Journal of Antimicrobial Chemotherapy (2007) **60**, 214–236
doi:10.1093/jac/dkm109
Advance Access publication 5 June 2007

JAC

Counterfeit or substandard antimicrobial drugs: a review of the scientific evidence

Theodore Kelesidis[1]†, Iosif Kelesidis[1]†, Petros I. Rafailidis[1] and Matthew E. Falagas[1,2]*

[1]Alfa Institute of Biomedical Sciences (AIBS), Athens, Greece; [2]Department of Medicine, Tufts University School of Medicine, Boston, MA, USA

There is growing universal concern regarding counterfeit medications. In particular, counterfeit antimicrobial drugs are a threat to public health with many devastating consequences for patients; increased mortality and morbidity and emergence of drug resistance. In addition, physicians treating these patients lose their confidence in the medications used and report high levels of bacterial resistance. The problem with fake and suboptimal medications got worse with the advent of the World Wide Web; a significant proportion of medications that are sold through Internet pharmacies is counterfeit. Various initiatives of the WHO (the International Medical Products Anti-Counterfeiting Taskforce) are hopefully going to tackle this very important public health issue. In this article, we review the available evidence in peer-reviewed articles and World Wide Web information resources regarding the issue of counterfeit antimicrobials.

Keywords: low-quality antimicrobials, quality testing, fake antimicrobial agents

Introduction

Drug quality is currently receiving renewed international attention.[1] Over the past decade, there has been an increase in public awareness of the existence of counterfeit and substandard drugs,[2–5] which have been increasingly reported in developing countries where drug regulations are ineffective.[6–14] Although practically all types of pharmaceutical products have been shown to be involved, the existing data suggest that anti-infectious agents, particularly antibiotics and antiparasitic agents, are the most counterfeited products in developing countries.[1,15,16]

To implement effective countermeasures against counterfeit and substandard drugs, there is a need for more data to define the extent of the problem. The issue of poor quality drugs has been discussed more in the mass media including newspapers than in the biomedical literature. Many reports that this topic are however anecdotal, which makes quantitative assessment difficult.[10,17] Few studies have been reported that systematically examine drug quality,[7–12] and have investigated poor quality drugs in terms of correct amount of active ingredient present. More specifically, although drugs that treat serious diseases such as malaria, tuberculosis, AIDS or other infections are more often the object of counterfeits,[18,19] there have been scarce reports that systematically review data of low-quality antimicrobials. Therefore, we performed a review of the available scientific evidence on counterfeit and/or substandard antimicrobial drugs. More specifically, we set out to explore the causes and prevalence of this problem and summarize the categories of antimicrobials that have been reported to be counterfeit or substandard. We then discuss the characteristics of these low-quality antimicrobials, their consequences to patients and in our society and finally what interventions have been put into place to cope with this menace.

Literature review

Two reviewers (T. K. and I. K.) independently performed the literature search, study selection and data extraction. The following terms were used in searches of the PubMed database (1966–2006): 'counterfeit drugs', 'substandard drugs', 'fake drugs', 'substandard antimicrobial agents', 'fake antimicrobial agents', 'counterfeit antimicrobial agents', 'substandard antibiotics', 'fake antibiotics' and 'counterfeit antibiotics'. Magazine and newspaper articles were searched for with Google and we screened articles related to the initially identified publications to expand our data sources.

Definitions

The subject of overall drug quality has been addressed in several WHO publications.[20–22] Substandard drugs are genuine products

*Correspondence address. Alfa Institute of Biomedical Sciences (AIBS), 9 Neapoleos Street, 151 23 Marousi, Athens, Greece. Tel: +30-694-611-0000; Fax: +30-210-683-9605; E-mail: m.falagas@aibs.gr
†The first two authors have equally contributed to the work.

that have not passed the quality testing protocols previously set for each product.[23] The testing protocols and specifications are published in official pharmacopoeias such as the United States Pharmacopoeia (USP), the European Pharmacopoeia and the WHO International Pharmacopoeia. In addition, many countries have published their own pharmacopoeias. More specifically, substandard drugs have incorrect quantity of active ingredient, which could be secondary to excessive decomposition of active ingredient as a result of high temperature and humidity, and poor quality assurance during the manufacture of pharmaceutical products in less-developed countries.

One special class of substandard drugs is the class of counterfeit drugs. Several countries have their own definitions as to what constitutes a counterfeit drug and there is no consensus. This poses a problem in that what may be considered a counterfeit product in one country will not necessarily be so in another country. The WHO has defined counterfeit drugs as those that are deliberately and fraudulently mislabelled with respect to identity and/or source.[24] Counterfeit products include drugs with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredient or with fake packaging.[25] According to a WHO report, analysis of the content of a drug preparation cannot therefore determine whether or not the sample is counterfeit, because the inclusion of inappropriate quantities of active ingredient during manufacture cannot be identified as deliberate.[15]

Using the above definitions, the variations in active ingredient and weight above or below the recognized limits found in different studies in the current report point to problems in good manufacturing practice, deliberate counterfeiting or poor retail management. Although it is very important to make a clear distinction between the various terms for poor quality medications such as 'counterfeit', 'fake' or 'substandard' drugs in the majority of reports reviewed herein, it was not clarified whether the substandard drug was counterfeit or simply the result of a defect in the manufacturing process.[7,12] Thus, although these two terms are indicative of different problems that must be addressed using different strategies, we use the term 'counterfeit/substandard' drug, whenever the cause of the poor quality medication is not clear.

Causes of poor quality drugs

The poor quality of drugs has been linked to counterfeiting of medicines,[26] chemical instability especially in tropical climates,[27] and poor quality control during manufacture.[28] Many factors contribute to the increased prevalence of substandard and counterfeit medications. Much of the counterfeit drug trade is probably linked to organized crime, corruption, the narcotics trade, the business interests of unscrupulous politicians and unregulated pharmaceutical companies.[29,30] According to the WHO guidelines, factors that influence the prevalence of counterfeit drugs in any particular country include weak or absent drug regulatory authority, absence of a legal mandate for licensing of manufacture/import of drugs, lack of regulation by exporters and within free trade zones, proliferation of small pharmaceutical industries, complex transactions involving many intermediaries, high demand for curative and preventive drugs and vaccines exceeding supply, high prices and inefficient cooperation among stakeholders.[1] The WHO Essential Drug Program has failed in most countries[31] because of personal financial interests at local, national and foreign levels or a black market. Studies indicate that a country's capacity to restrict dangerous drugs depends heavily on its wealth.[9] It is surprising that almost a third of WHO member countries have poor means of controlling counterfeit medications.[30] In these circumstances, the market for counterfeit and substandard drugs becomes a lucrative one. In addition, lack of good manufacturing practices (GMP) is common in local pharmaceutical industries in most developing countries because of many hurdles such as frequent power cuts and shortage of water.[9] In addition to the existence of substandard drugs, assurance of the stability of pharmaceuticals marketed in developing countries (most of which have tropical climates) is a challenging issue as poor storage conditions, high temperature and high humidity conditions generally enhance chemical degradation and may alter the biopharmaceutical properties of the drugs,[32,33] as it has been shown for antibiotics such as tetracyclines.[34] Finally, medicine sellers often exhibit lack of concern about expiration dates and storage conditions, especially in poor settings and in the absence of national control, and this can increase the spread of substandard antimicrobials.[35,36] Manufacture of generic versions of patented drugs for humanitarian reasons may also be abused in developing countries.[37]

In contrast, in developed countries such as the USA, other factors contribute to the spread of counterfeit medicines. For example, it is well known that underinsured or uninsured individuals and some states and local governments are turning to the Internet and foreign pharmacies, particularly what they believe to be safe, reputable Canadian pharmacies, to find less costly medications. However, Internet pharmacies, even licensed ones in Canada, are increasingly buying from foreign sources themselves to meet American demand[38] and thus import of counterfeit and substandard medications may be enhanced. Finally, certain antimicrobials such as artemisin derivatives are not only confined to Asia and Africa but also to other countries of the industrialized world as they have a natural plant origin and tourists commonly buy them in the tropics as a standby treatment and they are also readily available on the Internet.[39]

Prevalence of counterfeit and substandard antimicrobials

The magnitude of the drug-counterfeiting problem is considerable and is difficult to gauge as any true estimate of prevalence is difficult. The WHO estimates that up to 10% of the world's pharmaceutical trade—25% in developing countries—consists of fakes,[18,40] whereas up to 25% of all drugs consumed in poor countries are thought to be counterfeit or substandard, according to the figures from the US Food and Drug Administration (FDA).[41] Many studies have tried to provide estimates of prevalence of counterfeit/substandard antimicrobials [Table S1, available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/)].

A search of the medical literature yields a limited number of primary published research reports concerning counterfeit drugs and much of the information is only found in the grey literature and newspapers. Few published studies describing the prevalence of counterfeit anti-infectives provided sufficient methodological details to interpret the results[6,7,11,12,14,36,42–59] and to

control for potential bias or other factors such as instability of some medicines,[42] whereas only in very few studies, there was random sampling with adequate description of methods.[7] In the current review, we analyse the major studies that have been published regarding counterfeit/substandard antimicrobials (Tables 1 and 2) and also describe the separate categories of these antimicrobials, which include antibiotics, antiviral and antiparasitic agents and vaccines.

Categories of poor quality antimicrobials

There have been reports of substandard/counterfeit drugs in almost all categories of antimicrobials including antibiotics and drugs used to treat tuberculosis, malaria and HIV/AIDS. In the developing world, antibiotics and antiparasitic agents, the drugs that are most needed there, are the counterfeiters' favourites. Other pharmacotherapeutic groups were represented in almost equal frequencies.[60] There are 8–10 times more reports for counterfeit antibiotics and 2–3 times more reports for antiparasitic drugs in comparison with other counterfeit drugs.[60]

Antibacterial agents

A wide range of antibacterial agents have been found to be substandard or fake (Tables 1 and 2). Although no part of the world is exempted, southeast Asia and Africa seem to be particularly plagued by counterfeited antibacterial agents. Especially 'old' antibiotics, such as penicillin, tetracycline, trimethoprim–sulfamethoxazole and chloramphenicol, are among the favoured counterfeited antimicrobials.[6]

Antituberculosis (anti-TB) drugs

A substantial number of anti-TB drugs from several countries, particularly fixed-dose combinations, were found to be substandard [Table S2, available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/)]. In contrast, some other studies have shown good quality of anti-TB drugs.[61–63]

In contrast to other medications, anti-TB drugs are stable under storage conditions, so substandard levels are usually not caused by instability.[61,64] Specific, robust and simple colorimetric methods such as thin-layer chromatography (TLC) can be used for the detection of substandard TB medications, especially in many Third World countries with relatively modest laboratory facilities[63] where resources such as HPLC are not available or routine use is impractical.[65] These substandard anti-TB medications can lead to emergence of drug resistance. Patients receiving a lower therapeutic dose than would be required for their treatment due to a substandard anti-TB drug could lead to drug resistance and treatment failure, despite 100% adherence to the treatment regimen by patients.[65,66]

Antiviral agents

Counterfeit antiviral agents such as oseltamivir and interferon and antiretroviral agents have been reported [Table S3, available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/)]. Most of these reports, however, are anecdotal. More specifically, the recent report of substandard/counterfeit antiretroviral agents either alone or in combinations is very alarming [Table S3, available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/)]. On the other hand, in one study, drug content among generic antiretroviral preparations containing the non-nucleoside reverse transcriptase inhibitor nevirapine has been studied, and no substandard preparations were identified.[51] Importantly, the recent discovery of counterfeit antiretrovirals raises the prospect of a disastrous setback in the treatment of AIDS in areas such as sub-Saharan Africa, unless vigorous action is taken now.

Antiparasitic agents

Antimalarials

The quality of antimalarial drugs is especially crucial, given the widespread nature of the disease and its importance to global public health.[67] As more than 40% of the world's population is at risk of malaria, antimalarial drugs have become a favourite target of counterfeiters. In the last years, many articles reported examples of counterfeit and substandard antimalarial medicines in developing countries (Tables 3 and 4). In a WHO survey of seven African countries, 20% to 90% of antimalarial drugs failed quality testing.[68] Many studies have reported that a considerable proportion of antimalarial drugs obtained from east African countries is of poor quality[7,12,17,69] and that even counterfeits of new antimalarial drugs, such as artesunate and mefloquine, are circulating in southeast Asia.[14,70,71] Counterfeit artemisinins are a significant problem in southeast Asia[14,55,72] and are expected to become a serious problem in Africa where artemisinin combination therapy is being implemented.[39] The problem of antimalarial drug resistance as a result of counterfeit drugs has been addressed in recent reports.[73] Considering the importance of antimalarial treatment in the tropical developing countries, where malaria is endemic and is the first cause of death for children, the presence of counterfeit and substandard drugs on the pharmaceutical market is a risk to the life of millions of people.

