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05

# Anti-Protozoal Drugs: Resistance Mechanisms and Sustainable Control Strategies Under One Health Stewardship

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**Summary:** In both human and veterinary medicine, protozoal infections continue to present substantial health and financial challenges, and the increasing prevalence of drug-resistant protozoa has made treatment approaches even more difficult. An overview of anti-protozoal medications, their modes of action, and therapeutic significance in the management of illnesses such as coccidiosis, babesiosis, trypanosomiasis, leishmaniasis, and giardiasis is given in this chapter. It draws attention to the molecular and physiological processes, such as altered drug targets, activated efflux pumps, changes in metabolic pathways, and strengthened antioxidant defenses, by which protozoa acquire resistance. Recent developments in surveillance tools and alternative therapy approaches are highlighted, along with current difficulties in diagnosis, restricted drug supply, and the development of multidrug resistance. Maintaining the efficacy of currently available anti- protozoal drugs requires monitoring mechanisms and encouraging safe drug use.

**Keywords:** Protozoal infections, Drug resistance, Mechanisms, Veterinary parasitology

## INTRODUCTION

Protozoal illnesses such as coccidiosis, babesiosis, giardiasis, and trypanosomiasis pose a serious and generally underestimated threat to animal health globally. These illnesses affect a wide range of animals, including poultry, livestock, and companion animals, with significant welfare, economic, and production effects. *Eimeria spp.* causes particularly severe damage in chickens, calves, and lambs. Clinical indicators in young animals include diarrhoea, weight loss, and mortality. In cattle, *Eimeria zuernii* and *Eimeria bovis* infections can hurt growth and survival, reducing livestock profitability and herd health. Another important disease, bovine babesiosis, caused by *Babesia bovis*, is a major economic burden in Latin America, parts of Africa, and Australia (Mshelia et al., 2019; Vial & Gorenflot, 2006). Losses are caused by animal mortality, reduced output, and high treatment and tick-control.

Livestock not only reduces productivity but also jeopardises rural economies. The loss of draught capacity in affected animals has a direct influence on crop productivity, making this disease a socioeconomic hazard in affected countries (Giordani et al., 2016). Similarly, though more widely recognized in human health, it has a significant veterinary footprint. Recent systematic evaluations estimate a global incidence of around 13.6% among nonhuman animals, with greater rates in livestock species like cattle and rats (Ballweber et al., 2010). Furthermore, a 2025 analysis emphasizes the broader parasitic burden: 21% of dogs in the United States have intestinal parasites, and more than half of household cats in Europe have at least one internal or external parasite, many of which are protozoans that affect animal health and may pose zoonotic risks. These data reflect more than just veterinary issues; they indicate cross-sectoral challenges affecting public health, ecosystem integrity, and food security.

### Economic, welfare, and food-security impacts

According to research presented at the World Buiatrics Congress held in 2024, internal and external parasites cost cattle producers worldwide more than US $21 billion per year, with anticipated rising beef consumption emphasizing the need for better parasite management. Protozoal infections such as babesiosis and trypanosomiasis cost money not just via clinical losses, but also through disease control, treatment, and indirect economic disruptions such as lower traction power and interrupted value chains (Blake et al., 2020).

In addition to cattle, companion animals have health challenges ranging from gastrointestinal distress to chronic infections, which, while less quantified, significantly impair welfare and raise veterinary care expenses. This simultaneous influence on productivity and well-being emphasizes the importance of rigorous, evidence-based veterinary treatments that include both efficacy and ethics.

### Historical Evolution of Antiprotozoal Therapy

The path to successful antiprotozoal medicines in veterinary medicine has been distinguished by steady, but cautious, advancement. Early treatment drugs, such as sulfonamides and thiamine analogues like amprolium, provided the first control choices, albeit with limited efficacy and resistance potential (Chapman, 2014; Jeffers, 1974). More complex classes, such as triazine coccidiostats (e.g., toltrazuril, diclazuril), nitroimidazoles, and diamidines (e.g., diminazene aceturate), have been introduced over time, providing broader spectrum activity and improved

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pharmacokinetic profiles (Giovanoli et al., 2022). Nonetheless, mechanical complexity, pricing hurdles, and safety concerns have impeded broad innovation, particularly in low-income countries. This history highlights the delicate balance between therapeutic advancement and increasing resistance.

