Clinical pharmacology in leishmaniasis: treatment optimization of a neglected disease
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Quality of medicines for neglected tropical diseases: an urgent matter

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Abstract

The international community concentrates its efforts on the fight against counterfeit medicines. However, patients with neglected tropical diseases are particularly at risk of receiving substandard medicines, as a result of general system deficits, poor practices and negligence, rather than intentional fraud. Structural negligence and poor practices in pharmaceutical production should never be considered less important than intentional fraud, because their consequences are equally serious for the final user. Due to an unfortunate mix of factors – underfunding of disease control programmes, lack of resources of the national regulatory authorities and lack of corrective measures at (inter)national level – substandard medicines often go undetected, or are discovered only after a heavy morbidity or mortality toll has been paid. Measures should be urgently developed to ensure that drug quality issues are anticipated, rather than dealt with a posteriori. The WHO should play a central role here. We plea that the WHO should prioritize activities aimed at strengthening regulatory capacity and oversight in resource-limited countries, including the support of national drug quality testing laboratories and the inclusion of medicines for neglected diseases in the Prequalification Programme. The major international pharmacopoeias should include monographs for medicines for neglected tropical diseases. Measures to protect neglected patients from dangerous medicines cannot be further postponed.
Defining poor-quality drugs: substandard versus counterfeit

There is broad evidence from scientific literature and anecdotic reports that the plague of poor quality medicines disproportionately hits the poorest populations [1,2], suffering from infectious and often neglected diseases [3,4], and living in countries with weaker or under-resourced national Regulatory Authorities (RA) [5,6]. Poor-quality medicines are currently categorized into substandards and counterfeits, according to the World Health Organization (WHO) substandards are:

“genuine medicines produced by manufacturers authorized by the national RA, which do not meet quality specifications set for them by national standards” [7]

While counterfeits are:

“medicines that are deliberately and fraudulently mislabelled with respect to identity and/or source” [8,9]

The definition of counterfeits is thus solely based on the concept of “fraudulence” and the deliberate mean-spirited intent of their manufacturer. To complicate matters, these definitions cannot be regarded as mutually exclusive: counterfeits are usually also substandards, e.g. if they contain incorrect amounts of active ingredients. Issues related to intellectual property (IP) protection are specifically not within the scope of these WHO definitions. Nevertheless, IP issues and commercial trade interests have contributed to the fact that the issue of counterfeit medicines received more international consideration than substandard medicines. Counterfeits as a whole are considered by many to be a greater threat to the public than substandards, though we believe this to be a fallacy. The game of definitions, has led the international community to concentrate almost all of its efforts on the fight against “fake medicines” with copious initiatives and consortia [10–13], while seriously neglecting the global picture of assuring good-quality medicines in general [14]. We argue that patients suffering from neglected tropical diseases in resource-poor countries are particularly at risk to be confronted with substandard medicines and that the focus of concerted actions from the international community should be shifted from counterfeits to the more structural problem of substandard medicines in resource-poor countries to better protect these vulnerable patients.
Structural substandard practices and negligence of quality standards

The current definitions are not always adequate to describe the complexity of the situation in resource-poor countries [15], as exemplified by a serious case of a poor quality medicine recently identified in Bangladesh. As described more elaborately by Dorlo et al. [16–18], a poor-quality medicine supposedly containing the active pharmaceutical ingredient miltefosine did not contain any miltefosine at all, nor any other active ingredients or related degradation products. The medicine, authorized by the national competent authorities, was manufactured locally for distribution within the Bangladeshi national elimination programme for visceral leishmaniasis. The lack of active ingredient surfaced after reports of abnormally high numbers of treatment failures. The number of fatalities - visceral leishmaniasis is inevitably fatal without proper chemotherapy - remains unreported.

This case does not easily fit in the current WHO definitions. The product should be considered as a substandard, admittedly a euphemistic terminology for a product not containing any active pharmaceutical ingredient, because it was authorized by the government for use within the national elimination programme. Whether it can be additionally regarded as a counterfeit is more difficult to answer, because one should prove the “deliberate or fraudulent” intent of the manufacturer. Irrespectively of the definition, however, a serious anomaly occurred which was not detected at any level of the quality control system. This may be due to a lack of resources, to negligence, or even to fraudulence, but whatever the cause, the outcome for the final users remains the same: unnecessary morbidity and mortality that could have been prevented. In resource-poor countries, substandards are the predictable result of structural negligence of quality standards or poor practices by manufacturers (e.g. lack of identification tests on incoming active ingredients or lack of checks of compliance with pharmacopoeial standards on outgoing batches) [1]. Structural negligence and/or substandard practices in pharmaceutical production should never be considered less important than a ‘deliberate or fraudulent’ action, because their consequences are equally serious for the final user.

