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One Health

Editorial Commentary

Ivermectin against COVID-19: The unprecedented consequences in Latin America

Ivermectin (IVM) is a member of the large-spectrum macrocyclic lactone antiparasitic group with a multiple mechanism of action and practically no side-effects to the host animal, when used at its therapeutic dose. The drug was developed 50 years ago and is recommended to control parasitic infestations in animals and humans (*i.e.* ascariasis, river blindness and lymphatic filariasis) [1]. The drug is available in different formulations making it very popular in preventive veterinary medicine. Apart from being a Nobel Prize-winning drug, *endo-* and ectoparasites have developed a strong tolerance to IVM since the 1980s with increasing reports in the last two decades. This condition has pushed researchers to develop monitoring tests and strategic protocols to reduce the rate of parasite selection [2].

In Brazil and in most of Latin American (LATAM) and Caribbean countries, IVM has been prescribed and widely used for the preventive treatment of the severe acute respiratory syndrome coronavirus (SARS-CoV-2) immediately after the publication of its *in vitro* effect against the virus [3]. In the early stages of the new coronavirus disease (COVID-19) people were also bombarded by the false promises, such as the immunological and antiviral protection of IVM. Most of the treatment decisions did not follow any medical, pharmacological or epidemiological recommendations and the medical community took the one-size-fits-all attitude based on the fact that the drug was affordable and exceptionally safe. A number of researchers were cautious about these widespread indications and started warning medical doctors and the population to evaluate and reject the idea of self-medication and self-dosing with IVM [4].

At that time, the wonder drug was starting to peak in sales everywhere, and from then on we noticed a sharp increase in the number of reports dealing with the prescription of an unconfirmed therapy. In June 2020, right in the middle of the first COVID-19 wave, the sales of IVM skyrocketed as 12 million packages were sold in Brazil alone (www.iqvia.com). The record sales were also related to the decision of mayors of three cities totaling 300,000 people, who have organized a voluntary mass treatment recommending three tablets of 6 mg of IVM on

three occasions 15 days apart. Moreover, the population of Peru were also encouraged by their former President Mr. Martín Vizcarra to take IVM (https://elcomercio.pe/politica/martin-vizcarra-recomienda-uso-de-ivermectina-pese-a-falta-de-evidencia-cientifica-covid-19-coronavirus-nczg-noticia/). The medical and political decision for these and other mass treatments were misleadingly based on prevention, the possible reduction in hospitalization time, and the reduction in the total number of deaths. In a similar vein, countries that did not produce IVM in LATAM and Africa (approx. 500 million people) were desperate to obtain IVM at US\$3.5 a package. Unfortunately, and after all these investments, the shape of COVID-19 curves did not exhibit any modification when comparing groups of treated and untreated people from the same area (Office of the Secretary of Health: https://www.saude.pr.gov.br/Pagina/Coronavirus-COVID-19).

As early as January 2021 the COVID-19 condition in LATAM got out of hand and this unprecedent situation was described in *The Guardian* (https://www.theguardian.com/world/2021/jan/24/brazil-covid-coronavirus-deaths-cases-amazonas-state?CMP=fb_gu&utm_medium=Social&utm_source=Facebook&fbclid=IwAR2L1JhPN1o17b4xKMLdFKgDLlsGP1K86OSnkFJjiBTHb0pI9KkClSoWsB0#Echobox=1611490368, as a complete massacre and a horror film, referring to overcrowding in 100% of the hospitals in Manaus, the capital of the state of Amazonas, North of Brazil. Most hospitals throughout the entire region were overwhelmed by the surge of the new P1 variant of the COVID-19, with a 200-people daily death rate, confirming the devastating situation. IVM may have contributed to this terrible situation since a team of infectologists described that more than 90% of the patients in the ICU admitted to having taken IVM as a preventive treatment for COVID-19 in the state of Rio Grande do Norte (*The Intercept* - https://theintercept.com/2021/03/19/cfm-290-mil-mortos-por-covid-19/?fbclid=IwAR2rdKPymgbPJqZWvpHad0E-XFKB3YUghE_N9OKr9SCwb8EuKwzSrl6ty_w) and at INCOR in São Paulo, Brazil.

