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Short Communication

Ivermectin: repurposing a multipurpose drug for Venezuela's humanitarian crisis

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ABSTRACT

Ivermectin (IVM) is a robust antiparasitic drug with an excellent tolerance and safety profile. Historically it has been the drug of choice for onchocerciasis and lymphatic filariasis global elimination programs. IVM is an oral insecticide and is a standard treatment against intestinal helminths and ectoparasites. The current humanitarian crisis in Venezuela is a regional public health threat that requires immediate action. The public health system in Venezuela has crumbled because of a 70% shortage of medicines in public hospitals, low vaccination campaigns, and the mass exodus of medical personnel. Herein we discuss the repurposing of IVM to attenuate the burden imposed by the most prevalent neglected tropical diseases (NTDs) in Venezuela, including soil-transmitted helminths, ectoparasites and, possibly, vector-borne diseases, such as malaria. In addition, novel experimental evidence has shown that IVM is active and efficacious in vitro against Chagas disease, Leishmaniases, arboviruses, and SARS-CoV-2. In crisis-hit Venezuela, all these infectious diseases are public health emergencies that have long been ignored and require immediate attention. The versatility of IVM could serve as a powerful tool to tackle the multiple overlapping endemic and emergent diseases that currently affect Venezuela. The repurposing of this multipurpose drug would be a timely therapeutic approach to help mitigate the tremendous burden of NTDs nationwide.

1. Ivermectin: beyond Paul Ehrlich's original vision

A single therapeutic agent that can simultaneously help mitigate multiple neglected tropical diseases (NTDs) is an essential humanitarian tool to combat disease in the developing world. Beyond Ehrlich's vision of the "magic bullet" as a compound targeting a single pathogen in an exclusive and highly precise fashion, ivermectin (IVM) has emerged as the first multi-target drug to tackle a broad range of endoparasites and ectoparasites, viruses, and disease-transmitting vectors [1].

Many tropical and subtropical regions, such as Venezuela, are endemic to numerous infectious agents with overlapping demographic and geographic distributions. Examples include gastrointestinal helminths, such as *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whipworm) and *Necator americanus* (hookworm), as well as clinically relevant protozoan infections, such as the Leishmaniases, American trypanosomiasis (Chagas disease) and malaria. In addition, tropical areas are fertile ground for a plethora of endemic viral (mostly arboviral) infections, such as Dengue, Zika, Yellow fever, and Chikungunya [2].

The history of IVM as a deworming drug is well documented. IVM was derived from the avermectins produced by *Streptomyces avermitilis*, an actinobacterium isolated by Satoshi Omura and his research group at the Kitasato Institute and Kitasato University in Japan. The drug was developed for veterinary and clinical use by William Campbell and colleagues at Merck and Co. Current generic formulations are mixtures of avermectin derivatives that must contain at least 80% 22,23-dihydroavermectin-B1a and not more than 20% 22,23-dihydroavermectin-B1b [1]. IVM is a potent agonist of glutamate-gated chloride channels, causing major neuromuscular

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disruption in many invertebrates, including nematodes and arthropods. Although its antiparasitic mechanisms are not completely understood, evidence supports a prominent immunoregulatory role for IVM in humans. Immunoregulatory compounds usually develop little to no resistance over time and this may explain the consistent efficiency of IVM despite decades of use in the treatment of human parasitic infections [1].

Although IVM is regarded as a robust antiparasitic drug, its myriad alternative uses continue to be underestimated. IVM has an excellent tolerance and safety profile and is the drug of choice for global elimination programs for onchocerciasis and lymphatic filariasis; however, the full therapeutic potential of this drug to combat multiple diseases-causing agents has yet to be determined [3].

Hereby we propose a call for action to use IVM as a strategy to combat the most preponderant NTDs and other emergent diseases in crisis-hit Venezuela.

