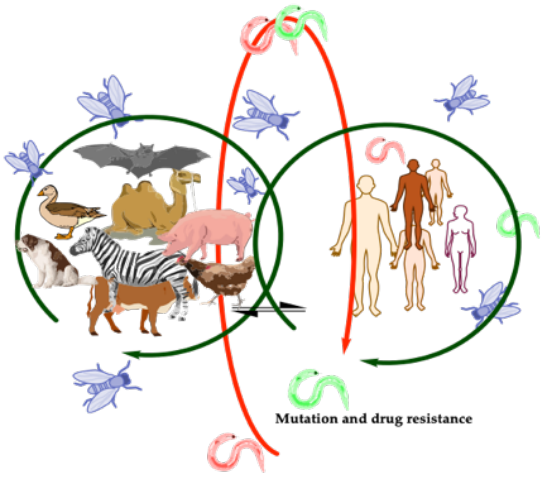

Minimizing the risk of rapid-onset (cross) resistance in PVBD drug development [strategies to assess the risk of rapid resistance developing].

18th March 2024

Online event

One Health drugs against parasitic vector borne diseases in Europe and beyond

OneHealth*drugs*

On this online workshop we are exploring the risks of drug resistance among parasitic agents of vectorial transmission and the challenges posed in the detection of drug resistance in the field.

BOOK OF ABSTRACTS

Meeting Venue
Online event

Microsoft Teams Platform
MeetingID: 377 487 650 657
Passcode: tdVbKZ

Organizing committee:
Clara Madureira Lima, WG. 6 leader
Harry de Koningh, WG.6 vice .leader
Alfonso T. Garcia Sosa, WG.5 leader
Chiara Borsari, WG.5 vice leader

***OneHealthDrugs* WG.5-WG.6 online workshop**

"Minimizing the risk of rapid-onset (cross) resistance in PVBD drug development [strategies to assess the risk of rapid resistance developing]"

18th March 2024

Anthelmintic resistance in canine heartworms and hookworms: lessons for human parasites

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Antiparasitic drug resistance has developed globally in parasites of livestock and horses, which are intensively treated to maintain productivity. Resistance has been much less common in parasites of companion animals (dogs and cats). This situation has recently and dramatically changed in the USE for two important canine parasites, the heartworm *Dirofilaria immitis* (a filariid) and the hookworm *Ancylostoma caninum*. Closely related nematodes parasitize humans, in which resistance, though suspected, has not yet been rigorously proven. Resistance to all macrocyclic lactones is increasingly found in heartworms, manifest by loss of potency against all stages and characterized by associated but not causative genomic markers. Hookworm populations resistant to all approved anthelmintics (macrocyclic lactones, benzimidazoles and pyrantel) are increasing at an alarming rate. Causative alleles in the isotype-1 ß-tubulin gene have been found at positions 167 and 134 and are diagnostic; markers for resistance to the other anthelmintics have not been identified. Although only about half of pets receive anthelmintic treatment and the parasite population in refugia has been thought to be high, resistance in both these species appears to have arisen in dog populations housed in kennels that received intensive (monthly) treatment with minimal influx of new hosts or parasites: highly limited refugia. Once selected, resistant parasites escaped confinement and have spread widely. Based on these cases, anthelmintic resistance in human parasites will be more likely to evolve in isolated populations with limited influx of vector species or new populations of untreated parasites, and epidemiological surveys should perhaps be targeted at such areas.

Acknowledgment
The author acknowledges Canada Research Chairs, NSERC and the American Heartworm Society for financial support.

***OneHealthDrugs* WG.5-WG.6 online workshop**

"Minimizing the risk of rapid-onset (cross) resistance in PVBD drug development [strategies to assess the risk of rapid resistance developing]"

18th March 2024

The problem of drug resistance in Animal Trypanosomiasis.

Morrison, Liam

[a] University of , Country; [b] University of , Country etc.
e-mail presenter

Animal Trypanosomiasis remains one of the most important infectious constraints on agriculture across sub-Saharan Africa, and forms of the disease also occur in Asia and South America. However, we have a very limited armoury of drugs to combat the disease –the last new drug was introduced to market in the 1960s. Long term extensive use of a limited number of compounds has inevitably resulted in resistance being an increasingly reported problem. However, animal trypanosomiasis is a complex disease, caused by several genetically distinct species of trypanosomes. This results in complications in drug development with the need for efficacy across distinct pathogens, and also means that mechanisms of, for example, drug uptake and drug resistance, can differ between the species. Additionally, our understanding of the true extent and impact of resistance in the field is limited, reflecting the neglected nature of the disease. This talk will provide an overview of current knowledge in the area, and highlight gaps and priorities for future research.

***OneHealthDrugs* WG.5-WG.6 online workshop**

"Minimizing the risk of rapid-onset (cross) resistance in PVBD drug development [strategies to assess the risk of rapid resistance developing]"

18th March 2024

LeishGenApp: A novel genomic platform for drug resistance prediction in *Leishmania infantum*

Authors: Martí-Carreras J., [a*] Carrasco M.[a,b*], Noguera-Julián M. [a], Roura X.[a,b], Ferrer Ll. [a,b], Francino O. [a,b]

