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EDITORIAL

Neglected tropical diseases in Europe: rare diseases and orphan drugs?

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Abstract
Neglected tropical diseases are becoming more and more frequent in Europe due to the increasing immigration from endemic areas. Nonetheless specific treatments are scarcely available in many European countries, since they are neither officially licensed nor marketed. Only a few referral health centres can afford to access drugs for NTDs due to complex bureaucracy and high cost, importing or providing them via the WHO. Health professionals and institutions in this domain should solicit other stakeholders (such as NGOs, the civil society, scientific societies) to sensitize health authorities to improve access to treatment for such debilitating diseases.

Keywords Neglected tropical diseases · Orphan drugs · Access to care · Migrants · Parasitic

Manuscript

Neglected tropical diseases (NTDs) are a group of diverse communicable diseases which are highly prevalent in tropical countries, causing a significant burden of morbidity, mortality, suffering and economic loss [1]. Moreover, their burden is particularly significant in low-income countries and in marginalized populations living in poverty, in close contact with vectors and animal reservoires of infectious diseases, and with limited access to safe water, sanitation and health care. Neglected tropical diseases mainly affect neglected populations.

They contrast to the so-called "big three" (malaria, tuberculosis and HIV infection), which drain most attention, interest, research and financing worldwide. This is one of the reasons why NTDs are called neglected.

The NTDs list defined by the World Health Organization (WHO) includes: Buruli ulcer, Chagas disease, dengue and chikungunya, dracunculiasis, echinococcosis, foodborne trematodiases, human African trypanosomiasis, leishmaniasis, leprosy, lymphatic filariasis, mycetoma, chromoblastomycosis and other deep mycoses, onchocerciasis, rabies, ectoparasites, schistosomiasis, soil-transmitted helminthiases, snakebite envenoming, taeniasis/cysticercosis, trachoma and yaws [2].

Some of these diseases are potentially fatal (e.g., strongyloidiasis, African trypanosomiasis, dengue), and some of them cause severe disability (e.g., schistosomiasis, filariasis, Chagas disease).

The migration from low-income countries to Europe, as well as international travels, are making these conditions more and more frequent nowadays even out of endemic areas [3, 4], but the European health systems are far to be prepared to face these increasing challenges.

Most NTDs are parasitic and deserve-specific treatment. Being categorized under "rare diseases" in Europe (although they affect more than 1 billion people in endemic countries), the status of their specific treatment is often referred to as orphan drugs, which allows them gaining profit incentives by the law in Europe [5]. Moreover, none of these drugs used to treat NTDs is listed under the orphan drugs in Italy (Orphanet) [6] nor the national drugs formulary contains the most part of them. This situation does happen also in other European countries, mostly because NTDs are rare; drugs are often old and cheap, so that their market has a limited appeal to the pharma industry and trade. Therefore, their access in Europe is often difficult, despite extensive

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Table 1 Orphan drug licensing in Italy, Spain and Germany

Drug	Main target conditions	License AIFA Italy	License AEMPS Spain	License BfArM Germany
Benznidazole	Chagas disease	No	No	No
Diethylcarbamazine	Lymphatic filariasis	No	No	No
Eflornithine i.v.	African trypanosomiasis	Withdrawn	No	No
Ivermectin tabs	Strongyloidiasis, onchocerciasis	No	No	Yes (for scabies only)
Meglumine antimoniate	Leishmaniasis	Withdrawn	Yes	No
Melarsoprol	African trypanosomiasis	No	No	No
Miltefosine	Leishmaniasis	No	No	Yes
Nitazoxanide	Giardiasis amoebiasis, cryptosporidiosis	No	No	No
Praziquantel	Schistosomiasis, cestodes, trematodes	No	No	Yes
Primaquine	P. vivax/P. ovale malaria	Withdrawn	No	No
Quinacrine*	Refractory giardiasis	No	No	No
Suramin	African trypanosomiasis	No	No	Yes
Thiabendazole	Strongyloidiasis, ancylostomiasis	Withdrawn	Withdrawn	No
Triclabendazole	Fascioliasis	No	No	No

*Not in the WHO essential medicines list

donations are improving availability in endemic countries worldwide [7].

