

2.10 Medicine quality, physicians, and patients 12

2.10 Medicine quality, physicians, and patients 124

ESSENTIALS Poor-quality medicines negate the enormous advantages of modern pharmaceuticals and lead to avoidable morbidity and mortality; loss of confidence in medicines and healthcare systems; economic losses for patients, their families, governments, and the pharmaceutical industry; and—for anti-infectives—engender pathogen drug resistance. There are many examples of both falsified (due to fraudulent production) and substandard (due to in-factory negligence) medicines, vaccines, diagnostic tests, and devices. The evidence base informing our understanding of their epidemiology is poor, but it is becoming clearer that the distribution of poor-quality medical products varies greatly around the world in both time and place. Formal chemical analysis is highly sophisticated, expensive, and rarely available in many countries. New portable diagnostic devices offer hope that they could empower medicine inspectors and pharmacists to obtain objective evidence for selection of suspicious samples for formal analysis. Caveat emptor (buyer beware) is vital: patients, pharmacists, nurses, and physicians should observe their medicines and be alert when the packaging, medicine taste, or side effects change; when they are surprisingly inexpensive; and when they are associated with unexpected treatment failure and puzzling clinical syndromes. Much greater international effort is needed for the sharing of data about poor-quality medicines so that detection can be acted upon and patients protected.

Introduction Most patients, doctors, and pharmacists tend to assume that the medicines they take or provide are of good quality and that poor-quality medicines are a problem of the distant past or are far away. However, there have been numerous problems with deliberate falsification of medicines and poor-quality production since medicines were first manufactured. Attempts to ensure that countries have a safe and efficacious medicine supply have led to great improvements in medicine regulation in the wealthier world over the last century. However, poor-quality medicines are still with us. There is growing, but belated, concern that much of the developing world's supply of medical products, including medicines, vaccines, diagnostic tests and devices, in particular its supply of anti-infective drugs, are of poor quality. There are also less frequent but important problems in wealthier countries. The enormous investment in pharmaceuticals, research, development, registration, clinical trials, and trade will ultimately be pointless and harmful if the medicines patients take contain insufficient, incorrect, or dangerous ingredients.

Definitions There

has been considerable debate and confusion over definitions for the different types of poor-quality medicines. This has arisen because of poor science and because of tension between the defence of commercial interests and the public health importance of enhanced access to good quality medicines. Here, we use the term falsified to mean poor-quality medicines that are deliberately and fraudulently produced, substandard for those that are poor quality because of unintentional but negligent errors in factory production and degraded for those that left the factory as good quality but deteriorated through not following Good Pharmacy Practice in the distribution chain. The distinction is important as the underlying human motivation and regulatory actions needed for falsified and substandard medicines differ. The term falsified is preferred to 'counterfeit' as the latter is argued to be primarily an intellectual property and trade term rather than concerned with patient outcome and public health. The use of falsified and substandard terminology was agreed at the World Health Assembly in 2017. Substandard medicines usually contain either too little or too much active pharmaceutical ingredient (API) or are of poor bioavailability, leading to low blood levels. Falsified medicines often, but not always, contain no API or the wrong API. The amount of active ingredient is not sufficient information to determine accurately whether a medicine is falsified. Inspection of the packaging, that reveals deception for falsified medicines, is usually required. Epidemiology Products of both the innovative and generics industry, in the private and public sectors, for both expensive and inexpensive medicines