2. Venezuela: a desperate call for action

The current humanitarian crisis in Venezuela is a regional public health threat that requires immediate action. The public health system in Venezuela has crumbled because of a 70% shortage of medicines in public hospitals, low vaccination campaigns, and the mass exodus of medical personnel. Marginalized populations, including urban and rural poor along with long-vulnerable indigenous communities [4], are most affected. These communities also have precarious water and sanitation systems and poor hygiene practices (WASH) that create a freeway for enteric pathogen transmission.

Massive migration motivated by crime, violence and poverty, along with the re-emergence and expansion of formerly controlled NTDs in Venezuela have simultaneously created a human disease exodus without precedent. This phenomenon has an ever-increasing spillover effect into neighboring countries, particularly Colombia and Brazil [2]. In the context of this crisis, Venezuela needs a therapeutic agent that can simultaneously help mitigate multiple endemic NTDs and other emerging diseases.

3. Ivermectin activity against nematodes and ectoparasites

IVM showed promise in Venezuela through the unmatched success of the WHO's Onchocerciasis Elimination Program for the Americas (OEPA) [5]. Starting in 1993, mass drug administration (MDA) of IVM in a biannual or quarterly fashion has interrupted transmission in 11 of the 13 hyperendemic foci in the region [5] by eliminating microfilaria and inhibiting their release from gravid female adult worms [1,5]. Two remaining foci in the Venezuelan and Brazilian Amazonia are still to be adequately controlled. These are regions where the most vulnerable indigenous Yanomami communities live. Recent MDA efforts have achieved a 70% decrease in onchocerciasis transmission and morbidity in the Venezuelan focus, highlighting the feasibility of complete interruption with minimal resource investment [5].

Control of intestinal nematodes has been difficult in Venezuela. Many nematodes fall into the category of soil-transmitted-helminths (STHs), which constitute one of the most common causes of morbidity nationwide. IVM induces neuromuscular disruption in nematodes [1] and is highly effective in combination with albendazole/mebendazole against *Strongyloides stercoralis, Enterobius vermicularis*, roundworms, whipworms and hookworms [6]. Recent reports have placed prevalence rates for STHs in rural Venezuelan communities as high as 65% [7], but this is likely to be an underestimate because of the lack of consistent surveillance. Cardinal clinical features of STH infections in children include malnutrition, anemia, stunting of somatic growth and intellectual development, fatigue, impaired concentration and memory and an overall reduction in school attendance [6]. IVM-based MDA approaches have the potential to reduce the prevalence of STH infections, thus increasing community productivity and economic development in the future. IVM is effective against scabies and is the only registered drug for ectoparasitic infections in the WHO's 21st Model List of Essential Medicines [8]. As no epidemiological bulletins have been issued by the national government in recent years, scabies in Venezuela could have already reached epidemic proportions.

4. Ivermectin against malaria

The incidence of malaria in Venezuela reached an astonishing 411 586 reported cases in 2017, many with evidence of mixed *Plasmodium* infection. Inadequate WASH conditions fueled by illegal mining created additional mosquito breeding habitats in proximity to a susceptible transient population. The surge in malaria cases has strained the remaining public health resources in Venezuela, and has led to a spillover to neighboring countries [2].

Massive IVM-based vector control is a promising tool for malaria surveillance in low-income countries. Classic methods, such as indoor residual spraying or insecticide-treated nets, may be insufficient over time, mainly due to the increased behavioral adaptation displayed by *Anopheles* mosquitoes that selectively avoid insecticide-impregnated objects and develop new exophilic tendencies [9]. IVM-based vector control not only takes advantage of its endectocide effects to break the malaria cycle of transmission by killing mosquitoes that feed on IVM-treated humans, but it can also inhibit parasite replication inside the vector [10,11]. Therefore, it can rapidly reduce the mean incidence of malaria infections [1,9]. For these reasons, repurposing orally-administered IVM could be a sensible complement to the long-established vector-control protocols [1,9]. This is particularly appropriate for Venezuela, where national malaria incidence increased 10-fold over a decade, and where persistent hot-spots make disease control particularly difficult [2].