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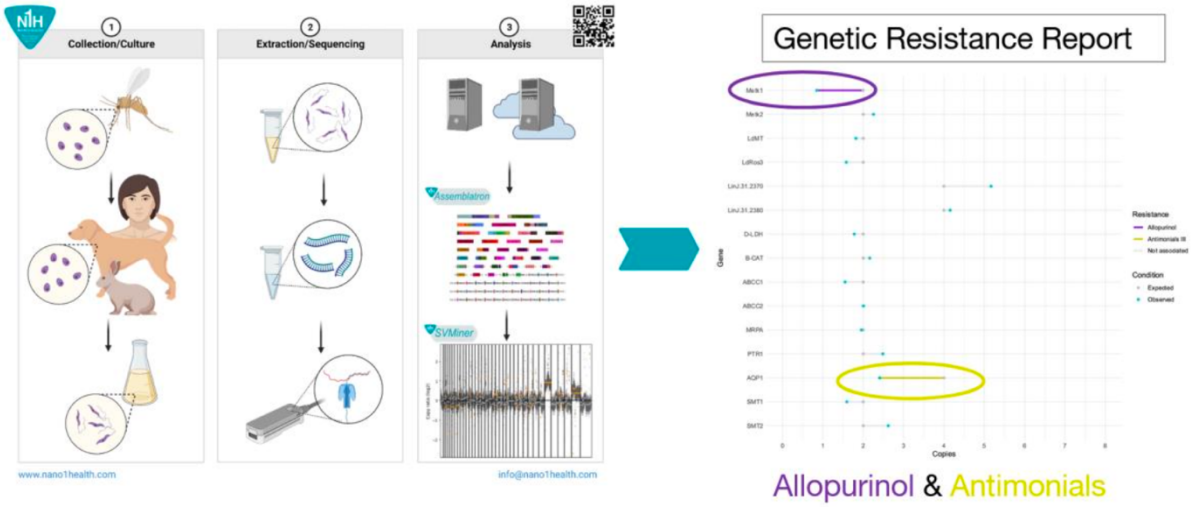
The emergence of drug-resistant strains of *Leishmania infantum* infecting both canine and human populations constitutes an escalating menace, which requires a comprehensive One Health approach for containment. Moreover, the inherent genomic instability of Leishmania sp. [1], joined with its protein expression modulation through copy number variation (CNV) [2], poses formidable challenges in identifying and exploiting genetic alterations linked to such resistances.

In an attempt to develop a novel diagnostic tool for identifying drug resistance biomarkers in *L. infantum*, we introduce LeishGenApp (https://www.nano1health.com/en/), a cutting-edge genomic analysis platform to identify genetic resistance predisposition to Allopurinol, trivalent antimonials, Miltefosine, amphotericin B and paromomycin [3]. Leveraging nanopore sequencing technology, we analyzed 46 *L. infantum* isolates sourced from canine and human hosts from Spain, Italy, Israel and Portugal. Sequencing was performed using ligation and transposase libraries with R9.4.1 and R10.4.1 flowcells on a GridION platform (basecalling by Guppy v6.1.2 to 7.1.4; 'SUP' model).

Genome *de novo* assemblies from canine (23) and human (13) isolates revealed pervasive gene dosage variability at both chromosomal (ploidy) and sub-chromosomal (CNV) scales. We meticulously curated a panel of resistance biomarkers, targeting the most relevant drugs for combating *L. Infantum* by analyzing a set of 15 copy-number variation genes via nanopore sequencing. Strikingly, drug-resistance biomarkers were discerned in a staggering 80% (29 out of 36) of the isolates, with 44% of the isolates with genetic resistance to more than one treatment, attesting to the rampant prevalence of drug resistance within *L. infantum* populations inhabiting the Mediterranean basin. Resistance to antimonials was the most prevalent one in the isolates analyzed.

The advent of LeishGenApp brings a change in drug resistance identification in *L. infantum* isolates. The versatility of this novel genomic application portends its adaptability across diverse pathogenic realms,

heralding a transformative era in precision medicine diagnostics.



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Acknowledgment

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***OneHealthDrugs* WG.5-WG.6 online workshop**

"Minimizing the risk of rapid-onset (cross) resistance in PVBD drug development [strategies to assess the risk of rapid resistance developing]"

18th March 2024

"Canine leishmaniosis in Africa: What do we have and what do we need?"

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Abstract

Canine leishmaniosis (CanL) is a globally distributed vector-borne zoonotic disease caused by protozoan parasites of the genus *Leishmania*. Female phlebotomine sand flies serve as biological vectors, with dogs acting as the primary reservoir in domestic environments, contributing to the endemicity of the parasite. While prevalent in tropical and subtropical regions, Canine leishmaniosis is also endemic to the Mediterranean basin and South America. Additionally, it exhibits varying prevalence rates, surpassing 40% in specific endemic regions, in both rural and urban areas across Africa, including countries such as Morocco, Tunisia, Algeria, Egypt, Sudan, Kenya, and Ethiopia. The clinical presentation of the disease encompasses diverse forms, including cutaneous, mucocutaneous, and visceral manifestations. Dogs may display skin lesions, ocular abnormalities, weight loss, lethargy, lameness, and other nonspecific signs. Visceral leishmaniasis, characterized by systemic involvement, represents the most severe form and can be fatal if left untreated.

Despite its significant contribution to the disease's epidemiological landscape, detecting infections in canines and providing proper treatment for clinically diagnosed animals pose major challenges for veterinarians and local authorities in Africa. This challenge is further compounded by the potential for zoonotic transmission to humans, emphasizing the disease's public health implications. The adoption of a One Health approach underscores the importance of integrated efforts in surveillance, vector control, diagnosis, treatment, and education to mitigate the impact of canine leishmaniosis on both animal and human populations. Our presentation aims to provide updated insights into the current status of CanL in Africa, highlight existing gaps in diagnosis and treatment, and propose future perspectives for effectively addressing this zoonotic disease.

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