Other antiparasitic drugs

Except for antimalarial drugs, there are reports for substandard anthelmintics and other antiparasitic agents such as pentavalent antimonials [Table S4, available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/)], which contribute to poor compliance, therapeutic failure and the appearance of resistance in parasites.[74]

Other antimicrobial agents

Substandard/counterfeit antifungal agents such as griseofulvin and nystatin have been reported in Sierra Leone[75] and Ukraine,[76] respectively. In addition, there have been reports about substandard antiseptics such as betadine.[77] Finally, substandard/counterfeit vaccines have been reported [Table S4, available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/)] and according to a study, only 3 of 10 vaccine-producing countries in the Asia-Pacific region were assessed to have internationally acceptable standards for vaccine production and quality control and effective regulatory mechanisms.[78]

Table 1. Major studies regarding counterfeit/substandard antibiotics

Year (reference)	No. of drugs analysed	Country	Category of drugs studied	Method of detection of counterfeit/substandard drug	Results	Characteristics of counterfeit/substandard drugs	Pharmaceutical companies involved/country of manufacture
Hu *et al.*[159]	NR	China	macrolides: erythromycin, clarithromycin, roxithromycin, azithromycin, erythromycin ethylsuccinate, kitasamycin, luecomycin A_3, acetylspiramycin, acetyl-kitasamycin, midecamycin and meleumycin	FCIS consisting of two colour reactions based on functional groups in molecules of macrolide antibiotics and two TLC methods were developed for screening of fake macrolide drugs	two lots of capsules and one lot of granule had no active ingredients imitating erythromycin ethylsuccinate capsule and azithromycin granule, respectively, one lot of erythromycin tablets imitating roxithromycin tablets and two lots of meleumycin capsule imitating midecamycin capsule	no active ingredient, wrong ingredient, no colour change in sulphuric acid reaction	China
Kayumba *et al.*[32]	33	Rwanda and Tanzania	essential antimicrobials (amoxicillin capsules, metronidazole tablets, TMP–SMX tablet)	commercially available drug formulations, USP 24 dissolution tests, HPLC	at the time of purchase, the drug content of all the formulations was within the limits recommended by the USP 24, but after 6-month storage, the drug content of one sulfamethoxazole/trimethoprim was found to be substandard. Immediately after purchase, four formulations (three sulfamethoxazole/trimethoprim and one sulfadoxine/pyrimethamine combination) failed the USP 24 dissolution test. Except for three metronidazole, dissolution tests performed after 6 months of storage under simulated tropical conditions showed that drug release remained within the USP 24 recommended values. In total, 24% of the sampled formulations (8/33) failed the dissolution test	poor *in vitro* drug release profiles and dissolution [four formulations (three sulfamethoxazole/trimethoprim and one sulfadoxine/pyrimethamine combination)]. Some of the formulations tested were not stable in terms of drug content (one sulfamethoxazole/trimethoprim) and dissolution (three metronidazole formulations), upon storage under simulated tropical conditions	TPI (metronidazole), Holden Medica (metronidazole), Labophar (TMP–SMX, sulfadoxine and pyrimethamine), Shalina (sulfamethoxazole), ACE (TMP–SMX). Rwanda and Tanzania
Syhakhang *et al.*[42]	300	Laos	ampicillin, tetracycline	HPLC, potentiometric titration and ultraviolet spectrophotometry (UV). The identity was confirmed by TLC, UV or colour reactions	the percentage of substandard drugs decreased significantly from 46% to 22% (66 out of 300) between 1997 and 1999 ($P < 0.001$). Substandard ampicillin and tetracycline were reduced significantly from 67% to 9% and from 38% to 12%, respectively ($P < 0.001$). In total, 3% versus 1% contained no active ingredient, 12% versus 4% had too little or too much active ingredient and 35% versus 14% had weight variation outside pharmacopoeial limits	no active ingredient (ampicillin and tetracycline), too little (ampicillin) or too much (tetracycline) active ingredient, weight variation outside pharmacopoeial limits	24% (23 out of 97) of the drugs from Lao factories, 17% (24 out of 143) of the drugs from Thailand and 47% (17 out of 36) of the drugs of unknown origin were substandard
Prazuck *et al.*[36]	21	Northern Myanmar	antimicrobials (benzathine benzylpenicillin, ceftriaxone, chlortetracycline, ciprofloxacin, TMP–SMX doxycycline and erythromycin)	drug quantitative analysis was performed with titrimetry and visible UV spectrophotometry. Qualitative analysis was performed with TLC	among the 21 different specialty products, only 3 displayed the official 'registered' label. Three drugs were expired and the expiration date was not available for six others. One product did not contain the active drug declared (chlortetracycline) and did not show any *in vitro* activity against bacteria. Seven of 21 products (33%) did not contain the stated dosage (one more than stated dosage and six less than stated dosage). The highest deficit observed was 48% in two products (co-trimoxazole and benzylpenicillin). The dosage was not available for five drugs. As a result, only 8 of 21 products (38%) did not contain the stated dosage of active drug	inappropriate labelling, expired drug, no active ingredient (chlortetracycline), reduced active ingredient	Lombisin, Unicorn, China (chlortetracycline), Yong Fong, Myanmar (co-trimoxazole), China (benzylpenicillin), Helm Pharmaceutical GMBH, Hamburg, Germany (benzathine benzylpenicillin), Cadila Lab, Ahmedabad, India, Dr Reddy's Lab, Bollaram, India (ciprofloxacin), Remedica Ltd, Limassol, Cyprus (erythromycin and doxycycline), ICPA Lab Ltd, Bombay, India (TMP–SMX)
Taylor *et al.*[12]	581	Nigeria	antibacterial and antituberculosis drugs	HPLC	for all groups of drugs, antibacterial and antituberculosis agents, more than 50%	zero (metronidazole suspension), or very low [ampicillin (syrup and capsules),	most drugs that failed to pass the test were manufactured

Continued

Table 1. *Continued*

Year (reference)	No. of drugs analysed	Country	Category of drugs studied	Method of detection of counterfeit/ substandard drug	Results	Characteristics of counterfeit/ substandard drugs	Pharmaceutical companies involved/country of manufacture
					failed to comply with specifications. For some individual drug preparations, all samples assayed were within pharmacopoeial limits. These included trimethoprim and sulfamethoxazole tablets. No metronidazole suspension met pharmacopoeial specifications. Several antibacterial preparations contained very low quantities of active ingredient (ampicillin and amoxicillin 24% to 40%), and for five metronidazole suspension preparations, no active ingredient was detected	amoxicillin (syrup), pyrimethamine and sulfadoxine (syrup), cloxacillin (syrup and capsules) and ampicillin and cloxacillin (syrup and capsules)] quantities of active ingredient	in countries such as Malaysia, Switzerland, China, Holland, Nigeria, Pakistan, Romania, India, and UK or were of unknown origin
Okeke and Lamikanra[160]	5	Nigeria	five samples of ampicillin capsules		three of the five (60%) capsule samples from dispensing points were found to be of lower quality than the officially prescribed standards of pharmaceutical quality. The quality lapses observed were sufficient to bring about determinable differences in biological availability		
Laserson *et al.*[65]	71	Colombia, Estonia, India, Latvia, Russia and Vietnam	INH and RIF single and FDC formulations	TLC kit	overall, 10% (4/40) of all samples, including 13% (4/30) RIF samples, contained <85% of stated content. More FDCs (5/24, 21%) than single-drug samples (2/16, 13%) were substandard. Two RIF samples and one INH sample had an extra component	reduced content of active ingredient, extra component	NR
Kenyon *et al.*[156]	13	Republic of Botswana	FDC anti-tuberculosis (TB) drugs	TLC as a screening method, and UV or LC as confirmation	all 13 FDCs contained the stated drugs. However, four (31%) were substandard, including two (15%) with low rifampicin content, one (8%) with excessive rifampicin and one (8%) with excessive pyrazinamide. Both FDCs with low rifampicin contained four drugs and failed TLC screening. The FDC with excessive rifampicin was not detected by TLC screening. Using UV as the gold standard, the sensitivity of TLC for low rifampicin was 2/2 (100%) and the specificity was 9/10 (90%)	reduced (rifampicin) or excess (rifampicin and pyrazinamide) content of active ingredient	NR
Pillai *et al.*[161]	10 FDC formulations	South Africa	FDC anti-tuberculosis formulations	NR	C_{max} for rifampicin in 7 of 10 FDC formulations was not found to be bioequivalent to the reference administered as loose (separate) formulations	the poor relative bioavailability of rifampicin from some FDCs has been documented. The implications for tuberculosis programmes are extremely serious and warrant urgent attention	NR
Stenson *et al.*[48]	366	Laos	ampicillin (tablets and capsules) and tetracycline (tablets and capsules)	three tests were used: identity, assay and measurement of weight variation. The identity was confirmed by TLC, UV and colour reactions. Titrimetric, UV and HPLC methods were used for assay. Potentiometric titration method	12 (3.3%) out of the 366 drugs contained no active ingredient, 42 (11.5%) had levels of active ingredient outside acceptable limits in assay, 128 (35.0%) had excessive weight variation and 4 (1.1%) were managed badly in the pharmacy, 67% of ampicillin samples and 38% of tetracycline had bad quality	no active ingredient (ampicillin), low concentration of active ingredient (ampicillin and tetracycline), weight variation outside pharmacopoieal limits (all), bad retail management (ampicillin)	out of the 61 samples that were found to contain no active ingredient or to be substandard according to the assay, only 37 were labelled. Of these, 20 originated from Laos, 5 from Thailand and 3 from

Continued

Table 1. *Continued*

Year (reference)	No. of drugs analysed	Country	Category of drugs studied	Method of detection of counterfeit/ substandard drug	Results	Characteristics of counterfeit/ substandard drugs	Pharmaceutical companies involved/country of manufacture
							Vietnam, whereas 9 were of unknown origin
Nazerali and Hogerzeil[83]	789 samples of 26 brands of 13 essential drugs	Zimbabwe	injectable benzylpenicillin, amoxicillin, ampicillin, doxycycline, phenylmethoxypenicillin and tetracycline	NR. Drug quality was measured by level of active ingredient as percentage of stated content and by compliance (pass/fail) with assay standards of the BP. Drug stability was measured by comparing mean assay values at central and rural levels and by paired analysis of central and rural samples of the same batch	poor initial quality accounted for problems in injectable ampicillin (2/10 central samples failed, with 87% and 91% content). An aqueous formulation of injectable procaine benzylpenicillin showed moderate instability with 4% (1% to 6%) loss after 4.3 months but the assay remained within pharmacopoeial limits	reduced level of active ingredient	NR
Shakoor *et al.*[7]	96 (81 Nigeria, 15 Thailand)	Nigeria, Thailand	amoxicillin, tetracycline, TMP–SMX, ampicillin–cloxacillin	HPLC	36% of samples from Nigeria and 40% of samples from Thailand were substandard with respect to British Pharmacopoeial limits. One amoxicillin sample from Nigeria contained no active ingredient at all	zero (amoxicillin) or very low (amoxicillin, TMP–SMX, ampicillin–cloxacillin) quantities of active ingredient	the countries of origin were Nigeria, Italy, India, Pakistan, Thailand and UK, but no patterns emerged with respect to quality of product and country of origin
Roy[10]	137 brands	Bangladesh	ampicillin, TMP–SMX	NR	a significant proportion of a variety of drug preparations was substandard (27%). Ten brands of ampicillin were found to be substandard in this study and 8 of them had already been assessed as substandard by the regulatory authorities. This was also true of the two brands of co-trimoxazole suspension found to be substandard	it appeared that active ingredients had been deliberately kept below the required levels	NR
Taylor *et al.*[111]	40	Nigeria	antibacterial capsules and suspensions of amoxicillin		two amoxicillin capsules (0% and 50%) contained $\leq$50% of the stated amount of active ingredient. Ten other samples outside the BP range had at least 90% or up to 126%	the reason why BP requirements were not met is unknown. Decomposition is not likely to be a major factor (no large amounts of decomposition products found), poor quality assurance probably plays a part but the very small amounts found in some samples point to fraudulent manufacture or tampering	
Santosh *et al.*[162]	7 brands	India	tetracycline: chemical estimation of seven different marketed brands of tetracycline/HCl capsules for tetracycline content	fluorimetric method	chemical estimation of seven different marketed brands of tetracycline/HCl capsules for tetracycline content showed that six brands were not meeting the pharmacopoeia prescribed standards. The power content of four brands was well below the labelled amount of the standard drug. Comparative analysis of bioavailability of substandard versus standard product indicates that the use of substandard tetracycline products in undernourished subjects may lead to therapeutic failures and/or result in the development of resistant microorganisms	the dissolution rate and disintegration time of substandard drugs were in accordance with USP specifications. The bioavailability of substandard product as determined from 48 h urinary tetracycline excretion was significantly lower when compared with standard product both in well-nourished and in undernourished subjects. The plasma steady-state concentrations with the substandard product were below the generally recommended MICs, more so in undernourished subjects	NR

NR, not reported; FCIS, fast chemical identification test; TLC, thin-layer chromatography; TMP–SMX, trimethoprim–sulfamethoxazole; USP, United States Pharmacopoeia; UV, ultraviolet spectrophotometry; INH, isoniazid; RIF, rifampicin; FDC, fixed-dose combination; LC, liquid chromatography and BP, British Pharmacopoeia.