Nitazoxanide, suramin, eflornithine, melarsoprol, benznidazole, triclabendazole, miltefosine, diethylcarbamazine, praziquantel, thiabendazole, primaquine, meglumine antimoniate, and ivermectin, are just examples of medications for NTDs which, in spite of being included in the WHO essential medicines list [8] and not being replaceable by other ones, are not marketed in Italy. Most of them are not even licensed by the Italian drug regulatory agency (Agenzia Italiana del Farmaco—AIFA) [9] and for some of them the importation and distribution by public health centres and infectious diseases services are unfeasible. To sensitize the Ministry of Health and AIFA on the problem of low access to drugs for NTDs, following the meeting "Ivermectin days" held in Verona in November 2017, a network of partners was set up including representatives of the civil society, NGOs with focus on migrants' health, the Italian Society of Tropical Medicine and Global Health, and other Institutions dealing with NTDs. The poor accessibility of NTDs drugs is similar in Spain (Agenzia Española de Medicamentos y Productos Sanitarios—AEMPS) [10] and slightly better in Germany (Bundesinstitut für Arzneimittel und Medizinprodukte—BfArM) [11] (Table 1), and possibly in other European countries. Unregistered drugs must be searched abroad, and their provision requests complicated bureaucracy and a significant waste of time, making in fact them available only for selected referral centres. Physicians must prescribe these drugs under their own responsibility, and the costs, which are increased by the import process, often burden the patients. Many of them cannot afford to buy the drugs, and thus simply do not get treated.

As far as population movements from low-income countries to Europe are not due to arrest—they are actually on the rise—health authorities should face the problem and get organized to allow these conditions be properly treated. Public registries of stocking should be made available to public hospitals and outpatient clinics of National Health Systems, and drugs should be either imported or locally produced. Accessibility to "orphan" drugs for NTDs, which are becoming increasingly more common in Europe, should be improved, providing simple and rapid registration routes and reducing costs, to protect both the patients and the community.

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Compliance with Ethical Standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. WHO. World Health Organization, Working to overcome the global impact of neglected tropical diseases: First WHO Report on neglected tropical diseases (Geneva: World Health Organization 2010). http://apps.who.int/iris/bitstream/10665/44440/1/9789241564090_eng.pdf. Accessed 7 Oct 2018.
2. WHO. Neglected tropical diseases http://www.who.int/neglected_diseases/diseases/en/ Accessed 7 Oct 2018.
3. Schlagenhauf P, Weld L, Goorhuis A, Gautret P, Weber R, von Sonnenburg F, Lopez-Vélez R, Jensenius M, Cramer JP, Field VK, Odolini S, Gkrania-Klotsas E, Chappuis F, Malvy D, van

Genderen PJ, Mockenhaupt F, Jauréguiberry S, Smith C, Beeching NJ, Ursing J, Rapp C, Parola P, Grobusch MP, EuroTravNet. Travel-associated infection presenting in Europe (2008–12): an analysis of EuroTravNet longitudinal, surveillance data, and evaluation of the effect of the pre-travel consultation. Lancet Infect Dis. 2015;15:55–64. https://doi.org/10.1016/S1473-3099(14)71000-X. Epub 2014 Dec 2.

4. Lingscheid T, Kurth F, Clerinx J, Marocco S, Trevino B, Schunk M, Muñoz J, Gjørup IE, Jelinek T, Develoux M, Fry G, Jänisch T, Schmid ML, Bouchaud O, Puente S, Zammarchi L, Mørch K, Björkman A, Siikamäki H, Neumayr A, Nielsen H, Hellgren U, Paul M, Calleri G, Kosina P, Myrvang B, Ramos JM, Just-Nübling G, Beltrame A, da Saraiva Cunha J, Kern P, Rochat L, Stich A, Pongratz P, Grobusch MP, Suttorp N, Witzenrath M, Hatz C, Zoller T, TropNet Schistosomiasis Investigator Group. Schistosomiasis in European Travelers and Migrants: analysis of 14 years tropnet surveillance data. Am J Trop Med Hyg. 2017; 97:567–74. https://doi.org/10.4269/ajtmh.17-0034. Epub 2017 Jul 19.
5. Gerke S, Pattinson SD. EU marketing authorisation of orphan medicinal products and its impact on related research. Eur J Health Law. 2017;24:541–64. https://doi.org/10.1163/15718093-12341439.
6. Orphanet. http://www.orpha.net/ Accessed 7 Oct 2018.
7. WHO. Essential medicines donated to control, eliminate and eradicate neglected tropical diseases 2018. http://www.who.int/neglected_diseases/pharma_contribution/en/ Accessed 7 Oct 2018.
8. WHO. Model list of essential medicines 20th list (March 2017, amended august 2017) http://www.who.int/medicines/publications/essentialmedicines/en/ Accessed 7 Oct 2018.
9. AIFA. La Banca Dati Farmaci. https://farmaci.agenziafarmaco.gov.it/bancadatifarmaci/home Accessed 7 Oct 2018.
10. AEMPS. Find your medicine here. https://www.aemps.gob.es/cima/publico/home.html Accessed 7 Oct 2018.
11. BfArM. Medizinprodukte. https://www.bfarm.de/DE/Medizinprodukte/_node.html Accessed 7 Oct 2018.