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Drug resistant parasites and fungi from a one-health perspective: A global concern that needs transdisciplinary stewardship programs

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ABSTRACT

Antimicrobials including antibiotics, antiparasitic, and antifungals, are subjected to resistance. In this context, Public Health Organizations called for a One Health approach because antimicrobials used to treat different infectious diseases in animals and plants may be the same than those used in humans. Whereas mechanisms of resistance transmission from animals or environment to humans should be considered differently if related to prokaryotic or eukaryotic pathogens, their impact can be considered as a whole. In that respect, we discussed the use of anti-parasitic in animals including anticoccidials, anthelmintics, and insecticides-acaricides, and the use of azoles in the environment that may both favor the development of drug resistance in humans. In light of the current situation, there is an urgent need for a transdisciplinary approach through anti-parasitic and antifungal stewardship programs in humans, animals, and environment, especially in the era of COVID-19 pandemic that will probably aggravate antimicrobial resistance.

1. Introduction

Infectious agents responsible for diseases in humans, animals, and plants, are organized as bacteria, viruses, parasites, and fungi. Most of the anti-infectious drugs developed against those microbes are microbe-specific, namely antibiotics against bacteria, antiviral against viruses, antiparasitic agents against parasites, and antifungals against fungi, with few overlaps. A vast majority of those antimicrobials are subjected to resistance [1]. In this context, the World Health Organization, the Food and Agriculture Organization, and the World Organization for Animal Health, united in the fight against antimicrobial resistance called for a One Health approach because antimicrobials used to treat different infectious diseases in animals and plants may be the same than those used in humans [2].

Mechanisms of resistance may be different from prokaryotes and eukaryotes. Prokaryote including bacteria may acquire resistance genes directly from one to another following an antibiotic exposure. Therefore, resistant bacteria arising either in humans, animals, or in the environment, may easily spread their resistant phenotypes [3]. For eukaryotic pathogens including parasites and fungi, the mechanisms of resistance require more time than that of bacteria to reach a significant rate of therapeutic failures. Indeed, eukaryotes have a natural variability of their genomes including single nucleotide polymorphisms, protein redundancies, and transcriptional response to drug administration [4,5]. After a drug pressure, those events may provide a significant advantage to a sub-population. Those mechanisms of resistance are complex and require to be considered in the light of this complexity, including the biology of eukaryotic pathogens, the frequent use of common drugs, and the potential of pathogens to escape to treatment. Whereas mechanisms of resistance transmission from animals or environment to humans should be considered differently if related to prokaryotes or eukaryotes, their impact can be considered as a whole. One can anticipate that the permanent interplay between pathogens, human or animal hosts, and environment, will lead to an amplification loop of the drug resistance that need to be consider with more attention.

This review will focus on eukaryotic pathogens including parasites and fungi. The impact of drug resistance in parasitic diseases is responsible for a terrible disability-adjusted life year estimate. Indeed, increasing levels of drug resistance were documented for protozoan parasites [6] including *Plasmodium*, *Giardia, Leishmania*, *Trypanosoma,* or helminths [7]. Resistance of *Plasmodium* species to drugs is one of the reasons for stalling progress in malaria elimination. *Giardia*, a protozoan

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parasite of global importance for animals and humans, is associated with increasing rates of drug resistance and treatment failures for the most used drugs including metronidazole and albendazole [8,9]. Among fungi, *Aspergillus* and *Candida* are becoming increasingly resistant to antifungals [10]. Therefore, the issue of anti-parasitic and antifungal resistance must be more deeply integrated antimicrobial resistance global agenda in a One Health perspective. In that respect, the use of anti-parasitic in animals and antifungals in the environment that may both favor the development of drug resistance in humans are needed to be discussed.

