients believe that these medications will cure them, counterfeit drugs are often revealed only after a patient fails to recover[2].

The medicines supply is carefully monitored in the UK, but this is not the case in resource-constrained countries, where a range of factors are contributing to pharmaceutical counterfeiting. These include: lack of legislation; weak or absent regulatory authorities; demand exceeding supply; the high price of 'innovator drugs' (i.e. brand-name drugs); the difficulty in tracking transactions involving many intermediaries; and the lack of laboratories or field-tests to assess the quality of drugs.

Poor-quality medicines are divided into four main classes: counterfeit, falsified, substandard or degraded. But there are no universally-accepted definitions of these categories[3]. The World Health Organization (WHO) defines spurious/falsely-labelled/falsified/counterfeit (SFFC) drugs as follows[4]:

"A counterfeit medicine is one which is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredient or with fake packaging"

Falsified (fake) medicines do not contain the stated active pharmaceutical ingredient (SAPI) and may carry false representation of their source or identity. (A falsified drug could signal a potentially counterfeit product, which does not comply with intellectual property rights or may infringe trademark law)[5]. Substandard drugs are produced with inadequate attention to good manufacturing practices and may have contents or dissolution times that are outside accepted limits, due to poor quality control[6]. Degraded formulations may result from exposure of good-quality medicines to light, heat, and humidity. It can be difficult to distinguish degraded medicines from those that left the factory as substandard, but the distinction is important because the causes and remedies will be different.

The WHO's International Medical Products Anti-Counterfeiting Taskforce (IMPACT) estimates that up to 25% of the total medicine supply in less-developed countries is counterfeit[7]. Obtaining exact figures is very difficult, however, as the very nature of this trade means that it attempts to operate below the regulatory radar, and many suspect drugs remain undetected. The prevalence of poor quality drugs can only be known after a formal drug quality survey has been performed, and objective evidence of the quality of drugs available from most countries is lacking.

Alarmingly, if a medicine contains too few active pharmaceutical ingredient (APIs) to kill all the pathogens in a patient's body, it encourages the emergence of drug resistant strains. And because the poor are often limited to buying not just the cheapest product, but also the smallest pack size, that also makes it more likely that they receive inadequate doses of an active ingredient, further accelerating drug resistance. Poor quality medicines may also lead to distrust in the healthcare system

and threaten decades of progress in public health. It is simply unacceptable that the quality of drugs is poor or uncertain for the most disadvantaged people, who have the least resources and are attracted by the lower prices of counterfeit drugs.

ANTI-COUNTERFEITING TECHNOLOGIES

Several countries have recently ratified legislation to combat the sales of falsified medicines. The United States passed the drug quality and security act[8], while China and India have brought in legislation to use bar codes and adopt track-and-trace systems to check that quality-assured medications reach patients. Tagging technologies include radio-frequency identification or RFID[9], Microtags[10], NanoEncryption™ [11] and AuthentiTrack® [12], which allow manufacturers and distributors to track medicines through the supply chain. Microtags are micrometer-sized particles uniquely encoded with multiple levels of security information within a space of 50–110 micrometers (the size of a speck of dust). The tags are made of inert materials, are safe for human consumption and will not alter the potency of the medicine. The information they carry can be decoded with laser pens, optical scanners or other scanning technologies provided by the Microtag maker.

Global alarm about the emergence of antibiotic-resistant 'superbugs' is prompting wider use of these tagging technologies. In developing countries, generic antibiotics can be obtained without a prescription and little is known about their quality. Misuse of antibiotics – through unnecessary over-prescribing and sub-optimal dosing resulting from substandard antibiotics – engenders the development of resistance. The sheer volume of antibiotics sold daily, and their relatively low production cost, makes them a vulnerable target for counterfeiters, illegitimate internet pharmacies, and drug manufacturers who use poor manufacturing practices.

Antimalarial drugs are another vulnerable target. Considerable technical, financial and human resources are required to inspect, analyse and police the drug supply, all of which are lacking in most malaria-endemic countries. A systematic review of the literature reported that few surveys of antimalarial medicines used robust methodology, and that the majority

THE SHEER VOLUME OF ANTIBIOTICS SOLD DAILY AND THEIR RELATIVELY LOW PRODUCTION COST MAKES THEM A VULNERABLE GROUP OF DRUGS FOR TARGETING BY COUNTERFEITERS

did not differentiate between substandard and counterfeit medicines[13]. Surveys require epidemiological knowledge, and an adequate sample size from as wide a range of outlets as possible, to provide a reliable estimate of the frequency of poor quality drugs.

