

**Title:** Neglected tropical diseases in non-endemic countries in the era of COVID-19 pandemic: the great forgotten

**Running title:** NTDs in non-endemic countries & COVID-19

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**Teaser:** In non-endemic countries, the access to healthcare for migrants and other patients with NTDs may be hampered by new barriers linked to the COVID-19 pandemic. Low awareness of health care professionals on the opportunistic potential of some NTDs may lead to unfavorable outcome of COVID-19 patients treated with immunomodulatory drugs.

## Text

Neglected tropical diseases (NTDs) are a diverse group of 20 diseases affecting 1 billion people in 149 countries, mainly in tropical and subtropical regions, associated with poverty and frequently disattended by the public health and research agenda.<sup>1</sup> The COVID-19 pandemic has created more medical neglect and inequalities worldwide, healthcare delayed and health needs unattended, even in the most advanced health systems, for both chronic and acute conditions.<sup>2</sup> It will take time to appreciate the fuller, long-term effect on public health.

What we are seeing are both direct and indirect consequences of measures adopted to tackle the pandemic, and it is little surprise that the typical NTDs are being hit hardest in endemic countries, through a combination of newer (discontinuation of preventive chemotherapy campaigns recommended by the World Health Organization to reduce the risk of SARS-CoV-2 spreading)<sup>1</sup>, and longer-term factors (such as conflicts, embargoes, and social opposition to mass distribution and vaccination programs); a recent paper underlines the major threat of syndemic malaria, NTDs and COVID-19 in low and middle-income countries.<sup>3</sup>

In recent years also high-income temperate countries have seen an increase in imported NTD cases - mainly linked to migration, but also to international travels and commerce and to climate changes.<sup>4,5</sup> Schistosomiasis, strongyloidiasis, and Chagas disease are among the most relevant imported NTDs and migrants are those at highest risk for NTDs.<sup>4</sup> In addition, some temperate high-income regions are still endemic for some of these diseases: active transmission of leishmaniasis occur in Italy, Spain and other Mediterranean countries,<sup>6</sup> *Strongyloides stercoralis* infection is still prevalent in the Appalachian region of the United States of America (USA), in northern Australia and in focal areas of several European

countries such as northern Italy, Southern Spain, France and the mining regions of Belgium, especially in the elderly<sup>7</sup>. Plague is endemic in wild rodents in parts of the USA and Russia.<sup>8</sup>

Already before the COVID-19 pandemic upsurge, there were concerns about public health approaches, diagnostic delays and deficiencies in clinical management of NTDs in non-endemic countries. Healthcare professionals are poorly aware of these diseases, specific diagnostics and drugs may not be available in many facilities<sup>9</sup>, few guidelines are available on screening, diagnosing and treating, and when available, they are poorly implemented.<sup>10</sup>

The COVID-19 pandemic risks to further complicate the management of NTDs especially in the fragile population of migrants which traditionally has difficult access to the healthcare system and is at risk of being marginalized even more. Public health systems which have been stripped of resources overtime are now additionally stressed and resources redirected to tackle the COVID-19 situation, resulting in visits and laboratory tests being delayed if for other pathologies, on top of individuals not or postponing seeking medical care for fear of being exposed to COVID-19. This situation can result in increase of acute and chronic health issues from NTDs, with potentially severe and irreversible complications for diseases like schistosomiasis.<sup>9</sup> Moreover less research funding will be available for NTDs, as funds are being redirected towards COVID-19.

There are also potential concerns with some of the COVID-19 treatments. Several immunomodulatory drugs have been proposed and used to control the so-called “cytokine storm”, and WHO has recently issued a guideline for the use of corticosteroids in COVID-19.<sup>11</sup> The impact of this immunomodulatory therapy on the reactivation of latent infections is poorly known. NTDs such as strongyloidiasis, Chagas disease, and leishmaniasis are often overlooked unlike other infections such as viral hepatitis, HIV and tuberculosis. Although we know that each of these infections may act as an opportunistic disease in all

immunosuppressed patients with potentially severe and even fatal manifestations often difficult to identify since the symptoms may be aspecific.

Strongyloidiasis is the most concerning disease since even low-dose corticosteroids may induce a *S. stercoralis* hyperinfection and dissemination with very high fatality rate.<sup>12</sup> All migrants from highly-endemic countries and elderly patients from the endemic foci in temperate areas should be screened for strongyloidiasis using a combination of serology and direct detection on stool through parasitological or molecular methods or presumptively treated with ivermectin when testing is unavailable or delayed and when treatment with steroids is imminent.<sup>12</sup>

Concerning Chagas disease and leishmaniasis it seems unlikely that short courses of immunomodulatory drug could increase the risk of a severe reactivation. However, a serological screening in all COVID-19 patients at risk for Chagas disease (such as patients born in continental Latin American or from a continental Latin American mother) seeking medical attention would be useful. Chagas disease underdiagnosis surpasses 94% in non-endemic setting, so testing people at risk would help identify affected subjects and link them to care.<sup>11</sup> Moreover people with Chagas disease could have unidentified cardiac problems which could complicate the course of COVID-19 requiring a more strict follow-up.

Concerning leishmaniasis, clinical monitoring of patients currently living or exposed in the past in endemic areas who undergo immunosuppressive treatment is advisable to early detect manifestation such as unexplained prolonged fever, cytopoenia, and muco-cutaneous lesions.

In conclusions NTDs are diseases of poverty, sustained by social inequalities, whether in endemic or non-endemic, high-income countries where the most frequently affected subjects are migrants and to a less extent, international travelers and autochthonous subjects in delimited enclaves. COVID-19 can cause more neglect for NTDs affected patients but may

also represent an opportunity to screen at risk subjects seeking medical attention in this period for some of these diseases. It is important to raise awareness of health care professionals managing COVID-19 patients about strongyloidiasis and other potentially opportunistic NTDs in order to implement adequate management strategies. It is also important to resume screening programs for NTDs for refugees/migrants, when suspended for COVID-19, and to strengthen diagnostic and treatment capacities in areas that are underserved.

As health systems learn how better to cope with COVID-19, let's be reminded that NTDs, though rare in the general population, are disproportionately present in disadvantaged pockets of our populations in high-income countries.

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