Table 2. Categories and characteristics of reported counterfeit/substandard antibiotics

Category of antimicrobial	Countries where counterfeit/substandard drug was reported	Characteristics of counterfeit/substandard antimicrobials: no active ingredient	reduced active ingredient	wrong active ingredient	inappropriate labelling	others
Penicillins						
penicillin	Cambodia,[80] Madagascar,[46] Brazil,[93] Northern Myanmar[36]	Madagascar,[46] Brazil[93]	Brazil,[93] Northern Myanmar[36]		Cambodia,[80] Northern Myanmar[36]	
ampicillin	Laos,[42,48] Vietnam,[163] India,[164] Senegal,[49] Sierra Leone,[75] Bolivia,[165] Lebanon,[166] Indonesia,[93] Nigeria,[12] Zimbabwe,[83] Bangladesh[10]	Laos,[42,48] Senegal,[49] Sierra Leone,[75] Lebanon[166]	Bolivia,[165] Laos,[42,48] Indonesia,[93] Nigeria,[12] Zimbabwe,[83] Bangladesh[10]	Vietnam,[163] India[164]	Laos[48]	weight variation outside pharmacopoeial limits,[42,48] bad retail management[48]
ampicillin–clavulanate/ ampicillin–cloxacillin	Germany,[81] China,[167] Lebanon,[166] Nigeria,[12] Thailand[7]	China,[167] Lebanon[166]	Nigeria,[12] Thailand[7]			
amoxicillin	China,[167] Nepal,[168] India,[164] Thailand,[7] Sierra Leone,[75] Nigeria,[7,12,111,169,170] Cameroon,[46,169] Guinea[91]	Nepal,[168] Sierra Leone,[75] Cameroon,[46] Nigeria,[7] Thailand[7]	Nigeria,[12,111,169] Thailand[7]		Guinea[91]	
amoxicillin–clavulanate/ amoxicillin–cloxacillin	Philippines,[168] India[77,171]					
cloxacillin	Nigeria[12]		Nigeria[12]			
Cephalosporins						
cefador	USA[81]					
cefalexin	China,[172] Sierra Leone,[75] Brazil[81]	China[172]				
cefazolin	Ukraine,[76] Russia[81]	Ukraine[76]		Ukraine,[76] Russia[81]		
cefradine	USA[29]	USA[79]				
ceftazidime	Vietnam,[173] Phillipines,[168,171] India,[171] Mexico,[174] Russia[175]	Vietnam,[173] Russia[175]		Vietnam[173] (streptomycin)		
cefuroxime axetil	China,[176] India[164]			China[176] (cefuroxime sodium)		
cefotaxime	Russia[168]			Russia[168]		

Continued

Table 2. *Continued*

Category of antimicrobial	Countries where counterfeit/substandard drug was reported	Characteristics of counterfeit/substandard antimicrobials: no active ingredient	reduced active ingredient	wrong active ingredient	inappropriate labelling	others
Macrolides						
erythromycin	India,[159,171] Nigeria,[169] China,[159] Northern Myanmar[36]	China[159]	Northern Myanmar[36]			
azithromycin	China,[159] Russia,[119] Ukraine,[76] other[165]	China,[159] Russia,[119] Ukraine[76]				
roxithromycin	India,[159,171] China,[159] Russia,[76] Germany[76]		China,[159] contained erythromycin			
Chloramphenicol	Burma,[6] Cambodia,[80] India,[77] Nigeria,[169] Cameroon[46]	Nigeria,[169] Cameroon[46]			Burma[6] Cambodia[80]	
Tetracyclines	Burma,[6,36] Laos,[42] Cambodia,[54,57,80] India,[77,171] Sierra Leone,[75] Nigeria,[169] Brazil,[93] USA,[155] Northern Myanmar[36]	Burma,[6,36] Laos,[42] Cambodia,[54,57,80] Brazil,[93] Northern Myanmar[36]	Brazil,[93] Laos,[42] Northern Myanmar[36]		Burma,[6,36] Cambodia,[54,57,80] Nigeria,[170] Northern Myanmar[36]	unregistered product,[59] 26.6% of tetracycline tablets failed disintegration tests,[59] too much active ingredient,[42] weight variation outside pharmacopoeial limits,[42] expired drug,[36] reduced bioavailability and excessive degradation[34,162]
Sulphonamides co-trimoxazole	Thailand,[177] Burma,[6] Cambodia,[47] Nigeria,[169] Sierra Leone,[75] Nigeria,[170] Cameroon,[46] Cote d'Ivoire,[58] Rwanda and Tanzania,[32] Nigeria, Thailand,[7] Bangladesh,[10] Russia[178]	Cambodia,[47] Cameroon,[46] Thailand,[177,178] Russia[178]	Cote d'Ivoire,[58] after 6-month storage, the drug content of one sulfamethoxazole/trimethoprim was found to be substandard,[32] Nigeria, Thailand,[7] Bangladesh[10]	Burma[6]	Cote d'Ivoire[58]	poor *in vitro* drug release profiles and dissolution for three formulations of sulfamethoxazole/trimethoprim[32]
sulfamethizole sulfamethazine[155]	Australia,[92] Nigeria,[170] sulfamethazine[155]	sulfamethazine[155]	Australia[92]	Australia,[92] Nigeria[170]		
trimethoprim	Ukraine[175]					
Quinolones						
ciprofloxacin	India,[77,164,171,179] Nigeria,[170] Germany,[81] Haiti.[92] Ciprofloxacin is a frequently faked drug often sold via the Internet,[38] Northern Myanmar[36]	[38]		Northern Myanmar[36]	Northern Myanmar[36]	substandard drug induced bouts of diverticulitis,[92] inappropriate expiration date[36]

Continued

Table 2. *Continued*

Category of antimicrobial	Countries where counterfeit/substandard drug was reported	Characteristics of counterfeit/substandard antimicrobials				
		no active ingredient	reduced active ingredient	wrong active ingredient	inappropriate labelling	others
ofloxacin	China,[180] Pakistan,[52] Germany[81]			China[180]		
nalidixic acid	India[171]					
Metronidazole	Cambodia,[47] Nigeria,[169] Nigeria,[12] Cameroon,[46] Rwanda and Tanzania,[32] Kenya[181]	Cambodia,[47] Cameroon,[46] Nigeria[12]		Nigeria[170]		some of the formulations tested were not stable in terms of dissolution upon storage under simulated tropical conditions[32]
Aminoglycosides						
gentamicin	Nigeria,[169] Republic of Mauritius,[99] USA,[163] Europe,[81] counterfeit gentamicin sulphate within the USA[29,139,155]	USA[29,139,155,]	USA[29,139]			investigation showed gentamicin eye drops to be contaminated—*Pseudomonas aeruginosa* and other virulent bacteria were cultured from these vials[99]
neomycin	Nigeria,[169] Europe[81]				Nigeria,[75] Europe[81]	
amikacin	Cote d'Ivoire,[58] India[165]				Cote d'Ivoire[58]	
Lincosamides						
clindamycin/lincomycin	Germany,[81] China,[159] Sierra Leone,[75] Mexico[29,79]		Mexico drug diluted with contaminated water[29,79]			

Table 3. Major studies of substandard/counterfeit antimalarials

Year (reference)	No. of drugs analysed	Country	Category of drugs studied	Method of detection of counterfeit/ substandard drug	Results	Characteristics of fake/substandard drugs	Pharmaceutical companies involved/country of manufacture
Gaudiano *et al.*[82]	NR	Congo, Burundi and Angola	antimalarials (chloroquine, quinine and mefloquine)	a reversed-phase liquid chromatographic method	only 88.6% of declared active substance (quinine tablets) was found. Moreover, a high quantity of impurities was observed with respect to the reference preparation, indicating some degradation probably due to the bad storage conditions	in the majority of the cases, samples were without both primary and secondary packaging and tablets were packaged in a little plastic bag or enveloped with paper and the expiry date and strength of the active substance were written on a piece of paper. All samples were within the period of validity on the basis of the declared expiry date. Only for some samples, the company name and the lot number were available	Congo, Burundi and Angola
Lon *et al.*[59]	451	Cambodia	antimalarials [quinine sulphate tablets, chloroquine phosphate tablets, artesunate tablets, mefloquine hydrochloride tablets, tetracycline tablets/capsules, dihydroartemisinin (DHA) tablets and artemether tablets]	Mini-lab kits, TLC and disintegration tests	79% of these were not registered at the Cambodia Department of Drugs and Food (DDF). Twenty-seven percent of the samples failed the TLC and disintegration tests, all of them were unregistered products. The TLC and disintegration test results showed that the average failure rate of quinine was 71.7%, artesunate 19.7% and tetracycline 26.6%, followed by chloroquine 8.5% and mefloquine 7.7%. In this study, only 22 samples of DHA and 2 samples of artemether passed the tests. The overall result showed that 122 (27.1%) samples failed TLC and/or disintegration tests	unknown origins, wrong or incomplete labelling hologram similar to the genuine one, they were in different containers from the original ones, wrong active pharmaceutical ingredients, no active pharmaceutical ingredients, unregistered products	197 (43.7%) were labelled as produced in Thailand, 102 (22.6%) in China, 19 (4.2%) in Cambodia, 17 (3.8%) in Switzerland and 48 (10.6%) were claimed to be produced in Germany, India, Australia, France, Vietnam, Hong Kong, Korea, The Netherlands, England, Belgium, Cyprus and Malaysia. The remaining 68 samples were of unknown origin. Brainy Pharmaceutical, Guillin Pharmaceutical Works in China
Hebron *et al.*[182]	11 brands of one drug	Tanzania	antimalarials (11 brands of SP combination tablets)	HPLC, physical methods	all the brands passed all the quality specifications of the USP and BP in terms of hardness, friability, disintegration, assay and dissolution test, except for three brands that failed the hardness, disintegration or friability tests. One brand failed the hardness and disintegration test, one failed the hardness test, whereas another failed the friability test. All brands passed the assay test for the content of SP.	three brands that failed the hardness, disintegration or friability tests. One brand failed the hardness and disintegration test, one failed the hardness test, whereas another failed the friability test.	three of the brands were locally manufactured in Tanzania, whereas the remaining eight were imported. Four were from India, two from Kenya and two from Europe, where one of these was the innovator brand, Fansidar®
Amin *et al.*[90]	116	Kenya	antimalarials (SP and AQ)	spectrophotometric assay (AQ), HPLC (SP), dissolution apparatus	of 116 SP and AQ samples analysed, 47 (40.5%) did not meet the USP specifications for content and/or dissolution. Overall, ~45.3% of SP and 33.0% of AQ samples were found to be substandard. Of the substandard SP products, 55.2% were suspensions, whereas 61.1% of the substandard AQ products were tablets. Most SP failures were because of the pyrimethamine component	reduced content of active component, reduced dissolution	Kenya
Dondorp *et al.*[55]	188	Southeastern Asia Myanmar (Burma), Lao PDR, Vietnam,	antimalarials (artemisinin derivatives and mefloquine)	Fast Red TR dye technique, HPLC, based on packaging characteristics	of the 188 tablet packs purchased that were labelled as 'artesunate', 53% did not contain any artesunate. Of the 44 mefloquine samples, 9%	fake hologram (artemisinin), the visual characteristics (mefloquine) of the fake tablets were undistinguishable from the genuine product	Guilin Pharma, Mepha Ltd, Aesch-Basel, Switzerland (mefloquine)

Continued

Table 3. *Continued*

Year (reference)	No. of drugs analysed	Country	Category of drugs studied	Method of detection of counterfeit/ substandard drug	Results	Characteristics of fake/substandard drugs	Pharmaceutical companies involved/country of manufacture
		Cambodia and Thailand			contained <10% of the expected amount of active ingredient		
Basco[53]	284	Cameroon	antimalarials (chloroquine, quinine and SP)	a simple colour reaction test and semi-quantitative TLC	fifty (38%) of 133 chloroquine, 52 (74%) of 70 quinine and 10 (12%) of 81 antifolates had no active ingredient, an insufficient active ingredient, the wrong ingredient or unknown ingredient(s). The primary screening based on colour reaction showed that 42 (32%) of 133 chloroquine samples were counterfeit. Further analysis by TLC showed that 8 (9%) of 91 colour-positive samples contained <80% of the reference standard. The colour reaction suggested that 63 (90%) of 70 quinine samples contained a quinoline-type drug, the other 7 samples were clearly counterfeit with unknown ingredients. However, on further analysis, 45 of 63 colour-positive quinine samples were substandard. Of 78 SP samples, 10 (13%) had a negative colour reaction. There were no substandard medications of SP samples on further analysis of positive colour reaction	no active ingredient, an insufficient active ingredient, the wrong ingredient or unknown ingredient(s)	could not be specified with precision—unknown origin in majority of cases
Kayumba *et al.*[32]	33	Rwanda and Tanzania	antimalarials (quinine tablets and SP tablets), antimicrobials (amoxicillin capsules, metronidazole tablets, sulfamethoxazole/ trimethoprim tablet)	commercially available drug formulations, USP 24 dissolution tests, HPLC	at the time of purchase, the drug content of all the formulations was within the limits recommended by the USP 24, but after 6-month storage, the drug contents of one TMP–SMX and one quinine formulation were found to be substandard. Immediately after purchase, four formulations (three TMP–SMX and one SP combination) failed the USP 24 dissolution test. Except for three metronidazole and one quinine formulations, dissolution tests performed after 6 months of storage under simulated tropical conditions showed that drug release remained within the USP 24 recommended values. In total, 24% of the sampled formulations (8/33) failed the dissolution test	poor *in vitro* drug release profiles and dissolution [four formulations (three TMP–SMX and one SP combination)]. Some of the formulations tested were not stable in terms of drug content (one TMP–SMX and one quinine formulation) and dissolution (three metronidazole and one quinine formulations), upon storage under simulated tropical conditions	TPI (metronidazole), Holden Medica (metronidazole), Labophar (TMP–SMX, quinine sulphate, SP), Shalina (sulfamethoxazole), ACE (TMP–SMX), Elys Chemicals (quinine sulphate). Rwanda and Tanzania
Syhakhang *et al.*[42]	300	Laos	antimalarials (chloroquine)	HPLC, potentiometric titration and UV. The identity was confirmed by TLC, UV or colour reactions	of the 34 substandard chloroquine samples, 16 were manufactured as sugar-coated tablets by Lao factories and had tablet weight outside standard. Eight out of 35 chloroquine	too much active ingredient (tetracycline chloroquine), weight variation outside pharmacopoeial limits	24% (23 out of 97) of the drugs from Lao factories, 17% (24 out of 143) of the drugs from Thailand and 47% (17 out of 36) of the drugs of unknown origin were substandard