2.10 Medicine quality, physicians, and patients Paul N. Newton

2.10 Medicine quality, physicians, and patients 125 are circulating. There is considerable confusion over the extent of the problem. Many of the data have been collected using 'convenience' sampling and have often been interpreted and extrapolated uncritically. In order to be able to estimate, with confidence intervals, the proportion of the medicine supply in a community or area that is poor quality and to follow change through time and assess the impact of interventions, random sampling is required. Random lot quality assurance sampling may provide a cost-effective alternative to estimate whether the prevalence of poor-quality medicines exceeds a given threshold. The available evidence, although it should be viewed with caution, suggests that there is an important and neglected global problem, but that it is focal through time and space. Hotspots of poor-quality medicines will inevitably lead to focal excess mortality and morbidity. An epidemic of falsified oral artesunate containing no, or minimal, artesunate afflicted mainland Southeast Asia until recently and there remain severe problems with falsified artemisinin combination therapy across Central and West Africa. The WorldWide Antimalarial Resistance Network tabulates and maps accessible reports of the quality of antimalarials (<http://www.wwarn.org/aqsurveyor>). In the United States, over 700 patients were infected with *Exserohilum rostratum*, by being given glucocorticoid injections for chronic musculoskeletal pain from one compounding pharmacy, contaminated with this fungus. Sixty-one patients died. Some c.500 children died from renal failure after ingesting paracetamol containing the renal toxin diethylene glycol in south Asia, Africa, and Central America. In Singapore, 150 nondiabetic patients were admitted with severe hypoglycaemia because they had taken falsified erectile dysfunction medicines containing sulfonylureas. Contaminated substandard magnesium sulphate led to *Serratia* septicaemia in United States and gentamicin-resistant *Pseudomonas aeruginosa* in gentamicin eye drops in Mauritius led to severe eye infections, probably due to errors in manufacture rather than fraud. The national visceral leishmaniasis control programme in Bangladesh used 'miltefosine' that contained no miltefosine. Vaccines have also been affected by both falsification and substandard production, including falsified rabies and influenza vaccines. Expiry date tampering, to falsely lengthen the duration

that medicines and diagnostic tests can be legitimately sold, also occurs. Diagnostic tests have been falsified, as have surgical implants, such as cardiac stents, and insecticide-treated bednets that contained no insecticide. Dental and surgical equipment and electronic components have been falsified, causing patient harm. Detection The formal evaluation of the content and dissolution of medicines requires sophisticated equipment and consumables with highly trained staff and quality assurance/quality control (QA/QC). Medicine regulatory authority (MRA) laboratories in the wealthy world are likely to be equipped with mass spectrometry and high-performance liquid chromatography equipment with dissolution apparatus, for example. However, in most low- or middle-income countries such equipment, along with the necessary technical capacity, consumables, and QA/QC, are not available. In 2018 in Southeast Asia and Africa there are only 5 and 7 countries, respectively, with World Health Organization (WHO) prequalified laboratories for medicine quality analysis. Forensic techniques such as pollen analysis are rarely available. Over the last decade a plethora of portable devices have been invented and developed for the rapid evaluation of medicine quality in the field. These are based on principles such as Raman, near infrared, and image analysis. However, they have not yet been independently compared for diagnostic accuracy and cost-effectiveness, so the jury is still out. However, the hope is that these will empower medicine inspectors and pharmacists to screen medicine quality in the distribution chain and objectively select which samples should be escalated for formal analysis, rather than just relying on eyes and experience. Impact Poor-quality medicines can lead to serious individual health consequences, such as treatment failure due to suboptimal dosing, adverse reactions, and increased morbidity and mortality. They can undermine public confidence in health programmes and waste scarce resources. Patients might also suffer from surprising adverse effects from unexpected active ingredients. For example, falsified co-trimoxazole containing diazepam, metronidazole made of chloroquine, diazepam containing haloperidol, oseltamivir containing vitamin C, ceftazidime made of reused vials containing streptomycin and ofloxacin made of penicillin have been described. Therefore, it is crucial to check a patient's medication when faced with unexpected clinical syndromes. The world clearly has a problem, but the extent is uncertain, in part because the collation of such publicly accessible data has only recently started. There are clear examples where patients have been harmed by poor-quality medicines. However, objective estimates of impact on patient outcome have been difficult. Logically, if a medicine has been shown to reduce mortality by 30% but the medicine taken has zero efficacy (because it contains no API), mortality will not be reduced by that 30%. In order to reliably conclude that a poor-quality medicine has harmed, evidence is needed that (a) a patient has suffered demonstrable harm, (b) proof that the patient took a particular medicine and (c) chemical analysis of that medicine demonstrating that it does not contain what it is stated to contain (or contains toxins). In much of the world, such linked-up evidence has been difficult to obtain. The first evidence-based estimate from modelling of the excess mortality suggested 122 350 under-five malaria deaths per year were associated with consumption of poor-quality antimalarials, representing 3.75% of all under-five deaths in a sample of 39 countries. This is a first approximation and will be refined as the objective evidence improves. Poor-quality medicines also have wider consequences on public health with loss of confidence in healthcare, spread of drug resistant pathogens, economic losses for producers and traders in the genuine articles, and increased burden for health workers. Modelling strongly suggests that underdosing is an important contributor to antimicrobial resistance. Therefore, if patients consume medicines containing low %API (usually substandard medicines) that result in blood levels within the window of selection, the risks of engendering resistance are high. Medicines containing none of the stated API (usually falsified medicines) may also contribute to drug