**Rising Threat of Drug Resistance and One Health Context**

Antiprotozoal medication resistance has increased over the past decade due to mechanisms (Table 1) such as target mutations, drug efflux, and metabolic bypass (De Koning, 2020). This has led to treatment failures in livestock and pets (Giovanoli et al., 2022). Poor drug handling, subtherapeutic doses, and over-the-counter usage have resulted in hotspots for resistance selection, particularly in areas with inadequate veterinary monitoring (FAO, 2021). This expanding dilemma lies at the intersection of animal health, public safety, and environmental integrity (Loken & Owen, 2021). The notion of One Health, which emphasizes the interconnection of human, animal, and environmental health systems, has become central in addressing such complex problems (FAO/OIE/WHO, 2022).

Antimicrobial resistance (AMR) is widely recognized as a One Health concern that necessitates cross-sector collaboration to maintain therapeutic efficacy and safeguard all species (FAO, 2021). Reviews by veterinary and environmental health specialists highlight how resistant traits can spread through environmental reservoirs, infecting water systems, farms, and healthcare settings alike. Furthermore, public health initiatives are increasingly incorporating One Health principles into veterinary education and policymaking to address AMR holistically. These achievements signify a shift away from treating diseases in isolation and toward developing integrated stewardship, where animal care, pharmacological regulation, environmental safeguards, and public policy intersect (FAO/OIE/WHO, 2022).

**OTHER EMERGING AND EXPERIMENTAL AGENTS**

**Quinazolinones and Aryl benzimidazoles**

Target microtubule assembly and mitochondrial activity. Under investigation, with limited veterinary use. Compounds derived from plants and herbs**;** Anticoccidial efficacy is exhibited by saponins, tannins, and essential oils (garlic, thyme, and oregano) (Franz et al., 2010; Abbas et al., 2012; Dhama et al., 2015). It is suggested as natural feed additives to lessen dependency on artificial medications (Gupta et al., 2019). Drugs enhanced by nanotechnology**;** Decoquinate or halofuginone encapsulation in nanoparticles enhances delivery and inhibits the development of resistance.

**Resistance Issues Across Miscellaneous Agents**

- Ionophores: Resistance is slow and steady, but cross-resistance within the group is frequent.
- Robenidine, Decoquinate, and Clopidol: High risk of resistance with long-term use.
- Halofuginone: Resistance in coccidia is becoming more prevalent.
- Integrated rotation programs that combine vaccinations, synthetics, and ionophores are essential for managing poultry resistance (Peek & Landman, 2011b).

**Regulatory and Stewardship Concerns**

Ionophores: Still commonly utilized in livestock, they are not considered "medically important antimicrobials" for people. Strict withdrawal periods are necessary for synthetic drugs (such as decoquinate and halofuginone) to prevent residues. Consumer pressure: As the demand for "antibiotic-free" chicken rises, some markets may phase out ionophores, turning instead to vaccinations and phytogenic additives.

In poultry production systems, where coccidiosis has the greatest financial impact (Blake et al.**,** 2020), the "miscellaneous" class of antiprotozoals comprising ionophores, decoquinate, halofuginone, robenidine, and clopidol are essential tool for veterinary medicine. However, resistance, safety concerns, and legislation will impact their role in the future. While ionophores remain the cornerstone of poultry coccidiosis control, growing consumer demand for "drug-free" meat may accelerate the adoption of probiotics **(**Czarnecki-Maulden**,** 1999), immunization (Chapman**,** 2014), and phytogenic alternatives (Abbas et al.**,** 2012). Decoquinate and halofuginone are important options for ruminant prophylaxis, especially against coccidiosis and cryptosporidiosis in calves and lambs. Their long-term sustainability will be linked to prudent incorporation into rotation and shuttle programs (Peek & Landman 2011a) and ongoing investigations into immunological **(**Blake & Tomley**,** 2014) and natural alternatives (Dhama et al.**,** 2015).

**RESISTANCE MECHANISMS IN PROTOZOAN PARASITES**

**Introduction to Protozoal Drug Resistance**

One of the biggest problems facing veterinary medicine is drug resistance in protozoan parasites (De Koning, 2020). Like bacterial antimicrobial resistance (AMR), protozoa have developed a number of adaptive methods that make therapeutic medicines less effective. However, due to the eukaryotic nature of protozoa, their genetic plasticity, and their capacity to endure within host tissues in the face of immunological pressure, protozoal resistance is frequently more complex (Giovanoli et al., 2022). Treatment failures, increased morbidity, decreased cattle productivity, and possible zoonotic spillover are all consequences of resistance (FAO/OIE/WHO, 2022).

The major protozoan groups affected include:

1. *Eimeria* spp. - coccidiosis in poultry and ruminants (Chapman, 2014).
2. *Babesia* spp. - babesiosis in cattle, dogs, horses (Mshelia et al., 2019).
3. *Trypanosoma* spp. - trypanosomiasis in cattle, camels, equines (Giordani et al., 2016).
4. *Giardia* spp. - giardiasis in dogs, cats, cattle (Ballweber et al., 2010).
5. *Trichomonas* spp. - trichomoniasis in birds and cattle (De Koning, 2020).