Continued

Table 3. *Continued*

Year (reference)	No. of drugs analysed	Country	Category of drugs studied	Method of detection of counterfeit/ substandard drug	Results	Characteristics of fake/substandard drugs	Pharmaceutical companies involved/country of manufacture
					samples (tablets) from Thailand also had weight variation outside standard. Among these, one with high tablet weight had also very high content of active ingredient. One chloroquine from France contained too high a level of active ingredient		
Minzi *et al.*[183]	33	Tanzania	antimalarials (SP and AQ tablets)	TLC and HPLC	all samples passed the identity test. 12 of 33 (36%) samples were of poor quality. In total, 10 of 33 (30%) samples, i.e. eight of 33 SP and two of 33 AQ, did not meet the USP specifications for dissolution. Among the AQ samples collected, 2 of 15 (13%) failed the dissolution test but all passed the assay for content, whereas 2 of 18 (11%) and 8 of 18 (44%) SP samples failed the assay for content and dissolution tests, respectively	the major reason for a drug being substandard was because of low dissolution rate of the active ingredients, whereas two samples had low content of active ingredient	SP samples of poor quality originated from Cyprus, Tanzania, India and AQ samples of poor quality originated from Kenya
Rimoy *et al.*[88]	2	Tanzania	antimalarials-sugar-coated (Dawaquin) and a plain formulation (Shellyquine) of chloroquine phosphate	HPLC	Shellyquine was significantly more bioavailable than Dawaquin ($P < 0.001$). Although the C_{pmax} for Dawaquin was higher than the required therapeutic level for sensitive *Plasmodium falciparum*, its blood levels may not guarantee a rapid clearance of parasites	reduced bioavailability of sugar-coated chloroquine phosphate	NR
Risha *et al.*[84]	22	Tanzania	antimalarials (SP, chloroquine)	HPLC, accelerated stability test	all formulations passed the pharmacopoeia requirements for the drug content. However, seven formulations (three acetylsalicylic acid, two SP and two paracetamol) failed to meet the USP 24 tolerance limits for dissolution. Another five formulations (three paracetamol and two chloroquine) failed to meet the dissolution tolerance limits after being subjected to an accelerated stability test under simulated tropical conditions for 6 months	reduced dissolution. Reduced stability to storage in tropical conditions for 6 months: chloroquine formulations that failed the stability test had a more than 40% reduction in the amount of drug released after 3 and 6 months of stability testing	Shelys, Flamingo (SP), Ellys (pyrimethamine), Rhône Poulenc Rorer, TPI (chloroquine tablets)
Newton *et al.*[14]	104	Southeastern Asia Cambodia, Laos, Myanmar (Burma), Thailand and Vietnam	antimalarials (artesunate)	Fast Red TR dye technique. Classification of samples based on physical characteristics including holograms, bar codes, printing and crimping (the impression of text into foil), packages by independent observer	of 104 shop-bought 'artesunate' samples from these countries, 39 (38%) did not contain artesunate and were counterfeit. Overall, 30 (29%) of the blisterpacks collected contained no artesunate. The results of examining the packaging of 84 samples gave complete agreement with the dye test. The authors suggest that in some tablets, artesunate may have been substituted with chloroquine based on the bitter taste of the tablets	superficially similar in colour, size and inscription, heavier than the genuine tablets, had disagreeable bitter taste, cheaper than their genuine counterparts, forged or no holograms on fake artesunate blisterpacks	Guilin Pharma (China) or repackaged by Atlantic Pharmaceuticals (Bangkok, Thailand)
Sulaiman *et al.*[184]	34	Sudan	antiparasitic agents (praziquantel)	NR	15 of the 19 brands were of satisfactory quality for all variables assessed (content of active substance, impurities, disintegration and	reduced gross mean weight of each tablet, the accompanying leaflet was in poor English and did not identify the name or	International Ltd Co., Canada

Continued

Table 3. *Continued*

Year (reference)	No. of drugs analysed	Country	Category of drugs studied	Method of detection of counterfeit/ substandard drug	Results	Characteristics of fake/substandard drugs	Pharmaceutical companies involved/country of manufacture
					dissolution). Three brands did not meet the standards of BP, USP or both, for impurities and formulation characteristics, but these issues were of limited magnitude and possibly not critical for safety and efficacy of the drug. One brand, however, was counterfeit and contained no active substance	address of the manufacturer, no active substance	
Taylor *et al.*[12]	581	Nigeria	antimalarials, anthelmintics (mebendazole)	HPLC	48% of the samples contained amounts of active ingredient outside the appropriate limits. For all groups of drugs, more than 50% failed to comply with specifications. For some individual drug preparations, all samples assayed were within pharmacopoeial limits. These included proguanil tablets, and quinine hydrochloride injection and syrups. No pyrazinamide tablets met pharmacopoeial specifications	zero (pyrazinamide tablets) or very low (pyrimethamine and sulfadoxine syrup) quantities of active ingredient	most drugs that failed to pass the test were manufactured in countries such as Malaysia, Switzerland, China, Holland, Nigeria, Pakistan, Romania, India and UK or were of unknown origin
Rozendaal[71]	NR	Cambodia	antimalarials (mefloquine, artesunate)	NR	most of the bottles with mefloquine tablets and about half of the artesunate blister packs sampled seemed to be fakes. For mefloquine and artesunate, two different varieties of fakes were found: a first-generation fake that was easy to distinguish from the genuine product and a second-generation fake that much more closely resembled the genuine product. A total of 242 drug vendors and pharmacies were mapped in 12 marketplaces, and 133, about half in each marketplace, were selected randomly for investigation. Fake artesunate was sold by 71% (86% sold the genuine product) and fake mefloquine by 60% (61% sold the genuine variety)	the fakes were frequently preferred by patients and village health providers because of the lower price. Given their widespread use, the fake malaria drugs are probably a major cause of mortality and morbidity due to malaria in Cambodia	mefloquine in Australia and artesunate in China
Ogwal-Okeng *et al.*[69]	53 tablets and 49 injectable forms	Uganda	antimalarials (chloroquine)	pharmacopoeial assays, visual and potentiometric analysis technique	up to 30% of the tablet samples and 33% of injection samples contained less than the stated amount of the active ingredient. 25% of tablet samples and 29% of the injection samples contained more than the standard concentration of active ingredient	reduced level of active ingredient, excess level of active ingredient	the majority of samples were manufactured in India (52%) and Kenya (18%). Other countries of origin were Uganda, China, Cuba and Pakistan
Stenson *et al.*[48]	366	Laos	antimalarials (chloroquine tablets)	three tests were used: identity, assay and measurement of weight variation. The identity was confirmed by TLC, UV and colour reactions. Titrimetric, UV and HPLC methods were used for assay	49% of chloroquine samples had bad quality	no active ingredient, low concentration of active ingredient, above indicated concentration of active ingredient, weight variation outside pharmacopoieal limits	most of the samples that were found to contain no active ingredient or to be substandard according to the assay were unlabelled. Those that were labelled originated from Laos, Thailand and Vietnam or were of unknown origin
van Wyk *et al.*[185]	3 brands	South Africa	anthelmintics (three rafoxanide products)	the drugs were tested against a known susceptible strain of	one of the three commercial formulations (of highly reputable companies) was markedly	reduced efficacy, sources of supply of different batches of active ingredient (with the result that the companies	South Africa

Continued

Table 3. *Continued*

Year (reference)	No. of drugs analysed	Country	Category of drugs studied	Method of detection of counterfeit/ substandard drug	Results	Characteristics of fake/substandard drugs	Pharmaceutical companies involved/country of manufacture
				Haemonchus contortus in sheep	substandard, with an arithmetic mean efficacy of 66.2% when compared with the efficacy of the other two, which also differed significantly from one another (Mann–Whitney, $P = 0.01$)	buying anthelmintics from them have no way of telling when a source of supply is changed)	
Shakoor *et al.*[7]	96 (81 Nigeria, 15 Thailand)	Nigeria, Thailand	antimalarials (chloroquine)	HPLC	36% of samples from Nigeria and 40% of samples from Thailand were substandard with respect to BP limits. Five substandard preparations (two chloroquine samples from Nigeria and three chloroquine samples from Thailand) contained no active ingredient at all	zero (chloroquine) or very low (chloroquine) quantities of active ingredient	the countries of origin were Nigeria, Italy, India, Pakistan, Thailand, UK, but no patterns emerged with respect to quality of product and country of origin
Abdi *et al.*[17]	NR	Tanzania	antimalarials (chloroquine tablets of nine different brands)	NR	tablets were tested for active ingredients and for dissolution rate. All brands complied with the USP requirements for amount of chloroquine (>97%). The eight brands of ordinary tablets also passed the dissolution test, the sugar-coated tablets did not (only 39% dissolved in 45 min, required minimum 75%)	the sugar-coated tablets of chloroquine did not have appropriate dissolution rate. Dissolution is an important determinant of bioavailability and may have resulted in this reported chloroquine treatment failure in a patient with malaria	Tanzania
Petralanda[157]	12 samples (9 different manu-facturers)	Amazonian region	antimalarials (primaquine)	NR	50% of the samples did not conform to the USP qualitative requirements and none conformed to the quantitative requirements. One of three samples analysed by the BP qualitative criteria did not conform to those either. Chemical concentration of the active ingredient varied from 19% to 168% of the concentration indicated on the label, which made the total dose of primaquine received by the patients either insufficient or excess (toxic levels)	insufficient or excess chemical concentration of the active ingredient, reduced quality	NR
Taylor *et al.*[111]	40	Nigeria	antimalarials (tablets and syrup formulations of chloroquine)		three samples of chloroquine tablets (0%, 0%, 42%) contained ≤50% of the stated amount of active ingredient	the reason why BP requirements were not met is unknown. Decomposition is not likely to be a major factor (no large amounts of decomposition products found), poor quality assurance probably plays a part but the very small amounts found in some samples point to fraudulent manufacture or tampering	NR

NR, not reported; TLC, thin-layer chromatography; USP, United States Pharmacopoeia; BP, British Pharmacopoeia; SP, sulfadoxine–pyrimethamine; AQ, amodiaquine; UV, ultraviolet spectrophotometry.

Table 4. Categories and characteristics of counterfeit/substandard antimalarials

Category of antimicrobial	Countries where counterfeit/substandard drug was reported	Characteristics of counterfeit/substandard antimicrobials: no active ingredient	reduced active ingredient	wrong active ingredient	inappropriate labelling/packaging	others
Chloroquine	Africa in Cameroon,[53] Cote d'Ivoire,[58] Guinea,[46] Sierrra Leone,[75] Sudan,[17] Nigeria,[7] Uganda[69] and Tanzania[84]	7,17,46,48,53, 59,91,111	7	46,53	59	very high concentration of active ingredient,[48,58] poor dissolution due to storage,[84] reduced bioavailability,[17] weight variation outside the standard, especially in sugar-coated brands of chloroquine[1]
Primaquine	Amazon region of South America,[157] Namibia[186]		157			excess active ingredient,[157] different morphology of fake primaquine tablets[186]
Mefloquine	Southeastern Asia in Cambodia[54,55,59,71] and in Burma,[54,55] Thailand,[55] Laos[55] and Senegal[92]	59,71,187	59	54,59	59	low dissolution rate[59]
Sulfadoxine–pyrimethamine (SP)	Nigeria,[26,188] Cameroon,[46,53] Sierra Leone,[75] Zambia,[189] Cotè d'Ivoire,[58] Nigeria,[12,188] Tanzania,[32,84,182] Rwanda,[32] Kenya[90]	46	53	53	58	failed dissolution testing.[182] In most reports, pyrimethamine accounts for a disproportionate number of dissolution and content failures[50,89,90]
Quinine sulphate	Southeastern Asia in Cambodia,[47,54,56,57,59] in Vietnam,[56] in Africa in Cameroon,[46,53] Congo, Burundi and Angola,[82] Rwanda and Tanzania,[32] Nigeria[190] and in USA[191]	54,190	82	59	82	high quantity of impurities,[82] poor dissolution[32]
Artemisin (ART) derivatives artesunate	Southeastern Asia[70] and more specifically in Burma,[14,55] Burma/Thailand,[14,39,55] Thailand,[56] Cambodia,[14,54–57,59,71,72,192] Vietnam,[14,55,56] Laos,[14,55,56,72] China[56] and Africa in Cameroon[39]	14,45,55,56,72	39	39	39	
artemether	Cambodia[193]	39,193,194	59	59	59	failed disintegration tests[59] have altered physicochemical characteristics[193]
dihydroartemisinin	Cameroon[39,194]	39,193,194				
Halofantrine	Nigeria, Ghana, Sierra Leone,[104,118,195,196] and from WHO[197]	118,195		104		

Characteristics of substandard/counterfeit drugs

Counterfeit drug products come in many variations. Some do not contain any of the active (pharmaceutical) ingredients (AI) or include the ingredient in harmful amounts. Other preparations come from an unacceptable source or are differently formulated, may contain unacceptably high levels of impurities or impurities such as mould or packaging that falsifies the product's true expiration date, whereas others contain a completely different active ingredient.