Reliable surveys are essential to justify and promote the political action that would create the mechanisms needed to assure drug quality[14].

METHODS TO TEST MEDICINES
1. Visual and physical inspection
The first step in determining the quality of a medicine is to look for the key features of any high-quality medicine. The package should include a list of active ingredients, the name and address of the manufacturer, storage conditions, batch or lot number, dates of manufacture and expiry, and directions for use. An instruction leaflet (in the appropriate language and without any spelling errors) should be enclosed with the tablets. The tablets themselves should match the authentic product in their shape, size, and colour. If the solid dose formulation is crumbling, chipped or cracked, it may indicate a substandard or degraded medicine. However, in my experience it can be difficult to persuade manufactures to supply genuine product for comparison. Pharmaceutical manufacturers employ overt anti-counterfeiting strategies such as visible holograms, as well as invisible covert features to mark the authenticity of their products. Sadly, holograms can also be counterfeited, as was the case for packages of antimalarial artesunate in South East Asia that claimed to be manufactured by Guilin Pharmaceutical Co. Ltd[15].

2. Laboratory tests
A well-equipped medicines quality control laboratory (MQCL) is a crucial component of any drug quality assurance system. It

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should be equipped with a range of analytical equipment (see below), as well as quality-assured reference standards, all of which is cost intensive. An MQCL also requires staff with a high level of technical expertise and experience of method development.

High-performance liquid chromatography (HPLC) is an analytical technique used to separate specific compounds, and then identify and quantify them based on how long they take to separate, and their spectrophotometric properties. HPLC can be coupled to various detectors, but the **ultraviolet photodiode array (UV-PDA)** is regarded as the 'gold standard' for drug quality analysis because it offers accuracy, specificity and precision in quantifying the amount of APIs present. It is, however, relatively expensive and requires greater expertise to operate, which demands extensive training and technological support.

HPLC can also be coupled to a **mass spectrometer (LC-MS)**. Although this gives analysts abundant chemical information, it also relies on tedious, time-consuming sample preparation, and typically requires a reference standard to determine API levels.

However, more recent MS technologies avoid sample preparation and give almost instantaneous results. Direct analysis in real time **(DART)** MS allows the analyst to hold a tablet in front of a mass spectrometer and get information about its composition in seconds[16,] while desorption electrospray ionization **(DESI)** MS involves spraying a solvent at the tablet to free APIs for analysis[17].

Dissolution testing offers a valuable prediction of the in vivo bioavailability and bioequivalence of tablets and capsules, by measuring the amount of drug released into a dissolution media (liquid) over time. The presence of incorrect excipients, as well as poor manufacturing processes, may contribute to poor dissolution resulting in

lower bioavailability. Indeed, an epidemic of malaria on the Afghan-Pakistan border was confirmed to result from the poor bioavailability of locally-procured substandard antimalarial drugs[18]. These tests require a sophisticated dissolution apparatus, as well as analytical equipment (HPLC with UV-PDA) and reference standards, which are expensive and may be difficult to obtain. Furthermore, analysts need to have access to the dissolution information that is expected for each medication, and the tests are both labour- and cost-intensive.

Nuclear magnetic resonance (NMR) spectroscopy is a powerful tool that allows analysts to determine the structures and relative concentrations of molecules in a sample without active pharmaceutical reference standards. For example, NMR analysis of the hydrogen and phosphorous (^{1}H and ^{31}P) atoms in the anti-leishmanial drug miltefosine helped to prove that a generic version procured from Bangladesh did not contain the SAPI[19].

3. Screening techniques

Thin layer chromatography (TLC) is an inexpensive, simple, flexible and effective method for verifying the identity of a formulation. It requires a variety of chemical reagents and plates, reference standards of the SAPIs, and some basic training for the analyst. For example, two TLC-based tests can check the quality (falsified or authentic) of the most effective antimalarial drugs, artemisinin combination therapies (ACTs), in the absence of a MQCL[20].

Many developing countries do not have the technical, financial, or human resources required to inspect and police the drug supply[7]. Thus simple and affordable field methods provide a practical means of rapidly monitoring drug quality. Portable labs – in particular the **Minilab®**, a ready-to-use TLC

CONVENIENCE SURVEYS CONDUCTED IN SOUTH EAST ASIA IN 2000/1 AND 2002/3 SUGGESTED THAT 38% AND 53% OF THE ARTESUNATE BLISTER PACKS OBTAINED FROM PHARMACIES AND SHOPS WERE COUNTERFEIT.

kit from the German Pharma Health Fund (GPHF)[21] – provides a versatile means for initial screening of many drug formulations, including antimicrobials, antimalarials, and antiretrovirals. Currently 713 GPHF-Minilab units are used globally across 92 countries to fight the counterfeit drug trade.