Disproportionally affecting neglected tropical diseases

The Bangladeshi case is only one of many cases of poor quality medicines in resource-limited countries [1]. To date, the urgency of drug quality has been internationally recognized and acknowledged in the field of malaria [19–22]. The steep increase in resistance patterns to the traditional antimalarials has raised awareness among care providers and policy makers: extensive surveys have been undertaken to assess
impact of poor-quality medicines [22–27], and initiatives have been launched to tackle and correct the problem [28–30]. Conversely, the issue of drug quality has been largely ignored in the field of neglected tropical diseases, even if scattered reports show that serious problems exist [31–36]. For visceral leishmaniasis, for instance, at least three other reports have been published, originating from India, Nepal and Sudan [34–36], of which two concerned a substandard branded generic sodium stibogluconate product that resulted in increased cardiotoxicity. It is striking that all these cases came to the light only *after* observing abnormally high failure rates or life-threatening toxicities [34,35,37], while the poor practices at the manufacturing site could have been detected *in advance* by stringent regulatory inspections, and the quality of the batches provided to the control programme could have been tested *before* they were released and reached the patients. Ironically, the lack of a private market for drugs for neglected tropical diseases is generally thought to take away any financial incentives and thus to spare this kind of therapeutics from any deliberate counterfeiting activities [38]. However, lack of stringent quality specifications in official tenders for procurements of these medicines in the public sector, intended for national control programmes, predictably result in a purchase from the cheapest possible supplier, with no regard to quality. Due to these procurement policies, patients suffering from neglected tropical diseases may therefore be disproportionately at risk to be exposed to substandard medicines.

**Prioritizing *a priori* solutions**

Measures should be urgently developed to ensure that quality problems are anticipated, rather than be dealt with *a posteriori*. The lack of capacity of national RA, and the lack of structural external support to such RA unfortunately weakens their oversight and impedes stronger and comprehensive preventive actions to be enforced to pharmaceutical manufacturers and distributors suspected of systematic negligence of quality standards, both local and foreign. The WHO should prioritize activities aimed at strengthening the regulatory capacity and oversight in resource-limited countries, including the support of national or regional drug quality testing laboratories. In the public sector, appropriate procurement and tender procedures should be developed, with well defined quality criteria for manufacturers and products [39] and well defined procurement policies [40], and they should be public, in order to maximize the transparency of the selection process and the accountability to the citizens. At international level, guidance should be given on the quality assurance and assessment criteria of pharmaceutical products for neglected tropical diseases. In 2001, the WHO has created the Prequalification Programme [41], which covers the fields of HIV/AIDS, malaria, tuberculosis and reproductive health, to “make quality priority medicines available for the benefit of those in need”. This objective is achieved through the “evaluation and inspection activities,
and by building national capacity for sustainable manufacturing and monitoring of quality medicines”, thus based on structural preventive measures that may impede poor-quality medicines to reach the patients. The Prequalification has become vital for anyone involved in the bulk purchase of good quality medicines. We therefore plea that its scope should be extended to medicines for neglected tropical diseases such as leishmaniasis. Quality assurance is further complicated by the lack of these medicines’ monographs in the major international pharmacopoeia’s. In an effort to resolve this issue, the United States Pharmacopeia (USP) has recently opened up an online section, the USP Medicines Compendium [42], to make good quality standards available in the public domain, also for drugs against neglected tropical diseases. Nevertheless, at the moment most monographs still concern antimalarial and antiretroviral drugs, with only sparse considerations to drugs for neglected tropical diseases. Access to specific technical expertise and resources remains difficult to acquire for under-resourced RA’s in developing countries.

**Concluding remarks**

Political commitment and concerted actions are needed to prevent that any poor-quality medicines further endanger the lives of patients suffering from neglected tropical diseases. To date, because of the lack of a solid quality assurance framework and of sufficient investments in strengthening the capacity of RA’s, cases of poor-quality medicines for neglected tropical diseases cannot be prevented, and they are only discovered after many unnecessary deaths or complications. The WHO Executive Board has brought a resolution to this year’s 65th World Health Assembly [43] which established a new Member State mechanism to advance international collaboration on the specific topic of “substandard/spurious/falsely-labelled/falsified/counterfeit medical products”. One of the tasks of this new Member State mechanism will be to develop new definitions for poor-quality drugs, based on public health considerations. This may be the prime opportunity to refocus definitions as well as public health-oriented corrective actions on the dangers of structural substandard medicine production both in and for insufficiently regulated countries. Measures to protect neglected patients from dangerous medicines cannot be further postponed.
References