Inappropriate packaging

Fake pharmaceuticals often have the same appearance as the brand name and generic drugs they mimic. They are generally

indistinguishable in their outward packaging, and pill colour, shape, size and markings; they even have electronic bar codes, which pharmacists scan to verify drug authenticity.[79] In developing countries, many of the purchased drugs without packaging were counterfeit.[53] Examples of antimicrobials with false packaging and labelling include antibiotics such as penicillin,[48] chloramphenicol,[6] tetracyclines,[6,36,54,57,80] co-trimoxazole,[58] quinolones[36] and aminoglycosides[75,81] and antimalarials such as chloroquine,[53] mefloquine,[59] quinine[82] and artesunate.[14,44,61,70]

Reduced stability and bioavailability

Several studies that have reported on the stability of essential drugs under real storage conditions in the tropics[27,33,83,84] in warehouses and in some wholesale pharmacies may not be satisfactory for ensuring the integrity of drug products.[85–87] Antibiotics in particular, e.g. ampicillin,[88] may degrade during transportation or storage at temperatures above 25°C and high humidity.[33] Other drugs, however, may be stable under such conditions[83] and there are studies that have shown that high storage temperatures do not affect adversely the content of many antibiotics including penicillins and tetracyclines[12,83] and this may suggest that the most likely cause of low quality is to be found during manufacturing.[48]

Moreover, interactions may occur when products are stored at high temperature and humidity, consequently reducing the dissolution rate.[85] Although many substandard antimicrobials may contain the appropriate amount of active ingredient, they can have suboptimal activity and this may be due to reduced bioavailability. Examples include tetracyclines,[34] co-trimoxazole,[32] metronidazole,[32] pyrimethamine,[50,89,90] chloroquine[91] and mefloquine.[59]

Reduced concentration of active ingredient

Low concentration of active ingredient in antimicrobials may be the result of poor manufacturing or could be the effect of poor transport and storage conditions and often it is not possible to distinguish between these two causes (Tables 2 and 4). Decomposition was the cause of poor quality in a number of samples,[7,88] but as it has been shown that many antibiotics may be stable even under tropical conditions,[83] overall poor manufacturing appeared to be the prevalent cause of low quality.[7,48] However, the effect of storage conditions on drug quality has not been assessed in all studies.[42] Finally, reduced concentration of active ingredient could also be the result of dilution of drugs with other substances such as contaminated water[29,79] or sugar.[92]

Altered chemical content

Additionally, counterfeit drugs may be characterized by altered odour because they contain diluted active ingredients, or in many cases harmful additives. Sometimes, the counterfeit drugs are chemically identical to the real product, making them counterfeit generics; however, most fakes contain inactive or harmful ingredients. The capsules or tablets may contain, for example, a wrong antibiotic such as erythromycin,[39] or they may contain only worthless flour, starch or powder.[29,39,93,94] Notorious recent real examples include neomycin eye drops and meningococcal vaccine made of tap water, ampicillin consisting of turmeric and antimalarials and antibiotics containing no active ingredients.[14,26,71,95]

Methods for the detection of counterfeit/substandard antimicrobials

Several methods have been used for the detection of substandard medications including inspection, dissolution assays, colorimetric methods and chromatography techniques such as HPLC, TLC, Mini-lab and mass spectrometry [Table S5, available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/)]. Visual control, dissociating tests or simple colour reaction tests reveal only very rough forgeries. Fast, easy, reliable and non-expensive methods of drug screening are essential, especially in developing countries in the setting of lack of systematic control of the pharmaceutical market and the absence of specific regulations. Finally, new technologies such as near infrared spectroscopy[96] and X-ray powder diffraction method[97] have been increasingly used for the detection of counterfeit antimicrobials.

Consequences of counterfeit and substandard anti-infectives

The use of low-quality drugs can result in adverse clinical outcomes such as lack of effect and treatment failure, risk of development of bacterial resistance, toxicity or side effects,[14,42,66] all of which contribute to the burden of disease and consequently to excess mortality and morbidity.[3] However, to the best of our knowledge, there are no reports (e.g. cohorts) that have studied these consequences of low-quality drugs in a systematic approach using adequate scientific methodology. The potential risk of counterfeit anti-infectious agents for individual and community health includes clinical aggravation leading to complications and even mortality from either the disease itself or possible toxic components in the product and selection of drug-resistant bacteria and parasites. These risks have been described on the basis of cases, case series or even epidemics in one case.[98]

Consequences for the patients

Counterfeit and substandard medicines could also cause adverse effects such as allergic or other side effects through excessive dose or due to the presence of potentially toxic active ingredients[53] or pathogenic contaminants,[99] as has been reported for some antimicrobials including antimalarials,[53,93,100–106] especially in paediatric formulations or when the drug has a narrow therapeutic window.[12]

In addition, there are many reports that anti-infective drugs of poor quality such as anti-TB agents and antimalarial drugs may cause treatment failure[7,9,13,48] and can lead to substantial morbidity or mortality.[71,93,100–103,107–109] Other studies report the number of deaths, which can be very high because of counterfeit drugs, such as the most well-known major incident

concerning 2500 deaths in Niger in 1995 from a counterfeit meningitis vaccination.[98]

Emergence of drug resistance

Other consequences of the problem of counterfeit and/or substandard antimicrobial drugs include the substantial effect on the growing global problem of antimicrobial resistance,[7,9,13,48] especially for diseases that are treated with combination therapy such as tuberculosis,[6,65,108] malaria due to *Plasmodium falciparum*[39,45,109] and HIV. Most drug failures are due to lower contents or dissolution scores, which is comparable with taking low doses of the drug. As a result although some bacterial agents are still susceptible to common antibiotics in industrialized countries, in some other developing countries, the proportion of multiresistant strains in various bacterial species has greatly increased.[36]

Moreover, substandard narrow-spectrum antibiotics may create the wrong impression that the antibacterial agents themselves are ineffective and, thus, lead prescribers to unnecessarily opt for newer broad-spectrum antibiotics that have not yet been copied by unscrupulous manufacturers as their first-line treatment for many infections.[99]

According to WHO, the consequences of this are obvious: (i) relatively cheap drugs will become ineffective; (ii) the loss of such drugs will require new drug development, which will be more expensive and will further disadvantage patients in the developing countries; and (iii) selection of drug-resistant pathogens will lead to increased morbidity, mortality and a significant economic burden on developing regions of the world.[110] Another risk of using counterfeit drugs is that with the increased mobility of persons, the transmission of drug-resistant strains of diseases from country to country and within regions will also increase.

Examples of substandard antimicrobials that lead to spreading of resistance include chloramphenicol and co-trimoxazole[6] and antimalarials[111] such as artemisinins,[39,112] chloroquine[113,114] and mefloquine.[115]

Other consequences

The counterfeiting of pharmaceuticals has serious consequences for consumers, healthcare providers, drug manufacturers and governments.[116] There can be significant decline in confidence in public health systems, healthcare professionals and in government agencies involved in distributing drugs.[116] Health practitioners can also lose confidence in the medications that they rely upon because of false reports of drug resistance.[45,117] On the other hand, the financial consequences of counterfeit medicines for the companies producing the genuine product can be enormous.[118–120] Finally, the financial impact for consumers can also be significant, mostly due to higher prices for drugs, especially in countries like the USA.[116]

Interventions

There is clearly no simple solution to the problem of counterfeit anti-infectives and several strategies are required. WHO has established guidelines against counterfeiting,[121] which require cooperation between government organizations, health workers, industry and civil society.[1,81,122–124] The Declaration of Rome, arising from the WHO International Conference on Combating Counterfeit Medicines, calls for the formation of an International Medical Products Anti-Counterfeiting Taskforce.[125,126] Moreover, as a response to the increased threat of counterfeit drugs in the USA and throughout the world, the US FDA established the Counterfeit Drug Task Force. Task force strategies for combating drug counterfeiting include using advanced technology, security business practices and regulatory requirements, creating rapid alert and response systems, developing education and public awareness programmes and addressing international issues.[68,127–130] FDA has also issued many measures to combat counterfeit antimicrobials in many publications.[127,130–141] WHO has issued guidelines for combating counterfeit medications,[1,6,15,22–25,46,50,57,77,95,98,122,126,142–150] but their effect in reducing counterfeiting of medications has not been assessed by studies.

However, although guidelines have been produced,[95] most developing countries do not have the infrastructure and financial resources to implement them.[1,12,75] For example, in Nigeria, efforts to control this problem were not very successful.[151] In contrast, other research efforts were more effective. Interventions developed by WHO to reduce fake antimalarials in southeast Asia involved drug packaging such as blister packaging, public information campaigns and assessments of drug quality and improved drug compliance.[152]

Increased legal measures,[153] including even death penalties (e.g. in China),[154] and increased inspection and drug regulation from governments have also been implemented as means to combat counterfeit drugs. However, there is only one published study examining the efficacy of such interventions,[42] in which the quality of antimicrobials was examined in districts in Laos before and 2 years after random allocation to either regular or enhanced drug inspection. Although drug quality improved substantially over the 2 years, no significant differences were found between the regular and enhanced drug inspection districts.[42] Prosecution of counterfeit antibiotics has been successful in some of the cases, e.g. in China.[155]

On the other hand, increased public awareness of the problem of counterfeit drugs is of paramount importance and governments and companies have issued warnings about specific counterfeited products. For example, Nigeria and Thailand have developed informative web sites and such campaigns had some success, e.g. in Cambodia.[45] WHO has issued guidelines that consumers should follow, such as to check for abnormal appearance of packaging, to avoid buying suspiciously inexpensive medicines and to buy only from licensed pharmacies; however, their effectiveness is unknown.[1]

Finally, interventions related to quality control and good manufacturing practice are necessary to reduce the prevalence of substandard drugs, but these are not complicated by criminal motives as is the case with counterfeit drugs.

Limitations of the review

Our review has several limitations including the inclusion of only studies in the English language and the search of only the PubMed database and major newspaper articles and Internet web

sites found through the Google search machine. In the current manuscript, we could identify few studies with sufficient methodology and as a result, conclusions regarding low quality of specific classes of antimicrobials could not be made in some cases. In many reports on the quality of drugs in developing countries, the terms counterfeit and substandard drugs have been used interchangeably and the authors often do not distinguish between counterfeit and substandard drugs. Many studies measure the percent of available drugs that do not meet minimum pharmaceutical standards or do not possess the proper quantity of active ingredients, but, in most of them, there was no criminal investigation on the source of the medications so it was not specified whether the substandard medications were also counterfeit.[53,156]

In addition, although in some studies the source of the low-quality antimicrobial agent is reported (Table 1), this source is not specified in the vast majority of the reports published and it is not possible to distinguish whether the reference is to a generic or to the original trade name product. This makes studying of the problem of substandard antimicrobials problematic with regard to application of GMP and the implementation of international standards in the manufacturing part of the industry.

Moreover, variability in definitions between different studies using different pharmacopoeial standards often makes direct comparisons difficult. Many of the previous reports on counterfeit drugs have been based on case reports on failure to attain the expected therapeutic effect, or reports investigating a small sample of products belonging to different classes of drugs.[10,15,157] Counterfeit drugs exist on the market sporadically, and the absence of counterfeit drugs in some studies could be due to the sampling window or sample size. Other reports constituting the WHO database have remained confidential, unpublished or published for limited distribution.[15] Finally, many of these studies had methodological limitations specifically with regard to sampling and data analysis and were not necessarily representative for the whole country that was studied.

Thus, despite the scale of the problem of low-quality medications, there is little research on poor quality drugs. There are very few studies on the prevalence of counterfeit and substandard drugs with sufficient methodology including random sampling.[12] Future research efforts are needed to clearly study the problem of low-quality medications with adequate design to avoid bias. Publications describing drug quality should also provide manufacturer's names as stated on the packaging,[108] but only a small portion of published studies provide this information.[158] Such data are required to better define the problem by providing reliable prevalence estimates and by examining the effectiveness of interventions to confine this menace.