The Tanzanian Food and Drugs Authority pilot-tested the Minilab® and found it to be relatively inexpensive and rapid, but that it detected only grossly substandard or wrong-drug samples. Ultimately, the Minilab® should be used in conjunction with robust laboratory-based testing[22]. This approach was recently used to assess the quality of two brands of antibiotics, amoxicillin and co-trimoxazole, manufactured in six countries and purchased in Ghana, Nigeria and Nigeria. All of the samples of amoxicillin complied with United States Pharmacopeia (USP) tolerance limits for dissolution testing, but 60% of co-trimoxazole tablets did not. But there was some disparity in the Minilab® results, highlighting that this portable laboratory should not be relied upon to make regulatory decisions[23].

4. Portable instruments

Hand-held devices based on spectroscopic methods are now being investigated as screening tools that can rapidly detect poor-quality drugs throughout the supply chain (see case study p138). Non-destructive spectroscopic techniques such as **Raman spectroscopy** and **near infrared (NIR)** are currently being evaluated for their ability to scan drug samples through the blister pack, without using the toxic chemicals or flammable solvents typically found in a MQCL. Both techniques rely on comparing characteristic spectral 'fingerprint' of a suspect medicine with a genuine sample. This necessitates access to a database of spectra, created by investigators, for every brand of medications from every manufacturer (see case study, p140).

One potential drawback of using Raman spectroscopy is that only the sample surface is probed, so if the SAPI is not evenly distributed throughout the entire tablet, the resulting content information may be inaccurate. Additionally, many pharmaceutical preparations contain highly fluorescent excipients, thus

A RECENT META-ANALYSIS REPORTED THAT 35% OF ANTIMALARIAL DRUG SAMPLES FROM 21 SUB-SAHARAN AFRICAN COUNTRIES, FAILED CHEMICAL CONTENT ANALYSIS.

affecting the quality of the spectrum. The TruScan® hand-held Raman device has successfully detected some counterfeits in the field, but it has not been useful to detect substandard medicines[24].

Unlike Raman spectroscopy, infrared (IR) spectroscopy has a larger depth penetration into the sample surface. Near-infrared spectroscopy (NIR) can reveal whether excipients are not in the correct proportions, suggesting that the medicine is counterfeit, but it cannot detect substandard medicines[25]. NIR is also relatively simple to miniaturise: for example, the SCiO NIR device, at present under validation, is a smart-phone-sized instrument that promises to be highly effective at checking the quality of medications in the absence of a MQCL[26]. Meanwhile, the US Food and Drug Administration (FDA) has recently started using its Counterfeit Detection Device CD-3 to screen tablets, packaging and even documents at ports of entry or in remote areas, although further development is still needed[27].

QUALITY OF ANTIMALARIAL DRUGS IN MALARIA-ENDEMIC COUNTRIES

A recent meta-analysis reported that 35% of antimalarial drug samples from 21 Sub-Saharan African countries, failed chemical content analysis[28]. The underlying research predominantly used the 'convenience' sampling approach, where research teams purchased medicines from drug sellers who were easily-accessible, or who were already thought to sell poor-quality medicines. Results based on this low-cost sampling approach can be useful in drawing attention to a potential problem. For example, convenience surveys conducted in South East Asia in 2000/1 and 2002/3 suggested that 38% and 53% of the artesunate blister packs obtained from pharmacies and shops were counterfeit[29].

But the convenience approach may not be

Table 1: Comparative strengths and weaknesses of the three sampling approaches used

SAMPLING APPROACH	ADVANTAGES	DISADVANTAGES
CONVENIENCE	• Rapid • Low cost	• Lack of defined sampling frame of standardised approach • Uncertainty in whether sampling is representative and therefore reliability of the estimates of drug quality obtained • Generalisability of findings may be weak • Results may be difficult to replicate
MYSTERY CLIENTS	• Use of defined sampling frame • Can yield representative sample from all types of outlets and/or brands • Low risk of sampling bias in samples collected, as outlets are unaware of survey • Reliability and generalisability of results should be strong • Results can be replicated	• Sample will only be as comprehensive and/or representative as the sampling frame that was used • Need to authenticate and update sampling frame increases time and cost of survey • Information on sources of poor quality drugs is limited to brand, batch and country of manufacture as stated on packaging
OVERT	• Use of defined sampling frame • Can yield representative sample from all types of outlets and/or brands • Results can be replicated • Can collect additional information at minimal additional cost to mystery approach	• Sample will only be as comprehensive and/or representative as the sampling frame that was used • Need to authenticate and update sampling frame increases time and cost of survey • Possible risk of sampling bias in samples collected, if some outlets refuse to be sampled or are aware of which samples might be poor quality and differentially withhold these • Reliability and generalisability of results may be compromised if sampling bias occurs

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representative of the places where patients actually buy their medicines, and it may also be biased: for example, if the collector consciously or subconsciously set out to procure or not procure poor-quality formulations (see Table 1)[30].