2. Anticoccidials used in animals and humans

In humans, *Cryptosporidium* is the most common diarrhea-causing coccidia worldwide leading to 2.9 million cases per year in children <2 years old in subsaharan Africa and responsible for malnutrition and cognitive impairment in children [11–13]. Cryptosporidiosis is mainly acquired through direct contact between infected human (anthroponotic transmission) or through water sources for *Cryptosporidium hominis*, but zoonotic or foodborne transmission also occur with subtypes of *C. parvum*. Indeed, *Cryptosporidium* was reported in cattle, poultry, dogs, cats, and many more animals including chimpanzees, lemurs, and gorillas [14]. Nitazoxanide while moderately effective is the only FDA-approved drug for the treatment of diarrhea caused by *C. parvum* in immunocompetent patients, but not licensed in Europe. Paromomycin is effective in 60–70% of non-HIV cases, but not FDA-approved. Nitazoxanide and paramomycin are also used alone or in combination for treatment of cryptosporidiosis in animals including ruminants, dogs, cats, horses, calves, sheep, and goats. Then, there are reasonable grounds for predicting that the uncontrolled used of these drugs in animals could lead to selection of drug-resistant *Cryptosporidium* that may infect humans through zoonotic or foodborne transmission.

In animals, infections by other protozoans including *Eimeria* and *Isospora* species are very common, especially in young birds and mammals, but these species are host specific. It induces a major economic impact due to reduced weight gain and increased mortality, particularly in poultry industry. It is also a serious disease in sheep, goats, cattle, rabbits, and pigs. In this context, the food animal industry is intensively using anticoccidial drugs, including prophylactic use in poultry throughout most of the growing period. The risk of underdosage due to feed administration is a real matter of concern. Anticoccidial agents are generally classified into either polyether ionophores (monensin, salinomycin, maduramicin, lasalocid) or synthetic chemicals (robenidine, decoquinate, halofuginone, nicarbazin, diclazuril). These drugs are licensed in the EU and the US as zootechnical feed additives (mainly for poultry) or as veterinary drugs (mainly for ruminants). *Eimeria* and *Isospora* being highly host specific, there is no risk for resistance selection between animals and humans. Nevertheless, a few anticoccidial agents have shown some antibacterial activity. Salinomycin has indeed an inhibitory effect on *Clostridium perfringens* [15], and monensin and salinomycin against Gram-positive bacteria including *Staphylococcus [16]. There is therefore a risk for selection of drug-resistant bacteria, which could be released in the environment and potentially transmitted to people working in close contact to animals, leading finally to inter-human transmission.*

3. Anthelmintics

Anthelmintics are considered helminth-specific, with few demonstrations of activity against virus including the antiviral effect of ivermectin [17] and activity against flagellates such as *Giardia* spp. [18]. Among the main anthelmintics, albendazole and mebendazole are definitively the most used both in human and veterinary medicine. Those benzimidazoles demonstrated broad-spectrum activity against intestinal nematodes or tapeworms infections and tissue nematode/cestode infections [19]. Inappropriate use of these major drugs led to a decreased efficacy linked to the selection of single nucleotid polymorphisms of the beta-tubulin gene or other mutations [20–23]. The concomitant large-scale use of these drugs among humans and animals is a major issue to be addressed before fixation of resistance in the parasite populations and high therapeutic failure rates. The problems caused by *Haemonchus contortus* infection in small ruminants is a well-known example of the consequence of anthelmintic resistance spreading [23–26]. Project of repurposing benzimidazoles as anti-cancer drugs may increase the problem of resistance in the future [19].

Praziquantel is a cestodicidal agent used in both human and veterinary medicine. Whereas most of cestodes are highly host specific, *Echinococcus* spp. and *Dibothriocephalus* spp. can infect humans and animals. Thus, the appearance of *Echinococcus* resistant strains to praziquantel would pose a major health concern considering the risk for an increase in human larval echinococcosis and resistance, and required new therapeutic approaches including the use of adjuvant to improve praziquantel efficacy [27]. Albendazole is the most efficient and safe drug to interrupt larval growth of *Echinococcus spp* [28,29] without evidence of resistance, leading to its use as a first-line anti-infective treatment for alveolar and cystic echinococcosis [28].