Conclusions

In summary, the data of the reviewed studies suggest that the problem of counterfeit and/or substandard antimicrobial drugs has a large dimension with considerable direct and indirect effects on global public health. The use of low-quality drugs can result in adverse clinical outcomes such as lack of effect and treatment failure, risk of development of bacterial resistance, toxicity, side effects and even deaths. This problem can have important implications on the everyday practice of healthcare providers because not only physicians but also patients lose confidence in the effectiveness of antimicrobials. In the current manuscript, we have summarized the body of scientific evidence in an effort to define the problem more clearly. Several strategies are required to combat the problem of counterfeit anti-infectives including cooperation between government organizations, health workers, industry and civil society and WHO has announced specific guidelines. However, many of these measures cannot be implemented in many developing countries because of the lack of resources and therefore there is need for international coordination to fight the menace of counterfeit/substandard antimicrobials.

Acknowledgements

This study received no funding.

Transparency declarations

None to declare.

Supplementary data

Tables S1–S5 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

References

1. WHO. *Counterfeit Drugs: Guidelines for the Development of Measures to Combat Counterfeit Drugs*. Geneva: WHO, 1999; 1–60.

2. Anon. Counterfeit drugs. *Bull World Health Organ* 1993; **71**: 464–70.

3. Anon. Quality control and essential drugs. *Lancet* 1997; **350**: 601.

4. Afu S. Incidence of substandard drugs in developing countries. *Trop Med Int Health* 1999; **4**: 73.

5. Verduin-Muttiganzi R, Verduin-Muttiganzi G. Assessment of the incidence of substandard drugs in developing countries. *Trop Med Int Health* 1998; **3**: 602.

6. WHO. *Counterfeit and Sub-standard Drugs in Myanmar and Vietnam*. Geneva: WHO, 1999; 1–55.

7. Shakoor O, Taylor RB, Behrens RH. Assessment of the incidence of substandard drugs in developing countries. *Trop Med Int Health* 1997; **2**: 839–45.

8. Pecoul B, Chirac P, Trouiller P *et al*. Access to essential drugs in poor countries: a lost battle? *JAMA* 1999; **281**: 361–7.

9. Menkes DB. Hazardous drugs in developing countries. *BMJ* 1997; **315**: 1557–8.

10. Roy J. The menace of substandard drugs. *World Health Forum* 1994; **15**: 406–7.

11. Hanif M, Mobarak MR, Ronan A *et al*. Fatal renal failure caused by diethylene glycol in paracetamol elixir: the Bangladesh epidemic. *BMJ* 1995; **311**: 88–91.

12. Taylor RB, Shakoor O, Behrens RH *et al*. Pharmacopoeial quality of drugs supplied by Nigerian pharmacies. *Lancet* 2001; **357**: 1933–6.

13. Wan Po AL. Too much, too little, or none at all: dealing with substandard and fake drugs. *Lancet* 2001; **357**: 1904.

14. Newton P, Proux S, Green M *et al*. Fake artesunate in southeast Asia. *Lancet* 2001; **357**: 1948–50.

15. Wondemagegnehu E. *Counterfeit and Substandard Drugs in Myanmar and Vietnam WHO/EDM/QSM/993*. Geneva: WHO, 1995.

16. Frankish H. WHO steps up campaign on counterfeit drugs. *Lancet* 2003; **362**: 1730.

17. Abdi YA, Rimoy G, Ericsson O *et al*. Quality of chloroquine preparations marketed in Dar es Salaam, Tanzania. *Lancet* 1995; **346**: 1161.

18. Pincock S. WHO tries to tackle problem of counterfeit medicines in Asia. *BMJ* 2003; **327**: 1126.

19. Ahmad K. Antidepressants are sold as antiretrovirals in DR Congo. *Lancet* 2004; **363**: 713.

20. Videau JV, Fundafunda B. Generic drugs: the hidden issues of quality and cost. *WHO Drug Information* 2000, 77–81.

21. WHO. Quality assurance of pharmaceuticals. Vol 1. Geneva: World Health Organization, 1997.

22. WHO. Quality assurance of pharmaceuticals. Vol 2. Geneva: World Health Organization, 1999.

23. WHO. *What Encourages Counterfeiting of Drugs?* http://www.who.int/medicines/services/counterfeit/faqs/16/en/index.html (16 July 2006, date last accessed).

24. Department of Essential Drugs and Other Medicines. *Counterfeit Drugs*. Geneva: World Health Organization, 1999.

25. WHO. Combating counterfeit drugs. http://www.who.int/medicines/organization.gsm/activities/quality_assurance/cft/counterfeit 2006.

26. ten Ham M. Counterfeit drugs: implications for health. *Adverse Drug React Toxicol Rev* 1992; **11**: 59–65.

27. Hogerzeil HV, de Goeje MJ, Abu-Reid IO. Stability of essential drugs in Sudan. *Lancet* 1991; **338**: 754–5.

28. Arya SC. Inadvertent supply of substandard drugs. *World Health Forum* 1995; **16**: 269.

29. Moken MC. Fake pharmaceuticals: how they and relevant legislation or lack thereof contribute to consistently high and increasing drug prices. *Am J Law Med* 2003; **29**: 525–42.

30. Carpenter J. US Pharmacopeia. *A Review of Drug Quality in Asia with Focus on Anti-infectives*. http://www.uspdqi.org/pubs/other/ANEReview.pdf, 2006.

31. Chattopadhyay S. Access to essential drugs in poor countries. *JAMA* 1999; **282**: 631.

32. Kayumba PC, Risha PG, Shewiyo D *et al*. The quality of essential antimicrobial and antimalarial drugs marketed in Rwanda and Tanzania: influence of tropical storage conditions on *in vitro* dissolution. *J Clin Pharm Ther* 2004; **29**: 331–8.

33. Ballereau F, Prazuck T, Schrive I *et al*. Stability of essential drugs in the field: results of a study conducted over a two-year period in Burkina Faso. *Am J Trop Med Hyg* 1997; **57**: 31–6.

34. Okeke IN, Lamikanra A. Quality and bioavailability of tetracycline capsules in a Nigerian semi-urban community. *Int J Antimicrob Agents* 1995; **5**: 250.

35. Murtarda M, Sessay B. Expiry dates on pharmaceuticals, some worrying realities in Sierra Leone. *Int Pharm J* 1994; **8**: 202–6.

36. Prazuck T, Falconi I, Morineau G *et al*. Quality control of antibiotics before the implementation of an STD program in Northern Myanmar. *Sex Transm Dis* 2002; **29**: 624–7.

37. Bouchie A. US policy may encourage counterfeit drugs. *Nat Biotechnol* 2003; **21**: 121.

38. Spake A. Fake drugs, real worries: high prices and the Internet are making U.S. patients easy prey. *US News World Rep* 2004; **137**: 46, 48, 50.

39. Newton PN, McGready R, Fernandez F *et al*. Manslaughter by fake artesunate in Asia-will Africa be next? *PLoS Med* 2006; **3**: e197.

40. Gibson L. Drug regulators study global treaty to tackle counterfeit drugs. *BMJ* 2004; **328**: 486.

41. Rudolf PM, Bernstein IB. Counterfeit drugs. *N Engl J Med* 2004; **350**: 1384–6.

42. Syhakhang L, Lundborg CS, Lindgren B *et al*. The quality of drugs in private pharmacies in Lao PDR: a repeat study in 1997 and 1999. *Pharm World Sci* 2004; **26**: 333–8.

43. O'Brien KL, Selanikio JD, Hecdivert C *et al*. Epidemic of pediatric deaths from acute renal failure caused by diethylene glycol poisoning. Acute Renal Failure Investigation Team. *JAMA* 1998; **279**: 1175–80.

44. Singh J, Dutta AK, Khare S *et al*. Diethylene glycol poisoning in Gurgaon, India, 1998. *Bull World Health Organ* 2001; **79**: 88–95.

45. Rozendaal J. Fake antimalarials circulating in Cambodia. *Bull Mekong Malar* 2000; **7**: 62–8.

46. La qualite des mιdicaments sur le marche pharmaceutique africain. Etude analytique dans trois pays. Cameroun, Madagascar, Tchad. Geneva: WHO, 1995. WHO/DAP/95.3.

47. Giminez F, Bruneton C, Narong Rith DY. Etude de la qualite des medicaments vendus et dispenses au Cambodge. *Med Mal Infect* 1997; **271**: 541–4.

48. Stenson B, Lindgren BH, Synhakhang L *et al*. The quality of drugs in private pharmacies in the Lao People's Democratic Republic. *Int J Risk Saf Med* 1998; **11**: 243–9.

49. Sow PS, Gueye TS, Sy E *et al*. Drugs in the parallel market for the treatment of urethral discharge in Dakar: epidemiologic investigation and physicochemical tests. *Int J Infect Dis* 2002; **6**: 108–12.

50. WHO. *The Quality of Antimalarials. A Study in Selected African Countries*. Geneva: World Health Organization, 2003; 1–67.

51. Penzak SR, Acosta EP, Turner M *et al*. Analysis of generic nevirapine products in developing countries. *JAMA* 2003; **289**: 2648–9.

52. Iqbal M, Hakimm S, Hussain A *et al*. Ofloxacin: laboratory evaluation of the antibacterial activity of 34 brands representing 31 manufacturers available in Pakistan. *Pak J Med Sci* 2004; **20**: 349–56.

53. Basco LK. Molecular epidemiology of malaria in Cameroon. XIX. Quality of antimalarial drugs used for self-medication. *Am J Trop Med Hyg* 2004; **70**: 245–50.

54. Smine A, Phanouvong S, Chanthap L *et al*. *Antimalarial Drug Quality in Mekong Countries*. http://www.uspdqi.org/pubs/other/AntimalarialPoster.pdf (16 July 2006, date last accessed).

55. Dondorp AM, Newton PN, Mayxay M *et al*. Fake antimalarials in Southeast Asia are a major impediment to malaria control: multinational cross-sectional survey on the prevalence of fake antimalarials. *Trop Med Int Health* 2004; **9**: 1241–6.

56. Phanouvong S, Reiss S, Smine A. *Why be Concerned about the Quality of Antimalarial and ARV Drugs? Poster Presented at 7th International Congress on AIDS in Asia and the Pacific, Kobe, Japan, 1–5 July 2005*. http://www.uspdqi.org/pubs/other/whyDrugQuality.pdf.

57. Fake anti malaria drugs in Cambodia: a danger to public health. Final Report, NCM—Cambodia, USP, WHO. Phnom Penh, Cambodia: National Center for Parasitology, Entomology and Malaria Control, 2005.

58. Legris C. La dιtection des mιdicaments contrefaits par investigation de leur authenticitι. ιtude pilote sur le marchι pharmaceutique illicite de Cote d'Ivoire. These pour le diplome d'ιtat de docteur en pharmacie soutenus ν la Facultι de Pharmacie Nancy le 16 decembre 2005. http://www.remed.org/html/theses.html (16 July 2006, date last accessed).

59. Lon CT, Tsuyuoka R, Phanouvong S *et al*. Counterfeit and substandard antimalarial drugs in Cambodia. *Trans R Soc Trop Med Hyg* 2006; **100**: 1019–24.

60. ten Ham M. Health risks of counterfeit pharmaceuticals. *Drug Saf* 2003; **26**: 991–7.

61. Ashokraj Y, Kohli G, Kaul CL *et al*. Quality control of anti-tuberculosis FDC formulations in the global market: part II-accelerated stability studies. *Int J Tuberc Lung Dis* 2005; **9**: 1266–72.

62. Ashokraj Y, Agrawal S, Varma MV *et al*. Quality control of anti-tuberculosis fixed-dose combination formulations in the global market: an *in vitro* study. *Int J Tuberc Lung Dis* 2004; **8**: 1081–8.

63. Ellard GA. The colorimetric analysis of anti-tuberculosis fixed-dose combination tablets and capsules. *Int J Tuberc Lung Dis* 1999; **3**: S343–6.

64. Agrawal S, Panchagnula R. *In vitro* evaluation of fixed dose combination tablets of anti-tuberculosis drugs after real time storage at ambient conditions. *Pharmazie* 2004; **59**: 782–5.

65. Laserson KF, Kenyon AS, Kenyon TA *et al*. Substandard tuberculosis drugs on the global market and their simple detection. *Int J Tuberc Lung Dis* 2001; **5**: 448–54.

66. Okeke IN, Lamikanra A, Edelman R. Socioeconomic and behavioral factors leading to acquired bacterial resistance to antibiotics in developing countries. *Emerg Infect Dis* 1999; **5**: 18–27.

67. Snow RW, Guerra CA, Noor AM *et al*. The global distribution of clinical episodes of *Plasmodium falciparum* malaria. *Nature* 2005; **434**: 214–7.

68. Surendran A. World agencies try to stem flood of fake drugs. *Nat Med* 2004; **10**: 111.

69. Ogwal-Okeng JW, Okello DO, Odyek O. Quality of oral and parenteral chloroquine in Kampala. *East Afr Med J* 1998; **75**: 692–4.

70. Green MD, Mount DL, Wirtz RA *et al*. A colorimetric field method to assess the authenticity of drugs sold as the antimalarial artesunate. *J Pharm Biomed Anal* 2000; **24**: 65–70.

71. Rozendaal J. Fake antimalaria drugs in Cambodia. *Lancet* 2001; **357**: 890.

72. Newton PN, Dondorp A, Green M *et al*. Counterfeit artesunate antimalarials in southeast Asia. *Lancet* 2003; **362**: 169.