In 2006, the WHO banned malaria medicines that contain just one active ingredient (such as artesunate), in favour of artemisinin combination therapies (ACTs) that contain more than one active ingredient. This treats the disease more rapidly: the artemisinin component kills the majority of the parasites at the start of the treatment, while the more slowly-eliminated partner drug clears the remaining parasites, in the hope that resistance will be slowed enough to allow for the development of a pipeline of efficacious drugs. Once ACTs had been enforced in malaria-endemic countries, it was believed that they would be in danger of being counterfeited. Hence, the Artemisinin-based Combination Therapy Consortium Drug Quality programme purchased over 10,000 artemisinin-containing antimalarials (ACAs) in 6 malaria endemic countries, from private sector retail outlets such as pharmacies and drug shops, following representative sampling approaches[31]. Outlets were selected at random in most countries

from lists obtained from the relevant government's ministry of health; whereas in other countries we initially conducted a pilot study by collecting samples using the 'convenience' approach to gain perspective on the type of outlets and brands of ACAs available.

Medicine samples were subsequently purchased using one of two approaches. Through the 'mystery client' approach, the person purchasing the medicines posed as a malaria patient or their relative; through 'overt sample collection', vendors were informed that we were going to analyse the quality of the medicines they sold, and samples were purchased once they consented. This allowed us to interview the vendor to obtain data on the availability and supply of antimalarials, their storage conditions, and the training of providers.

The collected samples were analysed in three different laboratories in the UK and the US. First, they were sent to the London School of Hygiene and Tropical Medicine (LSHTM), where they were logged and their packaging and blister packs scanned. Each tablet was weighed and its dimensions recorded on the database. Each sample was analysed using HPLC UV-PDA to measure the amount of APIs, which was then expressed as the percentage of the SAPIs and used to classify the quality of the sample. Duplicate samples from each packet of tablets analysed at LSHTM were sent to the US Centers for Disease Control and Prevention in Atlanta, where a random 10% were analysed for confirmatory HPLC-PDA results. A duplicate set was also sent to the Georgia Institute of Technology, Atlanta, for ambient MS analyses to verify the pharmaceutical ingredients present and identify any unstated compounds. Samples were classified as 'acceptable quality' if the SAPIs were present at between 85% and 115% of the SAPI quantity. Medicines outside this range, for either or both of the partner compounds, were classified as substandard. These substandard medicines were also examined to detect the presence of degradation products, caused by poor storage conditions such as heat and humidity. Medicines were regarded

WE NEED GREATER INVESTMENT IN DEVELOPING AND VALIDATING PORTABLE TECHNOLOGIES THAT CAN BE USED IN THE FIELD.

as falsified when either one of the SAPIs was not present. All results were compiled into a report and disseminated to the relevant ministries of health before being submitted as a manuscript to peer reviewed journals.

In these investigations of ACAs, we found no evidence of falsified medicines in 4,928 samples (over 50 brands) from Cambodia, Ghana, Rwanda and Tanzania. Of the 5,151 samples that were collected in Bioko Island (Equatorial Guinea) and Nigeria (over 142 brands), 1.9% were falsified i.e. they contained neither of the SAPIs. Instead, they contained compounds including chlorzoxazone (a muscle relaxant), ciprofloxacin (an antibiotic) or acetaminophen (paracetamol, a commonly used painkiller). The falsified medicines found in this research are far fewer than the 35% fakes suggested in previous reports. However, it is worth noting that substandard drugs were found in all the countries that we studied, with the most in Cambodia (31.3%), Ghana (37%) and Tanzania (12%); others were less than 8%.

The key strengths of this investigation are that representative sampling approaches were used to purchase a sizeable number of samples; these were analysed in three independent laboratories, using two different detection methods (HPLC with UV-PDA and MS)[30].

Representative methods to sample medicines are important for generating reliable estimates of the prevalence of poor quality drugs in a given country. However, this type of study is cost intensive, both for the purchase and analysis of drugs. It is important to establish affordable systems that sample medicines in a representative way, and develop robust laboratory techniques to analyse them on a regular basis. This will enable for the accurate quantification and tracking of the scale of poor-quality medicines that threaten the treatment of this life threatening disease.

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