resistance for some pathogens, such as malaria if they result in hyperparasitaemia and high gametocyte burdens.

126 section 2 Background to medicine Clinical trials have naively been regarded as immune from the issues of poor-quality medicines and medical devices but there is growing realization that their quality should be checked and documented or trials risk wrongly informing policy. Interventions For the individual health worker and patient—caveat emptor is vital. Patients may notice when their medications change in appearance, taste, or side effects. Greater awareness of the problem and suspicion in the face of puzzling clinical syndromes, treatment failure, and medicines that seem surprisingly inexpensive are needed. The problems of poor-quality medicines cannot be viewed in isolation. They are enmeshed with many other complex health system problems, especially the affordability and accessibility of medicines and the often-limited capacity of MRAs in LMICs. MRAs are the keystones for important interventions but only 20% of WHO member states are reported to have well-developed drug regulation and 30% have 'either no drug regulation or a capacity that hardly functions'. Strengthening MRAs, improving the oversight and QA/QC of medicine manufacturing collaboration with other key stakeholders such as procuring agencies, and facilitating patient access to affordable medicines are likely to be key factors in improving quality. A key neglected issue has been the woeful sharing of information between and within countries. There is no global system for the mandatory reporting, assessment, and dissemination of information on suspicious medicines. The more functional MRAs issue alerts and the revitalized WHO's new Rapid Alert System (<http://www.who.int/medicines/publications/drugalerts/en/>) facilitates information sharing on poor-quality medicines between MRAs. The e-drug (<http://lists.healthnet.org/mailman/listinfo/e-drug>) and e-med (<http://lists.healthnet.org/mailman/listinfo/e-med>) systems report medicine quality problems in English and French, respectively. In most of the world there is no legal duty for health workers, academics, or the pharmaceutical industry to report suspicions of poor-quality medicines to the national MRA. There is clearly an ethical duty to do so but this needs to become a legal duty. The Access to Medicine Index (<http://www.accesstomedicineindex.org/>) includes monitoring of the reporting of falsified medicines by the pharmaceutical industry to WHO and MRAs. Areas of uncertainty and controversy There are many other related important global issues that need to be addressed, such as the lack of an international coding system for identifying pills and capsules, poor-quality instruction sheets with medicines in small fonts and in user-unfriendly language. There is an urgent need for clear understanding that generic medicines per se are not counterfeit, and a need for an international convention making medicine falsification an international, extraditable, crime. We need better understanding as to how to engage with societies about medicine quality problems so that they do not inappropriately stop good quality medicines in the face of warnings of poor-quality products. More evidence is needed to understand how best to empower drug inspectors with the optimal new portable devices. It will be key to have an international capacity building and financial mechanism to support MRAs that lack resources to protect the medicine supply and better objective-collated data to inform policy. FURTHER READING Attaran A, et al. (2012). How to achieve international action on falsified and substandard medicines: a consensus statement. *BMJ*, 345, e7381. Caudron JM, et al. (2008). Substandard medicines in resource-poor settings: a problem that can no longer be ignored. *Trop Med Int Hlth*, 13, 1062–72. Fernandez FM, et al. (2011). Poor quality drugs: grand challenges in high throughput detection, countrywide sampling, and forensics in developing countries. *Analyst*, 136(15), 3073–82. Godlee F (2018). Why aren't medical devices regulated like drugs? *BMJ*, 363, k5032. Newton PN, et al. (2006). Counterfeit anti-infective medicines. *Lancet Infect Dis*, 6, 602–13. Newton PN, et al. (2014). Falsified medicines

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