73. Green MD. Antimalarial drug resistance and the importance of drug quality monitoring. *J Postgrad Med* 2006; **52**: 288–90.

74. Boelaert M, Le Ray D, Van Der SP. How better drugs could change kala-azar control. Lessons from a cost-effectiveness analysis. *Trop Med Int Health* 2002; **7**: 955–9.

75. Sesay MM. Fake drugs-a new threat of health care delivery. *Africa Health June/July 1988*, 2006; 13–5.

76. Pakharenko-Anderson A. *Building Legislation and Regulatory Implementation Environments: The Ukraine Experience*. First Global Forum on Pharmaceutical Anticounterfeiting, Geneva, Switzerland, 22–25 September 2002.

77. *Database on the Incidents of Counterfeit Medicines in the WHO-SEA Region*. http://www.searpharmforum.org/LinkFiles/Project_and_activities_CFM-full-report.pdf (16 July 2006, date last accessed).

78. Children's Vaccine Initiative. Working Group Meeting on Asia Initiative. Rockefeller Archives Center, New York, 28–30 July 1993, Document CVI/MAC-5/93.12.

79. Masland T, Marshall R. 'A Really Nasty Business'. Fake pharmaceuticals look like the real thing but they can be lethal. Newsweek, **36**, 5 November 1990.

80. Center for Combating Counterfeit Drug. *The Situation of Counterfeit Drug*. http://wwwapp1.fda.moph.go.th/drug/eng/zone_counterfeit/fak001.asp (16 July 2006, date last accessed).

81. Harper J. Counterfeit medicines survey report, Council for Europe. Strasbourg: Council of Europe Publishing, 2006.

82. Gaudiano MC, Antoniella E, Bertocchi P *et al*. Development and validation of a reversed-phase LC method for analysing potentially counterfeit antimalarial medicines. *J Pharm Biomed Anal* 2006; **42**: 132–5.

83. Nazerali H, Hogerzeil HV. The quality and stability of essential drugs in rural Zimbabwe: controlled longitudinal study. *BMJ* 1998; **317**: 512–3.

84. Risha PG, Shewiyo D, Msami A *et al*. *In vitro* evaluation of the quality of essential drugs on the Tanzanian market. *Trop Med Int Health* 2002; **7**: 701–7.

85. Saville DJ. Influence of storage on *in vitro* release of ibuprofen from sugar coated tablets. *Int J Pharm* 2001; **224**: 39–49.

86. Murthy KS, Ghebre-Sellassie I. Current perspectives on the dissolution stability of solid oral dosage forms. *J Pharm Sci* 1993; **82**: 113–26.

87. Pandit JK, Tripathi MK, Babu RJ. Effect of tablet disintegrants on the dissolution stability of nalidixic acid tablets. *Pharmazie* 1997; **52**: 538–40.

88. Rimoy GH, Moshi MJ, Massele AY. Comparative bioavailability of oral sugar-coated and plain formulation of chloroquine phosphate marketed in Tanzania. *Trop Doct* 2002; **32**: 15–7.

89. Kibwage IO, Ngugi JK. Sulphadoxine/pyrimethamine tablet products on the Kenyan market: quality concerns. *East Cent Afr J Pharm Sci* 2000; **3**: 14–9.

90. Amin AA, Snow RW, Kokwaro GO. The quality of sulphadoxine–pyrimethamine and amodiaquine products in the Kenyan retail sector. *J Clin Pharm Ther* 2005; **30**: 559–65.

91. Barbereau S. Guinιe: faux medicaments. *E-med* 12 January 2006.

92. Reidenberg MM, Conner BA. Counterfeit and substandard drugs. *Clin Pharmacol Ther* 2001; **69**: 189–93.

93. Silverman M, Lydecker M, Lee PR. The drug swindlers. *Int J Health Serv* 1990; **20**: 561–72.

94. Goodman PS. China's Killer Headache: Fake Pharmaceuticals. *Washington Post*, 30 August 2002.

95. World Health Organization. *Counterfeit Drugs Guidelines for the Development of Measures to Combat Counterfeit Drugs*. Geneva: WHO, 1999.

96. Scafi SH, Pasquini C. Identification of counterfeit drugs using near-infrared spectroscopy. *Analyst* 2001; **126**: 2218–24.

97. Maurin JK, Plucinski F, Mazurek AP *et al*. The usefulness of simple X-ray powder diffraction analysis for counterfeit control-the Viagra((R)) example. *J Pharm Biomed Anal* 2006; **43**: 1514–8.

98. Quality Assurance Program HTP/EDM Revised Drug Strategy 11 April 2000. http://www.who.int/medicines/library/qsm/who-edm-qsm-99-3/who-edm-qsm-99-3.pdf (2000).

99. Issack MI. Substandard drugs. *Lancet* 2001; **358**: 1463.

100. Milan MM. Doctors blame fake medicines for deaths. *The Sunday Times*, 1 November, 15. 1987.

101. Pandya SK. Letter from Bombay. An unmitigated tragedy. *BMJ* 1988; **297**: 117–9.

102. Masland T, Marshall F. The pill pirates. *Newsweek*, 5 November 1990, 18–23.

103. Okuonghae HO, Ighogboja IS, Lawson JO *et al*. Diethylene glycol poisoning in Nigerian children. *Ann Trop Paediatr* 1992; **12**: 235–8.

104. Wolff JC, Thomson LA, Eckers C. Identification of the 'wrong' active pharmaceutical ingredient in a counterfeit Halfan drug product using accurate mass electrospray ionisation mass spectrometry, accurate mass tandem mass spectrometry and liquid chromatography/mass spectrometry. *Rapid Commun Mass Spectrom* 2003; **17**: 215–21.

105. Alter K, Fernandez F, Green M *et al*. Analysis of counterfeit antimalarial drugs. *Eur Pharm Rev* 2004; **3**: 1–5.

106. Fernandez FM, Cody RB, Green MD *et al*. Characterization of solid counterfeit drug samples by desorption electrospray ionization

and direct-analysis-in-real-time coupled to time-of-flight mass spectrometry. *ChemMedChem* 2006; **1**: 702–5.

107. Jacobson A. What works? In: Dinh K, Hook C, Kindermans JM *et al.*, eds. *ACT Now For All Of The Asia Pacific Region To Get Malaria Treatment That Works. Access to Essential Medicines Campaign*. Australia: Medécins sans Frontières, 2004; 17–20.

108. Laing R, Vrakking H, Fourie B. Quality and stability of TB medicines: let the buyer beware! *Int J Tuberc Lung Dis* 2004; **8**: 1043–4.

109. Wernsdorfer WH. Epidemiology of drug resistance in malaria. *Acta Trop* 1994; **56**: 143–56.

110. Behrens RH, Awad AI, Taylor RB. Substandard and counterfeit drugs in developing countries. *Trop Doct* 2002; **32**: 1–2.

111. Taylor RB, Shakoor O, Behrens RH. Drug quality, a contributor to drug resistance? *Lancet* 1995; **346**: 122.

112. University of Oxford. Warning: At least Seven Types of Fake Artesunate are Being Sold in Mainland SE Asia. *Wellcome Trust SE Asian Tropical Medicine Research Units*, 2005.

113. Ringwald P, Same EA, Keundjian A *et al*. Chemoresistance of *P. falciparum* in urban areas of Yaounde, Cameroon. Part 1: surveillance of *in vitro* and *in vivo* resistance of *Plasmodium falciparum* to chloroquine from 1994 to 1999 in Yaounde, Cameroon. *Trop Med Int Health* 2000; **5**: 612–9.

114. Ringwald P, Bickii J, Basco L. Randomised trial of pyronaridine versus chloroquine for acute uncomplicated falciparum malaria in Africa. *Lancet* 1996; **347**: 24–8.

115. White NJ. Delaying antimalarial drug resistance with combination chemotherapy. *Parassitologia* 1999; **41**: 301–8.

116. Scheer A. http://www.abnh.com/security/Pharm_WhitePaper_WEBSITE.pdf, 2003.

117. Basco LK, Ringwald P, Manene AB *et al*. False chloroquine resistance in Africa. *Lancet* 1997; **350**: 224.

118. Cockburn R, Newton PN, Agyarko EK *et al*. The global threat of counterfeit drugs: why industry and governments must communicate the dangers. *PLoS Med* 2005; **2**: e100.

119. Lybecker K. *Rx roulette: Counterfeit Pharmaceuticals in Developing Nations, 2003*. http://www.lebow.drexel.edu/lybecker/Lybecker.pdf (16 July 2006, date last accessed).

120. Saywell T, McManus J. What's in that pill? *Far East Econ Rev* 2002; 34–40.

121. US FDA. Protecting consumers from counterfeit drugs. *FDA Consum* 2004; **38**: 12–3.

122. WHO. *Combating Counterfeit Drugs: A Concept Paper for Effective International Collaboration*. http://www.who.int/entity/medicines/services/counterfeit/CombatingCounterfeitDrugs_Conceptpaper.pdf (16 July 2006, date last accessed).

123. Newton PN, White NJ, Rozendaal JA *et al*. Murder by fake drugs. *BMJ* 2002; **324**: 800–1.

124. USP. *Ensuring the Quality of Medicines in Low-income Countries: An Operational Guide*. http://www.uspdqi.org/pubs/other/ensuringQualityOperationalGuide.pdf, 2006.

125. Burns W. WHO launches taskforce to fight counterfeit drugs. *Bull World Health Organ* 2006; **84**: 689–90.

126. WHO. *The Declaration of Rome*. http://www.who.int/entity/medicines/services/counterfeit/RomeDeclaration.pdf, 2006.

127. Combating counterfeit drugs: a report of the Food and Drug Administration. Rockville, MD: Food and Drug Administration, February 2004.

128. Vastag B. Alarm sounded on fake, tainted drugs: some wholesalers are a weak link in a dangerous chain. *JAMA* 2003; **290**: 1015–6.

129. US FDA. Update on counterfeit drugs. *FDA Consum* 2005; **39**: 6–7.

130. Young D. FDA launches new initiative to battle counterfeit drugs. *Am J Health Syst Pharm* 2003; **60**: 1712, 1715, 1720.

131. Food and Drug Administration, Rockville, USA. http://www.fda.gov/fdac/features/2006/206_influenza.html (2006).

132. http://www.fda.gov/oc.initiatives/counterfeit/report02_04.html (2004).

133. http://www.fda.gov/oc/initiatives/counterfeit/qa.html (2006).

134. Updates: Internet Vendors Warned About Unapproved Cipro. *FDA Consum* 2002; **36**: 4. http://www.fda.gov/fdac/departs/2002/102_upd.html.

135. US Food and Drug Administration. *Counterfeit Drugs: Questions and Answers*. http://www.fda.gov/oc/initiatives/counterfeit/qa.html (21 December 2005, date last accessed).

136. Ault A. FDA homes in on counterfeit and imported drugs. *Lancet* 2003; **362**: 1208.

137. FDA/U.S. *Customs Import Blitz Exams Reveal Hundreds of Potentially Dangerous Imported Drug Shipments. FDA News US Food and Drug Administration*, www.fda.gov/bbs/topics/NEWS/2003/NEW00948.html (29 September 2003).

138. James JS. FDA, companies test RFID tracking to prevent drug counterfeiting. *AIDS Treat News* 2005; **417**: 5–8.

139. Lueck S. FDA is faulted on fake drugs. *Wall St J*, **B4** (10 May 2000).

140. Young D. FDA clarifies importation law as Internet pharmacies proliferate. *Am J Health Syst Pharm* 2003; **60**: 729–30.

141. Young D. FDA declares actions to combat counterfeit drugs. *Am J Health Syst Pharm* 2004; **61**: 645–6, 650, 652.

142. Anon. *World Health Report 1999 Making a Difference*. Geneva: WHO, 1999, 49.

143. WHO. *Summary of WHO Counterfeit Drug Database as of April 1999, Unpublished Paper of the WHO Division of Drug Management and Policies*. Geneva: WHO, 1999.

144. WHO. *Effective Drug Regulation: What Can Countries Do*? Geneva: WHO, 1999; 1–53.

145. WHO Expert Committee on Specifications for Pharmaceutical Preparations. *World Health Organ Tech Rep Ser* 1999; **885**: i-156.

146. WHO. *World Health Organisation Counterfeit Drug Reports: 1999–October 2000*. www.who.int/medicines/library/pnewslet/pn300cfd.html (2000).

147. World Health Organization. *Substandard and Counterfeit Medicines*. Fact sheet 275, www.who.int/mediacentre/factsheets/2003/fs275/en/ (November 2003).

148. IFPMA. *Counterfeit Drugs: A Global Health Risk. Geneva Pharma Forum, International Federation of Pharmaceutical Manufacturers Association, Geneva, CICG*. www.psi.inc.org/issue.pdf (February 2004).

149. WHO. *Counterfeit Medicines*. http://www.who.int/mediacentre/factsheets/fs275/en (16 July 2006, date last accessed).

150. WHO. *World Health Organisation-Western Pacific Region Rapid Alert System*. http://218.111.249.28/ras/default.asp (2006).

151. Land T. Combating counterfeit drugs. *Nature* 1992; **355**: 192.

152. Gomes M, Wayling S, Pang L. Interventions to improve the use of antimalarials in south-east Asia: an overview. *Bull World Health Organ* 1998; **76** Suppl 1: 9–19.

