Antimalarial drug quality: methods to detect suspect drugs

Malaria is a major public health problem in the endemic countries of Africa, Asia and Latin America. Poor quality antimalarials are of major, but neglected, concern in the control of Plasmodium falciparum malaria. They cause treatment failure and economic loss, and engender drug resistance and loss of confidence in health systems. The emergence of resistance to the artemisinin derivatives in Asia bodes ill for malaria control in Africa, and strenuous efforts are needed to improve the quality of the world’s supply of antimalarials. This article reviews the problem and discusses methods available to determine the quality of antimalarials.

KEYWORDS: antimalarials, artemisinin, counterfeit, degraded derivatives, drug quality, HPLC, mass spectrometry, substandard, thin-layer chromatography

Malaria continues to be one of the major public health problems in Africa, Asia and Latin America. Plasmodium falciparum malaria is estimated to be the direct cause of 500 million cases and over 1 million deaths per year, mostly in women and children under the age of 5 years.[1,2] In children, progression of disease from mild to severe is particularly rapid.[3] Plasmodium falciparum has become resistant to many commonly used antimalarials such as chloroquine and sulfadoxine–pyrimethamine. In light of this, the WHO has recommended that all antimalarials should consist of a combination of an artemisinin derivative with a co-drug, such as lumefantrine, amodiaquine, piperaquine or mefloquine (artemisinin-based combination therapy [ACT]) for use as first-line treatment against malaria. This class of drugs is now first-line policy in most malaria-endemic countries.[4] Artemisinin derivatives (ARTs; artesunate, dihydroartemisinin, arteether and arteether) derived from the herb, quinghao (sweet wormwood or Artemisia annua L.; Asteraceae), are the most effective antimalarial drugs available, providing rapid cures. The recent emergence of ART-resistant P. falciparum, on the Thailand/Cambodia border,[5] is of very great concern, especially as there is evidence that drug-resistant falciparum malaria has spread from Asia into Africa.[6]

Poor-quality antimalarials have been a severe under-recognised public health problem, reducing the effectiveness of these drugs and threatening current treatment policies. There are three main types of poor-quality medicines: degraded, substandard and counterfeit. The WHO defines counterfeit drugs as those that are 'deliberately and fraudulently mislabeled with respect to identity and/or source', and may include those with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging.[10] Substandard drugs are produced with inadequate attention to good manufacturing practices and may have contents and/or dissolution times outside accepted limits, due to poor quality control.[10] In addition, 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 as the causes and remedies are different. Reports from Asia and Africa indicate that there is widespread production and distribution of counterfeit and substandard antimalarial drugs. However, it can be very difficult to differentiate between them, as it is not always clear whether the actions leading to the production of poor-quality drugs were deliberate. Ineffectiveness of antimalarial drugs is of major concern globally as poor-quality drugs undermine treatment, resulting in deaths from a curable disease and engendering drug resistance.

The problem of drug counterfeiting appears to be growing despite greater awareness with reports in newspapers, cinema and television campaigns, as well as information posted on the internet. The WHO/International Medical Products Anti-Counterfeiting Taskforce (IMPACT) estimates that counterfeit drugs constitute up to 25% of the total medicine...
supply in less developed countries [103], and in some countries the figure is thought to be as high as 50% [104]. However, obtaining exact figures is very difficult as the very nature of this trade means that it attempts to operate below the ‘regulatory radar’ and many suspect drugs remain undetected. Alarms may be raised when a poor quality product is serendipitously discovered, but the prevalence of poor-quality drugs can only be known after a formal drug-quality survey has been performed. It is unacceptable that the quality of drugs are poor or uncertain for the most disadvantaged people who are attracted by the lower prices of drugs and have the least resources. The use of counterfeit drugs results in people inadvertently consuming sawdust, paint and an array of other toxic or inert substances. Alarming, if the drug contains some active ingredient but too little to kill all the pathogens, it can lead to the emergence of drug-resistant strains. Because the poor can often afford to buy not just the cheapest product but the smallest pack size available from an outlet, the use of inadequate doses of an active ingredient further engenders drug resistance.

