Falsified medicines in Africa: all talk, no action

Poor-quality medicines and medical products, both substandard and falsified, cause avoidable morbidity, mortality, drug resistance, and loss of faith in health systems, especially in low-income and middle-income countries.[1–3] We report the analysis of two falsified medicines from Angola and discuss what lessons such a discovery could hold.

The tablets were seized at Luanda docks in June, 2012, after failing Minilab testing.[4,5] The seized shipment was enormous (1·4 million packets), and hidden in loudspeakers in a container from China.[4] One sample was labelled as an adult course of the vital antimalarial drug artemether-lumefantrine, and as being manufactured by "Novartis Pharmaceutical Corporation"; it also bore an Affordable Medicines Facility—malaria logo (figure). Another sample was labelled as the broad-spectrum anthelmintic mebendazole, and as being manufactured by "Janssen-Cilag SpA".

We analysed the tablets with an array of analytical platforms, including high-performance liquid chromatography, ambient ionisation mass spectrometry, Raman spectroscopy, Xray powder diffraction (XRD) analysis, *nuclear magnetic resonance spectroscopy, isotope-ratio mass spectrometry (IRMS)*, and botanical assays. Packaging was analysed with the portable counterfeit detection device CD-3 (see appendix for detailed methods).

No artemether, lumefantrine, or other active pharmaceutical ingredients were detected in the "artemether-lumefantrine" tablets by any of the chemical assay techniques. Brushite and three different yellow dyes (pigment yellow 3, pigment yellow 81, and pigment yellow 151) were detected. No mebendazole was detected in the "mebendazole" tablets, but the active ingredient levamisole (270 mg/tablet) was. XRD analysis revealed the presence of calcite ($CaCO_3$), with IRMS data suggesting that it was either hydrothermal or medical in origin. The CD-3 ultraviolet-visible and infrared images of the falsified and genuine packaging readily showed substantial differences between them. Language errors on the "mebendazole" packages were common, suggesting that the forger may have had some knowledge of English but little of French and Spanish.

Falsified artemether-lumefantrine has also been described across central and west Africa.[5] Such products will inevitably cause increased morbidity, mortality, and transmission, and could falsely indicate that artemisinin resistance had arrived. Additionally, modelling strongly suggests that underdosing is an important contributor to resistance.[6] Therefore, if patients consume co-circulating falsified and substandard medicines sequentially, so that heavy parasite burdens encounter low drug concentrations, the risks of engendering resistance are high.

The presence of the anthelmintic levamisole is also worrying because it has been withdrawn from many markets for human use owing to its association with agranulocytosis. The recent epidemic of necrotising vasculitis resulting from "cutting" cocaine with levamisole[7] suggests links between criminals who produce narcotics and those who produce falsified medicines.

These examples illustrate the major obstacles to improving the global medicine supply. First, there is no global system for the mandatory reporting, assessment, and dissemination of information on suspicious medicines. The seizure in Angola was first brought to public attention on Facebook after 5 months, and in the printed press after 11 months.[4] It was Facebook who first alerted those responsible for malaria control liaison at WHO. Although such reporting is commendable, it is grossly inadequate for tropical public health what proportion of African malaria patients and their families reads Facebook and the *Wall Street Journal*? Until 2011–12 (when it was invoked for the USA and EU), no nation had legislation requiring the pharmaceutical industry (which is often the first to know) to inform the relevant medicines regulatory authority (MRA) of drug falsification. It is extraordinary that, in 2014, such systems are widely in place for suspicious aircraft parts but not for suspicious medicines.[8] WHO's new Rapid Alert System facilitates information sharing on poor-quality medicines between medicines regulatory authorities (MRAs).[5] It should be mandatory and included in the International Health Regulations.[1] When pharmaceutical companies and others encounter suspicious medicines or medical products, there remains tension between commercial interests, the need to investigate, and the requirement to act quickly to safeguard public health. There is no consensus mechanism to adjudicate these decisions from a public health perspective. This stagnant system must change. All reports of suspect medicines known to the pharmaceutical industry and others should be reported to the WHO and MRA within 1 week for investigation, risk assessment, and appropriate dissemination. If those reporting wish delayed onward dissemination, an advisory committee of MRAs and WHO with independent advice should perform a rapid public health risk assessment. Compliance should be reported through a mechanism such as the Access to Medicine Index.

See Online for appendix

For the **Access to Medicine Index** see http://www.accesstomedicineindex.org/

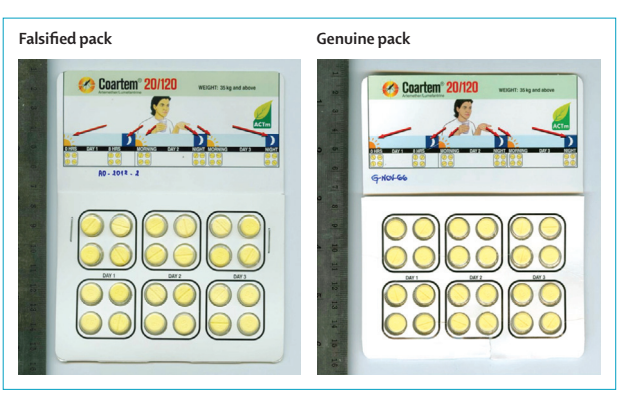

Figure: **Scanned pictures of samples**
Top=falsified blister; bottom=genuine blister.

Second, recent inaction regarding medicine quality has involved disputes over definitions from a trade and political perspective. These disputes must have damaged public health. The acronym NATO (no action—talk only), sadly reflects recent history. Extended discussion at World Health Assemblies culminated in 2011 with the formation of a Member State mechanism. However, chairmanship disagreements then apparently delayed discussion for 6 months.[9] The group now has meetings just once per year.

The terminology remains confused—for example, a recent US Institute of Medicine report on medicine quality[2] did not state clearly what term should be used for medicines that are poor quality but not falsified. Here we have used the distinction between falsified (or counterfeit or spurious medicines—ie, those deliberately and fraudulently mislabelled with respect to identity or source) and substandard medicines (ie, genuine medicines produced by authorised manufacturers that do not meet quality specifications set for them by national standards).[3] To avoid any intellectual property connotations, the term falsified is used here instead of counterfeit.[3] We believe that this is the clearest way forward.

Third, the extradition and prosecution of criminals, such as those trading in falsified medicines between China and Angola, is extremely difficult as falsification of medicine or medical products is not an international crime, and definitions and laws are inconsistent. An international public health convention could assist in combating criminal networks and provide a financing mechanism for MRA and factory support (ie, detecting and reducing factory errors or negligence).[3] The Insitute of Medicine favours soft-law solutions,[2] but the lack of legally binding force would neuter action.

Fourth, the enormous investment in accessible medicines and medical products without investment in checking their quality is profoundly illogical. WHO estimates that only 7% of sub-Saharan countries had a "moderately functioning MRA".[10] We cannot expect the world's medicine supply to improve without coordinated functional MRAs. They are essential for the interventions needed, and to ensure that the benefits of increased accessibility to free or inexpensive internationally financed medicines and inexpensive generics are translated effectively into improved public health. The Access to Medicines movement has been very important in improving access to essential medicines; however, much more emphasis is needed now on access to good quality medicines.

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