153. Stearn DW. Deterring the importation of counterfeit pharmaceutical products. *Food Drug Law J* 2004; **59**: 537–61.

154. Dhillon A. Bogus Drug-makers Warrant Death Penalty, Indian Minister Says. *South China Morning Post*, 11 July 2003.

155. Press Release, US Department of Justice (DoJ) (10 April 1997), quoted in Robert Cohen, Fine and Prison Time in Bogus-Drugs Case, THE STAR-LEDGER, 11 April 1997, at 8 (found at 1997 WL 8062165).

156. Kenyon TA, Kenyon AS, Kgarebe BV *et al*. Detection of substandard fixed-dose combination tuberculosis drugs using thin-layer chromatography. *Int J Tuberc Lung Dis* 1999; **3**: S347–50.

157. Petralanda I. Quality of antimalarial drugs and resistance to *Plasmodium vivax* in Amazonian region. *Lancet* 1995; **345**: 1433.

158. Newton PN, Green MD, Fernandez FM *et al*. Counterfeit anti-infective drugs. *Lancet Infect Dis* 2006; **6**: 602–13.

159. Hu CQ, Zou WB, Hu WS *et al*. Establishment of a fast chemical identification system for screening of counterfeit drugs of macrolide antibiotics. *J Pharm Biomed Anal* 2006; **40**: 68–74.

160. Okeke IN, Lamikanra A. Quality and bioavailability of ampicillin capsules dispensed in a Nigerian semi-urban community. *Afr J Med Med Sci* 2001; **30**: 47–51.

161. Pillai G, Fourie PB, Padayatchi N *et al*. Recent bioequivalence studies on fixed-dose combination anti-tuberculosis drug formulations available on the global market. *Int J Tuberc Lung Dis* 1999; **3**: S309–16.

162. Santosh KK, Raghuram TC, Krishnaswamy K. Bioavailability of different brands of tetracycline in undernourished subjects. *Int J Clin Pharmacol Ther Toxicol* 1992; **30**: 13–7.

163. Pharmaceutical Security Institute. *Media Reports on Pharmaceutical Counterfeiting*. http://www.psi-inc.org/reports.pdf (16 July 2006, date last accessed).

164. Chakravarty S, Unnithan S, Ram A. Deadly doses. *India Today*, 29 January 2001, 58–61.

165. Jahnke RW, Kusters G. Detecting counterfeit drugs-protection against counterfeit medicines using the GPHF-Minilab. *Mekong Malar Forum* 2001; **8**: 118–24.

166. Cockburn R. Counterfeit drugs—the other killer in Lebanon. *The Guardian (London)*, 10 December 1982.

167. GlaxoSmithKline Case Study. *Judicial Protection of IPR in China*. http://www.chinaiprlaw.com/english/news/news14.htm (7 April 2003).

168. Carpenter J. *A Matrix of Drug Quality Reports on USAID-Assisted Countries by the USP Drug Quality and Information Program, 2004*. http://www.uspdqi.org/pubs/other/GHC-DrugQuality Matrix.pdf (16 July 2006).

169. NAFDAC. NAFDAC Consumer Safety Bulletin. Abuja, Nigeria: National Agency for Food and Drug Administration and Control, 2002; 19–30.

170. Erhun WO, Babalola OO, Erhun MO. Drug regulation and control in Nigeria: the challenge of counterfeit drugs. *J Health Popul Dev Ctries* 2001; **4**: 23–34.

171. Mukerjee A. Pills that kill. *Outlook (Mumbai)*, 22 September 2003, 46–54.

172. Fake Medicines Taken off the Shelves. *People's Daily Online*. http://en1.chinabroadcast.cn/2600/2005-7-18/154@258529.htm (10 January 2006, date last accessed).

173. Power G. *Counterfeit Pharmaceuticals. First Global Forum on Pharmaceutical Anticounterfeiting*. Geneva, Switzerland, 22 September 2002.

174. Encenbarger W. Counterfeit drugs. *Readers Digest* 2003; **82**: 26.

175. Safemeds. *Weekly News Update*. http://www.safemedicines.org (10 January 2006, date last accessed).

176. *Thirteen Fake Bird Flu Vaccine-Makers Punished*, China: *Xinhua News Agency*. http:// news.xinhuanet.com/english/2005-11/07/content_3745572.htm (16 July 2006, date last accessed).

177. Cockburn R. Counterfeit drugs that are kill rather than cure. *Guardian (London)*, 29 June 1984.

178. Parfitt T. Russia cracks down on counterfeit drugs. *Lancet* 2006; **368**: 1481–2.

179. Spurious antibiotic brands with names of Zydus. Torrent on labels seized. *India: Pharmabiz (Mumbai) News Agency* 7 May 2003.

180. Rago L. *Counterfeit Drugs: Threat to Public Health. Global Forum Pharmaceutical AntiCounterfeiting*. Geneva, Switzerland, 22–25 September 2002.

181. Kibwage IO, Thuranira J, Migosi D. Quality performance of metronidazole tablet products on the Kenyan market. *East Afr Med J* 1991; **68**: 365–71.

182. Hebron Y, Tettey JN, Pournamdari M *et al*. The chemical and pharmaceutical equivalence of sulphadoxine/pyrimethamine tablets sold on the Tanzanian market. *J Clin Pharm Ther* 2005; **30**: 575–81.

183. Minzi OM, Moshi MJ, Hipolite D *et al*. Evaluation of the quality of amodiaquine and sulphadoxine/pyrimethamine tablets sold by private wholesale pharmacies in Dar Es Salaam Tanzania. *J Clin Pharm Ther* 2003; **28**: 117–22.

184. Sulaiman SM, Traore M, Engels D *et al*. Counterfeit praziquantel. *Lancet* 2001; **358**: 666–7.

185. van Wyk JA, Malan FS, van Rensburg LJ *et al*. Quality control in generic anthelmintics: is it adequate? *Vet Parasitol* 1997; **72**: 157–65.

186. Kron MA. Substandard primaquine phosphate for US Peace Corps personnel. *Lancet* 1996; **348**: 1453–4.

187. Rozendaal J. Fake antimalarials circulating in Cambodia. *Bull Mekong Malaria Forum 2000* 2000; **7**: 62–8.

188. Anon. Counterfeiting Abroad and Home: British Pharmaceutical Conference 2003. *Pharm J* 2003; **271**: 453–4.

189. Koch E, Simmm M, Wech M. La mafia des faux medicaments. *Courrier Int* 1994; **204**: 36.

190. Sowunmi A, Salako LA, Ogunbona FA. Bioavailability of sulphate and dihydrochloride salts of quinine. *Afr J Med Med Sci* 1994; **23**: 275–8.

191. Heath WJ. America's first drug regulation regime: the rise and fall of the Import Drug Act of 1848. *Food Drug Law J* 2004; **59**: 169–200.

192. Crampton T. Fake malaria pills haunt Asians. *Int Herald Tribune*, **1**, 25 August 2003.

193. Anon. Announcement on fake (imitation) drugs. *The New Light of Myanmar*, 9 November 2001.

194. Arrow KJ. Fake malaria drugs in Tanzania. *Marketletter*, 20 February 2001.

195. Chryss J. Transcript of 'File on 4': Counterfeit drugs [transcript of radio program]. Program number 04VY3040LHO, London: British Broadcasting Corporation, http://news.bbc.co.uk/nol/shared/bsp/hi/pdfs/fileon4_05102004_counterfeitdrugs.pdf (2004).

196. Nigerian National Agency for Food and Drug Administration and Control (2002 June). List of identified fake products [June 2002]. NAFDAC ref 20-12. Abuja (Nigeria): Nigerian National Agency for Food and Drug Administration and Control, 2002.

197. WHO. *World Health Organization Counterfeit Drug Reports: 1999–October 2000 [Table]*. www.who.int/medicines/library/pnewslet/pn300cfd.html (2001).

198. Shakoor O. *Drug Distribution and Fake Drugs in Nigeria*. Basel: Institute for Medical Information, 1989.

199. Apoola A, Sriskandabalan PS, Wade AA. Self-medication with zidovudine that was not. *Lancet* 2001; **357**: 1370.

200. James JS. *Counterfeit Drugs: Check Combivir, Serostim, Epogen. AIDS Treat News, 380*. http://www.aegis.com/pubs/atn/2002/ATN38003.html (31 May 2001).

201. Aoki N. Real Fears Over Phony Drugs: US Health Officials View Spate of Recent Cases as Evidence of Rising Trend. *Boston Globe, C1* (29 May 2002).

202. Drug Access. *Ethiopian Health Officials Warn Public Against Counterfeit Antiretroviral Drug*. http://www.kaisernetwork.org/daily_

reports/rep_index.cfm?hint=1&DR_ID=20261 (16 July 2006, date last accessed).

203. Lindegardh N, Hien TT, Farrar J *et al*. A simple and rapid liquid chromatographic assay for evaluation of potentially counterfeit Tamiflu((R)). *J Pharm Biomed Anal* 2006; **42**: 430–3.

204. Sundar S, Sinha PR, Agrawal NK *et al*. A cluster of cases of severe cardiotoxicity among kala-azar patients treated with a high-osmolarity lot of sodium antimony gluconate. *Am J Trop Med Hyg* 1998; **59**: 139–43.

205. Broussard P. Du Nigeria au Niger, d'ιtranges vaccins contre la mιningite. *Le Monde*, 26 October 1996.

206. Banerjee A. Fake polio vaccine kills 11 children in Nadia. *The Asian Age*, 5 April 1995.

207. Hajari N. 'Swallowing Bitter Pills'. *TIME (151)* 261–70, 26 January 1998.

208. Anon. *Charge Filed in Fake Flu Vaccine Investigation*. http://releases.usnewswire.com/GetRelease.asp?id=55817 (16 July 2006, date last accessed).

209. Hemachudha T, Mitrabhakdi E, Wilde H *et al*. Additional reports of failure to respond to treatment after rabies exposure in Thailand. *Clin Infect Dis* 1999; **28**: 143–4.

210. Rasmussen CM, Thomas CW, Mulrooney RJ *et al*. Inadequate poliovirus immunity levels in immunized Illinois children. *Am J Dis Child* 1973; **126**: 465–9.

211. Onoja AL, Adu FD, Tomori O. Evaluation of measles vaccination programme conducted in two separate health centres. *Vaccine* 1992; **10**: 49–52.

212. Mulligan KJ, Brueggemeyer TW, Crockett DF *et al*. Analysis of organic volatile impurities as a forensic tool for the examination of bulk pharmaceuticals. *J Chromatogr B Biomed Appl* 1996; **686**: 85–95.

213. Phillips G. World congress of pharmacy and pharmaceutical sciences: anticounterfeiting measures. *Pharm J* 2003; **271**: 465.

214. Green MD, Newton P, Fernandez F *et al*. Simple low-cost strategies to rapidly identify counterfeit drugs in developing countries. In: *SMI Conference Documentation, Editor. Combating Pharmaceutical Fraud and Counterfeiting*. London: SMI Publishing, 2003.

215. Deisingh AK. Pharmaceutical counterfeiting. *Analyst* 2005; **130**: 271–9.

216. Jahnke RW. Counterfeit medicines and the GPHF-Minilab for rapid drug quality verification pp. *Pharm Ind* 2004; **66**: 1187–93.

217. Jahnke R. The GPHF-Minilab Project. In: *SMI Conference Documentation, Editor. Combating Pharmaceutical Fraud and Counterfeiting*. London: SMI Publishing, 2003.

218. Richard WO, Andreas S. A concise quality control guide on essential drugs. Vol II: Thin Layer Chromatography. *German Pharma Health Fund eV (GPHF)*, Frankfurt, Germany, 2002.

219. Http://www.gphf.org/web_en/projekte/minilab/index.htm (2003).

220. Jahnke RW, Kusters G. Low-cost quality assurance of medicines using the GPHF-Minilab. *Drug Inf J* 2001; **35**: 941–5.

221. Green MD, Nettey H, Rojas OV *et al*. Use of refractometry and colorimetry as field methods to rapidly assess antimalarial drug quality. *J Pharm Biomed Anal* 2006; **43**: 105–10.

222. Green MD, Mount DL, Wirtz RA. Authentication of artemether, artesunate and dihydroartemisinin antimalarial tablets using a simple colorimetric method. *Trop Med Int Health* 2001; **6**: 980–2.

223. el Ashry SM, Aly FA, el Brashy AM. Studies of complex formation between the Bromophenol Blue and some important aminoquinoline antimalarials. *Arch Pharm Res* 1994; **17**: 415–9.

224. Takats Z, Wiseman JM, Gologan B *et al*. Mass spectrometry sampling under ambient conditions with desorption electrospray ionization. *Science* 2004; **306**: 471–3.

225. Cody RB, Laramee JA, Durst HD. Versatile new ion source for the analysis of materials in open air under ambient conditions. *Anal Chem* 2005; **77**: 2297–302.

226. Peng SX, Borah B, Dobson RL *et al*. Application of LC–NMR and LC–MS to the identification of degradation products of a protease inhibitor in dosage formulations. *J Pharm Biomed Anal* 1999; **20**: 75–89.