Similarly, there are increasing reports of substandard antimalarial medicines. They originate from genuine manufacturing plants and are a result of production errors and/or poor quality control [7]. They may contain too little or too much active ingredient. The former may result in therapeutic failure, and the latter in adverse effects, especially for medicines with narrow therapeutic indices. Even if the medicine contains the correct amount of active ingredient, if the formulation is incorrectly made, low bioavailability may result in subtherapeutic blood concentrations. Substandard sulfadoxine–pyrimethamine with poor bioavailability precipitated a malaria epidemic in Afghan refugee camps in Pakistan [8]. Substandard antimalarials, containing inadequate active ingredient or with poor bioavailability, are likely to be more important than counterfeits in the spread of drug resistance. In Africa, approximately 80% of the antimalarial treatments for childhood fevers are given in the home with shop-purchased (commonly unlicensed) drugs [9]. In a given year an African child will use antimalarials on average at least four-times [10]. To meet this demand there is a great diversity of drugs on sale in the market place. In 2004, for example, in Kenya alone there were found to be over 200 different antimalarial drugs and/or combinations (including sulfadoxine–pyrimethamine, sulfalene–pyrimethamine, amodiaquine and artether–lumefantrine) in circulation, and over 40% sampled were outside the limits of the pharmacopoeia [11].

A nationally representative retail sector survey of antimalarials carried out recently in Tanzania found that 36% of the antifolates tested (sulfadoxine–pyrimethamine and sulfamethoxy pyrazine–pyrimethamine), 24% of quinine tablets and 6% of amodiaquine tablets did not meet the US Pharmacopoeia specifications for the amount of active ingredient [12]. A study of the quality of antimalarials collected from public and private healthcare providers in southeast Nigeria found that 37% of the formulations (46% quinine and 39% sulfadoxine–pyrimethamine) tested did not meet the US Pharmacopoeia tolerance limits [13].

Some fake artesunate tablets from Southeast Asia have been found to contain subtherapeutic amounts of the active ingredient, or artesinin itself, a compound with lower antimalarial efficacy. Other fake artesunate tablets contain a wide variety of unexpected wrong ingredients such as metamizole, paracetamol, erythromycin and chloramphenicol, which would be clinically confusing in the event of adverse events [14,15]. Fake or substandard artesunate drugs containing subtherapeutic amounts of artesunate engender the spread of drug-resistant malaria [16]. To what extent resistance to artesinin derivatives on the Thai/Cambodian border [5] is the result of counterfeit ARTs containing subtherapeutic amounts of ART and/or substandard medicines is not known. Poor-quality antimalarials along with the widespread use of short courses of ART monotherapy, poor prescribing practices and poor patient adherence are likely to have been important contributors.

Most alarmingly, the first counterfeit ARTs and ACTs have already been described from six countries in West, Central and East Africa [17–19]. Large shipments of these drugs have been recently intercepted [20,21]. The expense and desirability of ACTs, the shift in antimalarial treatment policy to this class of drugs in Africa, where a high prevalence of poor-quality and counterfeited non-ACT antimalarials have been described [11,21–25], creates a very dangerous situation. Previously, even low-cost antimalarials, such as chloroquine, have been counterfeited, presumably because the economy of scale made this a profitable venture [26]. The characteristics of particular drugs (in terms of source, contents, date of expiry...
and so on) and their intake are essential for the correct interpretation of any implementation study of the use of ACTs. This information is difficult to obtain, because drugs are often used indiscriminately, and contents of tablets are not always known. For example, chloroquine is present in the blood of many patients in Africa who deny taking it or are unaware that they took it [27]. Factors preventing the detection of suspect antimalarials at an early stage of market penetration, when intervention has the greatest chance of success, include the lack of appropriate detection techniques, lack of inspections and the lack of routine systematic nationwide drug sampling from the diversity of different types of drug retailers. Accurate assessment of the prevalence of poor-quality drugs is essential, but challenging, given the diversity of products sold – in one part of one town in an African country, 51 different varieties of ARTs and ACTs were available for sale (Figure 1).