5. Ivermectin against Trypanosomatids

Amongst the trypanosomatid infections endemic to Venezuela are the Leishmaniases [2] and Chagas disease.

The Leishmaniases are a group of protozoan diseases with manifestations ranging from disfiguring cutaneous and mucocutaneous lesions to the life-threatening visceral form (Kala-azar). As a result of human migration, deforestation and climate change, a rapidly-increasing number of cases have been reported inside Venezuela (61 576 cases between 1990 and 2016) and exported elsewhere [2]. IVM has shown great promise as an endectocide against disease-transmitting vector, the phlebotomine fly (sandfly), with a maximum effect 1-2 days after administration [1]. Both commercially-available IVM and its experimental derivatives have shown antileishmanial activity against *Leishmania major* and *Leishmania amazonensis* in vitro at micromolar concentrations [1,12]. However, as maximum plasma concentrations of standard doses of IVM in vivo only reach peak nanomolar concentrations, further research should focus on the possible immunomodulatory role of IVM instead of its direct antiparasitic effect in *Leishmania* sp. infection. Repurposing IVM could open new ground for alternative therapeutic options to the painful, potentially toxic and prolonged therapy with pentavalent antimonials.

Chagas disease is caused by the protozoan *Trypanosoma cruzi* and transmitted by hematophagous triatomine bugs and is another chronic trypanosomatid infection with high cumulative prevalence in Venezuela. Unfortunately, its burden is difficult to estimate as the national program for disease surveillance and control was shut down by the national government in 2012 [2]. Nonetheless, recent surveillance samplings of triatomines from the capital district have revealed that up to 76.1% of the bugs were naturally infected, setting the stage for active transmission in large urban areas and the persistent hyperendemic foci that remain in rural communities of Venezuela [2]. Although no effective all-stage antitrypanosomal drug has so far been described, IVM has been reported to increase triatomine mortality [1]. Thus, IVM is emerging as a potential endectocide strategy for halting transmission in endemic Venezuelan soil and deserves further investigational evaluation.

6. Ivermectin against arboviruses and human coronavirus

The Venezuelan crisis has also favored transmission, expansion and export of arboviral infections. Notably, Venezuela ranked 3rd in the number of cases of Dengue reported (125 000) during the 2010 epidemic, while Chikungunya and Zika incidence reports have gone as high as 112 and 2124 cases per 100 000 people, respectively [2]. IVM has been shown to inhibit replication of many Flaviviruses (Dengue, Zika, Yellow fever) and other arboviruses, such as Venezuelan equine encephalitis virus, possibly targeting non-structural protein 3 helicase or nuclear import/export proteins [1,13,14]. However, these findings have been shown in vitro, and equivalent plasma concentrations to standard IVM dosage in humans remain to be determined as well as whether these would prove appropriate within therapeutic ranges. Further trials are required to assess the true impact of IVM in halting transmission of endemic arboviruses and its potential large-scale use in humans.

A more recent study reported the antiviral activity of IVM against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in vitro, possibly due to inhibition of importin $\alpha/\beta1$-dependent nuclear import of viral proteins [14]. The report also showed a 93% decrease in viral RNA at 24 h, and an effective clearance of all viral particles at 48 h. No toxicity effects were observed. As with *Leishmania* sp. infection, additional research is necessary to determine other potential effects of physiological concentrations of IVM on viral and host targets, including nicotinic receptor activity, immunomodulation and spike protein docking.

This is a clear example of the versatility of IVM against other emerging pathogens. However, controlled trials are required to prove its effects in humans, with careful consideration of the neurotoxic effects of IVM, which can be amplified in the context of a compromised blood-brain-barrier due to viral neurotropism and a pro-inflammatory state.

7. Ivermectin to enhance WASH- MDA Integrated Approaches

Combining WASH and MDA interventions can potentially reduce multiple NTDs as a long-term sustainable solution for many Venezuelan communities. In addition to deworming, STH transmission routes can be narrowed through WASH interventions that create barriers for parasites [15]. This approach, however, requires an effective drug such as IVM that can interrupt transmission of multiple nematodes to prevent reinfection. IVM is also effective against many ectoparasites that can be prolific in the same impoverished, overcrowded areas with inadequate sanitation and hygiene.