Whilst the world is witnessing a terrible humanitarian crisis in LATAM and the Caribbean with public health systems in complete chaos

with an exhausted team of frontline workers, this could be a perfect scenario for promising drugs to attenuate the severe damages caused by COVID-19 [5]. Corsello et al. [6] have put together an online drug-repurposing library that classifies a number of compounds from a built-in database. Therefore, it is now possible to look for drugs that have been tested *in vivo* and *in silico* for their mechanisms of action. Model studies have also determined that IVM docks in the region of leucine 91 of the spike and of histidine 378 of the ACE2 receptor of the virus. So far, IVM docking has been confirmed and it may interfere with the attachment of the spike to the human cell membrane, potentially reducing SARS-CoV-2 infection [7]. The many ongoing clinical trials in the world should give us some real proof as to whether this drug can really be repositioned [8] or whether it must be declared unfit for the job [9]. Even though there is a great expectation for encouraging data, we have seen no sound evidence of IVM's efficacy in the treatment of COVID-19.

Although the above modelling exercises are valuable, we see that after almost a year since the *in vitro* publication of IVM efficacy, communities are still being used as the experimental unit, wrongly assessing an unconfirmed drug in fast-declining national health systems. It is particularly important to mention the lack of scientific or clinical pharmacology follow-ups as a number of toxic effects of IVM overuse have been observed after 35 consecutive weeks of treatment or even with the use of ten times the antiparasitic therapeutic dose. Patients are showing signs of diarrhea, dizziness, abdominal pain, and vomiting, which are now being reported as common side-effects (above 5–10%) that have never been seen in such high frequency (please remember the 12-million IVM packages sold in a month). In addition to that, physicians are reporting increasing numbers of IVM-related hepatitis (12 cases in 3 months in the state of Bahia) including the need for organ transplant, hitting the desperate health system even harder.

Additionally, the large voluntary human consumption could even match the animal use with a massive environmental discharge of IVM. As it is known, livestock releases approximately 15 tons of IVM/year from fecal elimination in Brazil with an unmeasurable ecotoxicity impact. Our hypothesis is that the human intake of IVM could have a significant impact in urban sewage plants, ground water and city reservoirs. This environmental disequilibrium would definitely impose a direct high risk to the most vulnerable groups of indigenous communities, and black people living in the favelas, that have less access to potable water and hospital/health facilities. The experience from the last three decades in veterinary clinical practice also brings another preoccupation from the suppressive use of IVM, as this regimen may cause a significant selective pressure in non-target organisms, altering, for example, the microbiome functionality of millions of people in LATAM and the Caribbean. These multiple risk factors are of Global importance and may only be measurable in a few years due to their indirect clinical and gradual environmental effects.

Meta-analysis/observational studies (https://ivmmeta.com) are circulating in the scientific community and over the Internet, demonstrating the efficacy of IVM during the pandemic. However, most of the listed references fail to provide adequate methodologies, making them difficult to be validated. Major limitations include, small sample sizes, doses and frequency of IVM use, open-label studies, in which neither the participants nor the investigators were blinded to the treatments, the use of concomitant medications in addition to IVM, assuming that the efficacy resulted from IVM (https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/ivermectin/). Although there is still no real evidence of IVM's value in treating COVID-19, the National Institutes of

Health (NIH) has just released a new recommendation that is either for or against the use of IVM for the treatment of COVID-19 (https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/ivermectin/). The release focuses on the need for well-designed and well-conducted clinical trials to provide evidence-based guidance for the use of IVM in the treatment of COVID-19. To better inform the population, the Food and Drug Administration (FDA/USA) has also warned about the use of IVM against COVID-19 in March 2021.

The large social and economic consequences of the pandemic and the absence of any specific preventive or curative treatment of COVID-19 is of paramount importance to LATAM. In Brazil, the use of IVM is being regarded as a political fanatism, which could be punished by international tribunal [10]. Therefore, a word of caution is even more necessary today than ever before, as we are seen the rise of a third curve for the disease with an average of 4000 deaths a day in the country. IVM can be considered a classical drug that embraces the One Health initiative, but we must condemn its illegitimate and fabricated prescription. Moreover, we should pay attention to the World Health Organization (WHO) safety measurements to minimize the virus circulation, and advocate mass vaccination to safeguard the entire region.

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