4. Insecticides-acaricides

The risk related to the use of insecticides-acaricides is the selection of resistance in arthropods or vectors, which has been intensively described, especially for mosquitoes and ticks [30]. The side effect could be the indirect selection of resistant arthropods being able to bite or infest humans. The project of using mass drug administration (MDA) of ivermectin for humans and cattle as a malaria vector control combined with the classical use of macrocyclic lactones in ruminants for their endectocide activity has the potential to enhance the risk of generating resistance in mosquitoes as well as in soil-transmitted helminth infections of humans and livestock [31,32]. While there is not yet evidence of mosquito tolerance or resistance to ivermectin, risks mitigation strategies should take into account the doses and regimen proposed as MDA in humans, the residency time of the drug in treated humans or animals, and the persistence in the environmental water up to 4 months [33]. This example is a clear demonstration of the complex interplay between human and animal treatments against parasites, blood-sucking insects, and environment. The same indirect selection could be obtained with the use of pesticides in the environment leading to more resistant domestic flies and mosquitoes. These risks need to be assessed and followed by multidisciplinary teams working on vector control.

5. Azoles used in the environment and in humans

Most antifungals used in humans belong to three classes including azoles, echinocandins, and polyenes. Azoles are the most common class of antifungals used in patients suffering from aspergillosis [34]. Today, *Aspergillus* resistance to triazoles is a growing problem in humans [35] considering that the mortality rates of patients with voriconazole-resistant invasive aspergillosis are higher compared with voriconazole-susceptible infections [35]. Resistance mutations are commonly observed in the *Cyp51*A gene involved in cell wall synthesis which is the target of antifungal triazoles [36]. *Aspergillus* resistance in humans can be managed using antifungal susceptibility testing and local resistance surveillance. More challenging is the control of *Aspergillus fumigatus* resistance acquired in the environment which is attributed to the widespread use of azole-based fungicides against plant pathogenic moulds such as *Fusarium* and *A. flavus*. Azole drugs are dominated the agriculture fungicide market and a > 4-fold increase was reported in the United States during the 2006–2016 period [37]. As those fungicides have also an activity against *A. fumigatus* in the environment, inevitable exposure of *A. fumigatus* to azoles is responsible for the acquisition of resistance through the environment resulting in cross-resistance of *A. fumigatus* to medical azoles. It was recently demonstrated that the

prevalence of azole resistant *A. fumigatus* was positively correlated with residual levels of azole fungicides in soils [38]. Avian species highly susceptible to aspergillosis by moving between different environments including those with large amount of azole fungicides may play an important role in the dispersion of *Aspergillus* isolates, especially resistant strains. In this context, the frontier between drug resistance in humans and environment is not clear and horizontal scenarios should be taken into account as claimed by Hollomon [39]. Considering that the main burden of *A. fumigatus* resistance is the acquisition of resistance through the environment, the extensive use of azoles fungicides in the environment is a crucial element to consider in antifungal resistance control program as it has an impact on human's health.

6. Conclusions

Beside bacterial diseases, parasitic and fungal diseases are major public health issues in many parts of the word. Humans and animals are paying a terrible price to these pathogens. A large part of animal food consumed in the word is produced in countries were these diseases are preeminent, including Brazil, Nigeria, India, China, and others. National regulations for drug used in these countries may be different from EU or US regulations leading to an extensive use of food additives including anticoccidials. But food and/or live animals to feed population, as well as their infectious agents and resistant strains, are circulating around the world.

There is an urgent need to fight together against parasitic and fungal drug-resistant infections regardless who is responsible among humans, animals, caregivers, industry, or agriculture. Considering resistance to antimicrobials in humans, animals, or the environment, is mostly due to the misuse and overuse of drugs, communication, education, and training, among all involved partners would be a key factor of success. The role of the transdisciplinary approach through anti-parasitic and antifungal stewardship programs in humans, animals, and environment [40,41], is unquestionable because transdisciplinarity is expected to provide a more sustainable knowledge, experiences, and a better constituency in health policy. Some regulatory agencies (e.g. US-Environment & Pesticide Agency (EPA), and European Medicine Agency (EMA)) have already drafted guidelines to assess the potential impact of medicinal product, including antibiotics and antiparasitics. In that perspective, environmental risk assessment (ERA) is requested for some categories of human and veterinary products, to confirm that their use would not have any impact on other helminths or arthropods than the targeted parasites [33,42]. Beside those agencies, the World Health Organization, the Food and Agriculture Organization, and the World Organization for Animal Health (OIE), are other important partners, with support from academic societies. In the era of COVID-19 pandemic, this of utmost importance to consider a comprehensive and integrated health control policy to fight against the significant human threat of antiparasitic and antifungal resistance [43].

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Declaration of competing interest

The authors have no competing interest to declare.

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