The primary barrier, sanitation, can prevent fecal pathogens from reaching the environment through the safe collection and disposal of feces. Secondary barriers, such as water treatment and hand washing, and tertiary barriers, including cleansing of vegetables and kitchen utensils, interrupt the transmission route of parasites already in the environment and prevent them from reaching new susceptible hosts [16].

Previous cluster-randomized trials have shown the impact of WASH conditions in reducing roundworms [15,17,18] after deworming with albendazole. However, albendazole alone is less effective for treating other STHs, such as whipworms and hookworms [17,19]. But a co-administered IVM-albendazole treatment against STHs can have higher efficacy when compared with a single-dose albendazole treatment [17,19]. Other authors suggest that the combined IVM-albendazole MDA can maximize effects against malaria and STHs in areas where these diseases overlap in distribution [20].

8. Conclusion

Venezuela is in urgent need of humanitarian assistance. Despite recognition of the severity of the crisis by international organizations, efforts thus far have been unable to mitigate the crisis. Moreover, Venezuela's refugee crisis, the largest ever reported in the Western hemisphere, is reshaping Latin America's public health landscape. The crisis is allowing the formation of disease corridors to neighboring and other countries in the region, breaching their already vulnerable public health systems.

According to WHO statistics from 2006 and 2008, Venezuela ranked the lowest in deworming coverage of pre- and school-aged children amongst all 31 STH endemic countries in Latin American and the Caribbean [21]. Thus, in a multidisciplinary effort led by scientists, non-governmental organizations (NGOs) and several international organizations, such as Rotary, efforts have been put into the implementation of local deworming campaigns, the "Deworming Venezuela" project.

The versatility and broad therapeutic spectrum of IVM make it an outstanding tool against multiple overlapping endemic diseases in Venezuela. We propose that administration of IVM be incorporated with other deworming interventions and disease-control programs to assist those affected by the Venezuelan crisis.

Declarations

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2020.106037.

References

[1] Ivermectin Crump A. enigmatic multifaceted 'wonder' drug continues to surprise and exceed expectations. J Antibiot (Tokyo) 2017;70(5):495–505. https://doi.org/10.1038/ja.2017.11.

[2] Grillet ME, Hernández-Villena JV, Llewellyn MS, Paniz-Mondolfi AE, Tami A, Vincenti-Gonzalez MF, et al. Venezuela's humanitarian crisis, resurgence of vector-borne diseases, and implications for spillover in the region. Lancet Infect Dis 2019;19:e149–61. https://doi.org/10.1016/S1473-3099(18)30757-6.

[3] Speare R, Durrheim D. Mass treatment with ivermectin: An underutilized public health strategy. Bull World Health Organ 2004;82:562.

[4] Paniz-Mondolfi AE, Tami A, Grillet ME, Márquez M, Hernández-Villena J, Escalona-Rodríguez MA, et al. Resurgence of Vaccine-preventable diseases in Venezuela as a regional public health threat in the Americas. Emerg Infect Dis 2019;25:625–32. https://doi.org/10.3201/eid2504.181305.

[5] Botto C, Basañez MG, Escalona M, Villamizar NJ, Noya-Alarcón O, Cortez J, et al. Evidence of suppression of onchocerciasis transmission in the Venezuelan Amazonian focus. Parasit Vectors 2016;9:1–18. https://doi.org/10.1186/s13071-016-1313-z.

[6] Heukelbach J, Wilcke T, Winter B, Sales De Oliveira FA, Sabóia Moura RC, Harms G, et al. Efficacy of ivermectin in a patient population concomitantly infected with intestinal helminths and ectoparasites. Arzneimittel–Forschung/Drug Res 2004;54:416–21.