**Sampling strategies**

Objective evidence of the quality of drugs available in any country is lacking. Collecting such data is complicated, because if the sellers realise that they are to be a part of an investigation, there is the risk that they will either decline to take part or only sell what they know is good-quality medicine. So the threat of a drug quality survey, and that of subsequent enhanced inspection and regulation, may encourage vendors to sell authentic drugs, resulting in increased apparent availability of the good-quality product. Although this may increase drug quality temporarily, it also argues that medicine surveys should be carried out covertly to obtain an accurate estimate of the true scale of the problem. ‘Convenience’ surveys conducted in Southeast Asia in 2000/2001 and 2002/2003 suggested that 38 and 53%, respectively, of artesunate blister packs obtained from pharmacies and shops were counterfeit. However, this mode of sampling is flawed as it is potentially biased – under- or over-estimating the prevalence of poor-quality drugs. The bias will depend on, at least in part, whether the collector consciously or subconsciously set out to procure or not to procure poor-quality formulations. Both how and by whom samples are collected is likely to affect the results. Sampling frameworks, based on random sampling, either conventional random population sampling or random lot quality assurance sampling have been proposed as the way forward [28]. This should reduce the risk of bias and allow comparisons through space and time and assess the impact of interventions. The
sample size should be of sufficient magnitude and from as wide a range of outlets as possible to give a reliable estimate of the frequency of substandard or counterfeit drugs patients are exposed to. Because vendors are chosen using conventional random sampling, or lot quality assurance sampling, the risk of consciously or subconsciously biasing data is decreased and the samples collected are much more representative of medicines consumed by patients.

Technologies available for determining the quality of antimalarials

The ability to identify poor-quality medicines is a crucial component of a drug quality assurance system. Access to an affordable medicine quality control laboratory (MQCL) is essential to help ensure the quality of locally produced, imported or donated formulations used in a nation’s healthcare system. The WHO member states are encouraged to maintain MQCLs, but sadly this is not possible in many malaria-endemic countries due to lack of economic resources. There are only two WHO Prequalified Quality Control Laboratories in malarious Africa.[105] Factors contributing to pharmaceutical counterfeiting include lack of legislation, weak or absent regulatory authorities, demand exceeding supply, high price, transactions involving many intermediaries and the lack of laboratories or field tests.

Visual & physical inspection

Pharmaceutical manufacturers employ overt anticounterfeiting strategies, such as the use of visible holograms, as well as invisible covert features to mark the authenticity of their products. Sadly the holograms on packages of artemisinin labeled as manufactured by Guilin Pharmaceutical Co., Ltd (China) have been extensively counterfeited in Southeast Asia, and thus far 16 types of copies of the original have been found.[29]. The integrity of the packaging, the features of the blister pack with indented or printed batch number, and dates of manufacture and expiry, as well as the appearance of tablets, form the first steps in determining the quality of the product. Included on the package should be the list of active ingredients, name and address of the manufacturer, storage conditions, batch or lot number, expiry plus date of manufacture and directions for use. Enclosed with the tablets should be an instruction leaflet in the appropriate language without any spelling errors. Comparison with the authentic product in terms of the physical dosage form, shape, size, color and information (especially the correct use of language) can help identify a potentially suspect formulation. Furthermore, a substandard medicine may be indicated when the solid dose formulation is crumbling, chipped or cracked. An example of a counterfeit antimalarial easily distinguished by obvious physical features is illustrated on the Kenya Pharmacy and Poisons Board website.[106]. The printing on the blister packs of fake Duo-Cotecxin® (Zhejiang Holley Nanhu Pharmaceutical Co., Ltd, Jiaxing City, China) is easily rubbed away with a wet finger, and the location of the expiry date is different from the location on the genuine drug pack. In addition, the counterfeit tablets are larger in size than the genuine tablets.

Laboratory tests

Content analysis

Thin-layer & liquid chromatography

Thin-layer chromatography (TLC) is an inexpensive, simple, flexible and effective method for verifying the identity of a formulation. A variety of chemical reagents and plates are required to use this technique, as well as some basic training and a reference standard of the active pharmaceutical ingredients is needed to confirm the results. Figure 2 shows a recently reported method that utilizes TLC and 2,4-dinitrophenylhydrazine or 4-benzoylamino-2,5-dimethoxybenzene-diazonium chloride hemi (zinc chloride) salt as the reagents, resulting in pink or blue products, respectively, only in the presence of ARTs.[30]

Furthermore, TLC is useful for indicating impurities or even degradation products if they are in high enough concentrations. The technician who performs this test will need some training in chemistry to reliably interpret results. Ready-to-use TLC kits are available from the German Pharma Health Fund (GPHF; Frankfurt, Germany) e.V. Minilab®[107].

The GPHF Minilab®

Many developing countries do not have the technical, financial or human resources required to inspect and police the drug supply.[103]. Thus, simple and affordable field methods provide a practical means of rapidly monitoring drug quality. Portable laboratories, in particular the GPHF Minilab, provide a versatile means of initial screening of most antimalarial formulations. The Minilab uses a four-stage process to test for the quality of drugs:

Visual inspection of solid dosage forms and packages;
■ Tablet- and capsule-disintegration test for a preliminary assessment of drug solubility;
■ Simple colour reactions to identify drugs;
■ Semiquantitative TLC to check for quantities of active principal ingredient (API) present, which requires staff to be trained prior to using the MiniLab.

The Tanzanian Food and Drugs Authority piloted the use of the MiniLab kits and found it to be relatively inexpensive and rapid, but only grossly substandard or counterfeited samples could be detected. It is recommended that the MiniLab be used in conjunction with a MQCL [31].

**HPLC & mass spectrometry methods**

HPLC is an analytical technique used to separate, identify and quantify specific compounds. Separation is achieved by molecular interactions with a particular matrix, while identification and quantification is achieved by the retention times and spectrophotometric properties of the selected compound. HPLC can be coupled to a variety of detectors, such as the single wavelength ultraviolet/visible absorbance, fluorescence, photo diode array, electrochemical or refractive index. HPLC also allows coupling to a mass spectrometer (liquid chromatography-mass spectrometry [LC-MS]). However, these techniques necessitate a reference standard to determine the amount of API present in a sample. HPLC has several merits, such as accuracy, specificity and precision, but is relatively expensive and requires greater expertise; thus, the implementation of HPLC techniques requires considerable training and technological support.

Whilst LC-MS (Figure 3A) enables abundant chemical information to be obtained, this technique relies on tedious, time-consuming sample preparation. Recent developments to overcome these challenges have included open-air ionization techniques that can be used with mass spectrometry (MS). These techniques do not require sample preparation, and information on the contents of the sample being analyzed are available almost instantaneously. Direct analysis in real time (DART; Figure 3B) allows a user to hold a tablet in front of a mass spectrometer and, within seconds, a mass spectrum can be collected representing the chemical composition of that sample [32]. Desorption electrospray ionization (DESI; Figure 3C) is another MS technique that sprays a solvent at the tablet, resulting in ions that are analyzed as a mass spectrum [33]. These techniques provide a way for drugs to be quickly and simply screened for the presence of the expected API, wrong APIs and other chemicals possibly present in suspect samples.

**Dissolution tests**

*In vitro* dissolution testing offers valuable prediction of the *in vivo* bioavailability and bioequivalence of tablets and capsules. Dissolution tests measure the amount of drug released into the dissolution media with time.