[7] Incani RN, Ferrer E, Hoek D, Ramak R, Roelfsema J, Mughini-Gras L, et al. Diagnosis of intestinal parasites in a rural community of Venezuela: Advantages

and disadvantages of using microscopy or RT-PCR. Acta Trop 2017;167:64–70. https://doi.org/10.1016/j.actatropica.2016.12.014.

[8] Ventegodt S. World health organization model list of essential medicines. Ment Holist Heal Some Int Perspect 2015:119–34.

[9] Chaccour C, Rabinovich NR. Advancing the repurposing of ivermectin for malaria. Lancet 2019;393:1480–1. https://doi.org/10.1016/S0140-6736(18)32613-8.

[10] Kobylinski KC, Foy BD, Richardson JH. Ivermectin inhibits the sporogony of Plasmodium falciparum in Anopheles gambiae. Malar J 2012;11:381.

[11] Pinilla YT, Lopes SCP, Sampaio VS, Andrade FS, Melo GC, Orfanó AS, et al. Promising approach to reducing Malaria transmission by ivermectin: Sporontocidal effect against Plasmodium vivax in the South American vectors Anopheles aquasalis and Anopheles darlingi. PLoS Negl Trop Dis 2018;12:e0006221.

[12] dos Santos AR, Falcão CAB, Muzitano MF, Kaiser CR, Rossi-Bergmann B, Férézou JP. Ivermectin-derived leishmanicidal compounds. Bioorganic Med Chem 2009;17:496–502. https://doi.org/10.1016/j.bmc.2008.12.003.

[13] Mastrangelo E, Pezzullo M, De Burghgraeve T, Kaptein S, Pastorino B, Dallmeier K, et al. Ivermectin is a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity: new prospects for an old drug. J Antimicrob Chemother 2012;67(8):1884–94. https://doi.org/10.1093/jac/dks147.

[14] Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res 2020;178:104787. https://doi.org/10.1016/j.antiviral.2020.104787.

[15] Vaz Nery S, Pickering AJ, Abate E, Asmare A, Barrett L, Benjamin-Chung J, et al. The role of water, sanitation and hygiene interventions in reducing soil-transmitted helminths: Interpreting the evidence and identifying next steps. Parasit Vectors 2019;12:273. https://doi.org/10.1186/s13071-019-3532-6.

[16] Whitley L, Hutchings P, Cooper S, Parker A, Kebede A, Joseph S, et al. A framework for targeting water, sanitation and hygiene interventions in pastoralist populations in the Afar region of Ethiopia. Int J Hyg Environ Health 2019;222:1133–44. https://doi.org/10.1016/j.ijheh.2019.08.001.

[17] Moser W, Schindler C, Keiser J. Efficacy of recommended drugs against soil transmitted helminths: systematic review and network meta-analysis. BMJ 2017;358:j4307. https://doi.org/10.1136/bmj.j4307.

[18] Freeman MC, Clasen T, Brooker SJ, Akoko DO, Rheingans R. The impact of a school-based hygiene, water quality and sanitation intervention on soil-transmitted helminth reinfection: a cluster-randomized trial. Am J Trop Med Hyg 2013;89:875–83. https://doi.org/10.4269/ajtmh.13-0237.

[19] Palmeirim MS, Hurlimann E, Knopp S, Speich B, Belizario VJ, Joseph SA, et al. Efficacy and safety of co-administered ivermectin plus albendazole for treating soil-transmitted helminths: A systematic review, meta-analysis and individual patient data analysis. PLoS Negl Trop Dis 2018;12:e0006458. https://doi.org/10.1371/journal.pntd.0006458.

[20] Kobylinski KC, Alout H, Foy BD, Clements A, Adisakwattana P, Swierczewski BE, et al. Rationale for the coadministration of albendazole and ivermectin to humans for malaria parasite transmission control. Am J Trop Med Hyg 2014;91:655–62. https://doi.org/10.4269/ajtmh.14-0187.

[21] Ault S, Nicholls R, Saboya M, Gyorkos T. Workshop on integrating deworming intervention into preschool child packages in the Americas 2011:1–70.