![Figure 2. Detection of a counterfeited sample of Cotecxin®. (A) Analysis of Cotecxin samples collected from Nigeria showing the detection of a fake Cotecxin (left-hand side; Nig 26, note the lack of colour on thin-layer chromatography when compared with other samples; Nig 27, Nig 28 and reference drug; DHA on the far right-hand side). (B) HPLC chromatogram showing the presence of the DHA peak in sample ‘Nig 27’ and its absence from sample ‘Nig 26’ indicated by the dotted arrow at approximately 4.9 min. DHA: Dihydroartemisinin. Photo by H Kaur.](image)
following detailed protocols (official monograms) set out for most drugs in pharmacopoeias (e.g., European, British, the USA and the WHO International). The protocols outline the details of the test conditions – that is, the dissolution solvent/buffer, stirring speed, tolerance levels of the API and temperature for the assay. The presence of incorrect excipients, as well as poor manufacturing processes, may contribute to poor dissolution, resulting in lower bioavailability. Poor storage conditions resulting in decomposition products may also influence dissolution. Even if the quantity of API in a medicine is within specified limits, the amounts released may be lower due to poor dissolution characteristics. These tests require sophisticated dissolution apparatus, as well as the analytical equipment (HPLC) and reference API standards for calibrating the equipment, which are expensive and may be difficult to obtain. In many cases, reference standards may be obtained from the US Pharmacopeia or from the drug manufacturers. Pollen analysis has been used to obtain information on the flora in the area where raw materials were obtained and/or manufacturing performed [29].

**Portable technologies**

*Use of hand-held instruments based on refractometric, colorimetric & spectroscopic methods*

Inexpensive hand-held LED photometers are useful in measuring the absorbance intensities associated with colorimetric reactions of active ingredients in pharmaceutical preparations. Colorimetric methods have been published for the ARTs and other antimalarials [30,34–36]. Simple refractometers have also been shown to be useful in measuring dissolved active ingredients in appropriate solvents [36]. Other inexpensive and portable instruments are useful in measuring physicochemical characteristics such as pH, tablet weight, the viscosity of syrups and density of suspensions or solutions. For example, the pH of artesunate in aqueous alcohol is approximately 3.5, whereas some of the tested counterfeits had a pH of approximately 6.5. Tablet weights of fake Guilin artesunate tend to be approximately 10% more than the genuine [37]. A disadvantage of using colorimetric, refractometric and chromatographic techniques is that the sample is destroyed during the process.

![Figure 3. Mass spectrometric techniques used for identification for suspect drugs.](image)

(A) LC-MS results in retention times for a selected drug, but requires sample preparation. Both (B) DART-MS and (C) DESI-MS require no sample preparation and both result in a mass spectrum identifying select components in the sample.

DART-MS: Direct analysis in real time-mass spectrometry; DESI-MS: Desorption electrospray ionization; LC-MS: Liquid chromatography-mass spectrometry.
Nondestructive spectroscopic techniques such as Raman and near-infrared spectroscopy are currently being evaluated for the rapid detection of counterfeits. With these techniques, drug samples may be scanned through the blister pack, and no toxic chemicals or flammable solvents are necessary. Raman spectroscopy is a rapid technique that can be used to characterize samples in the field. It is based on the Raman effect, the scattering of light interacting with the different vibrational modes of the drug molecule. One potential drawback of using Raman spectroscopy is that only the sample surface is probed, so if the API is not evenly distributed throughout the entire tablet, the resulting content information may be inaccurate. Many pharmaceutical preparations contain highly fluorescent excipients, thus affecting the quality of the spectrum [38]. The spectra obtained using Raman spectroscopy cannot be de-convoluted into specific signals from different chemicals as it presents information regarding the functional groups in a molecule. In order to identify genuine samples, a fingerprinting method is used where a Raman spectrum is compared against a database that contains spectra from every type of antimalarial from every company that manufactures that drug. It is also important to ensure that interference from an excipient does not cause the sample to be wrongly characterized as a fake. This method has been successfully tested in the field for detection of counterfeits [38].

Infrared spectroscopy utilizes the fact that different drug molecules interact differently with infrared light when excited. Unlike Raman spectroscopy, infrared has a larger depth penetration into the sample surface, with the potential advantage that the homogeneity of distribution of the API throughout the tablet can be determined. Infrared spectroscopy, like Raman, uses the fingerprinting method in order to match the sample spectrum to a compound in the database. Near-infrared spectroscopy uses the near-infrared region of the electromagnetic spectrum (from approximately 800–2500 nm) and entails exciting the molecules in a sample and recording the unique fingerprint obtained. The method has been used to analyze excipients and may be used to demonstrate that they are not in the correct proportion, thus suggesting that the medicine is counterfeit [39].

X-ray fluorescence is a nondestructive technique that utilizes x-rays to determine which chemical elements are contained in a sample. x-rays bombard the sample and characteristic x-ray emissions result from different elements. This technique requires no sample preparation and is most commonly used for elemental analysis and to detect metals. Although the API is not measured directly, the elemental composition of counterfeit drugs tends to be quite different from that of the genuine. X-ray fluorescence is thus a powerful complementary tool for detecting fakes [Green MD, Fernandez FM. Unpublished data].

X-ray diffraction is based on the elastic scattering of x-rays by the crystalline structures organized and aligned in crystals. Powder diffraction is often used in identifying unknown samples. This technique compares the spectrum obtained from a specific sample to a database containing spectra from every expected possibility. This method is destructive, as the tablet must be crushed into a powder. This method can also be used to measure the relative abundance of the major components in the sample, and usually provides information regarding excipients that is not easily obtained by MS [29].

Conclusion
Producing counterfeit drugs is an easy endeavor, requiring only a tablet press, a printer, commonly found household materials and a malevolent mentality. Analytical tools are available that enable accurate detection and distinction of suspect drugs as substandard, degraded or counterfeit. Greater effort into lowering the cost of purchasing and maintaining these analytical devices, as well as standardization of protocols is needed. Simple, robust and inexpensive field methods are a useful alternative in identifying counterfeits by inspectors. Suspect drugs can then be sent for rigorous analyses to the MQCLs. In conclusion, people should not take the quality of their medication for granted. In countries with poor economies, support for drug regulatory agencies is not always a priority, but investment in improving medicine quality is likely to have important beneficial effects on public health.

Future perspective
Enormous effort is spent in determining the most efficacious antimalarials for country programs, but it is essential that the quality of the drugs subsequently used is monitored and good quality maintained. The techniques mentioned in this article can be used to check the quality of drugs, but are not available in the majority of the malarious world. Hence, there are few data to inform policy or to intervene. Further
research is needed on the extent of the problem, evaluations of appropriate methods for drug quality assessment, estimation of the impact of poor-quality antimalarials and on the utility of different interventions. In addition, better collaboration between academic research, the pharmaceutical industry, medicines regulatory authorities and the law-enforcement agencies will greatly help to ensure that the vulnerable are protected from poor-quality medicines. Enhanced regulation and quality assurance of the proliferating genuine manufacturers would help reduce the problem of substandard medicines.

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Executive summary

- Determining the true prevalence of suspect drugs, whether substandard, counterfeit or degraded, relies on the availability of chemical analysis facilities, appropriate sampling protocols and necessary expertise.
- Rapid tests for detection of counterfeits include colorimetric techniques, simplified dissolution tests, and thin layer chromatography.
- Traditional quality analysis techniques include HPLC and liquid chromatography-mass spectrometry.
- Field handheld instrumentation includes colorimeters, refractometers and handheld Raman and infrared spectrometers.
- Novel rapid screening techniques using mass spectrometry for detection have shown great promise in identifying fakes and drugs containing incorrect active ingredients. These techniques include desorption electrospray ionization and direct analysis in real-time mass spectrometry.

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** Provides the first report of a collaborative effort of scientists and INTERPOL in detecting and tracing the counterfeited antimalarial drug artemisane to traders in China who were prosecuted.