**Table 1.** Major anti-protozoal drug classes and their mechanism of action

| Drug Group / Example | Target Diseases | Mechanism of Action (Simplified) | Common Animal Use | Advantages / Key Points | Limitations / Precautions |
|---|---|---|---|---|---|
| *Triazines* (Toltrazuril, Diclazuril, Clazuril) | Coccidiosis | Disrupt nuclear division and mitochondrial activity of *Eimeria*, preventing oocyst formation | Poultry, calves, sheep, rabbits | Broad-spectrum, long-acting, slow resistance | Withdrawal time needed before slaughter; avoid overdosing |
| *Ionophores* (Monensin, Salinomycin, Lasalocid, Narasin) | Coccidiosis (prophylaxis) | Alteration in transport across parasite membranes causing osmotic lysis | Poultry, cattle, sheep | Highly effective in prevention, used in feed | Toxic to horses and dogs; overdose is fatal |
| *Sulfonamides* (Sulfadimidine, Sulfaquinoxaline, Sulfadiazine) | Coccidiosis, Toxoplasmosis, Babesiosis | Inhibit folic acid synthesis | Poultry, cattle, goats, dogs | Economical, broad use | Resistance common; kidney toxicity risk |
| *Amprolium* | Coccidiosis | Vitamin B1 (thiamine) antagonist — starves parasite | Poultry, calves | Safe, inexpensive | Prolonged use causes thiamine deficiency |
| *Nitroimidazoles* Metronidazole, Dimetridazole, Ronidazole) | Giardiasis, Trichomoniasis, Histomoniasis | Disrupt DNA synthesis in anaerobic protozoa | Dogs, cats, pigeons, turkeys | Potent against flagellates | Banned in food animals (carcinogenic risk) |
| *Quinoline Derivatives* (Decoquinate, Atovaquone, Buparvaquone) | Coccidiosis, Babesiosis, Theileriosis | Inhibit mitochondrial electron transport | Poultry, cattle | Preventive; effective early | Costly; resistance risk |
| *Diaminopyrimidines* Trimethoprim + Sulfa drugs) | Coccidiosis, Toxoplasmosis | Inhibit folate metabolism (DHFR enzyme) | Poultry, goats, sheep, dogs | Synergistic effect with sulfa drugs | Risk of anemia; ineffective alone |
| *Aromatic Diamidines* (Diminazene aceturate, Pentamidine) | Trypanosomiasis, Babesiosis | Interfere with DNA replication | Cattle, camels, dogs | Quick curative action | Toxic to CNS; injection site pain |
| *Carbanilides* (Nicarbazin) | Coccidiosis (prophylaxis) | Affects energy metabolism and oocyst formation | Poultry | Useful in broilers | Toxic in heat stress; limited use |
| *Hydroxynaphthoquinones* (Buquinolate, Clopidol) | Coccidiosis | Inhibit parasite respiration | Poultry | Feed additive use | Rapid resistance development |
| *Imidocarb Dipropionate* | Babesiosis, Anaplasmosis | Interferes with DNA replication and energy metabolism | Cattle, horses, dogs | Long-acting, prophylactic | Painful injection, toxic if overdosed |
| *Halofuginone* | Cryptosporidiosis, Coccidiosis | Inhibits protozoal development in gut cells | Calves, poultry | Preventive and therapeutic | Narrow safety margin |
| *Parvaquone and Buparvaquone* | Theileriosis | Block electron transport in mitochondria | Cattle | Highly effective therapeutic drugs | Expensive; resistance emerging |
| *Quinuronium and Ethidium Bromide* | Trypanosomiasis | Affect nucleic acid synthesis | Cattle, camels | Effective curatives | Local irritation, toxicity risk |
| *Decoquinate* | Coccidiosis (prevention) | Inhibits cytochrome-mediated respiration | Poultry, ruminants | Safe and preventive | Not effective therapeutically |
| *Ponazuril* (Toltrazuril metabolite) | Equine Protozoal Myeloencephalitis, Coccidiosis | Inhibits nuclear division and respiration | Horses, dogs | Long-acting, well tolerated | Costly; long withdrawal period |

Resistance emerges through a combination of genetic mutations, drug pressure, pharmacokinetic variability, and farm management practices**.**

**General resistance mechanisms in protozoa**

Protozoan parasites employ multiple mechanisms to survive drug exposure. The most important include (De Koning, 2020). Genetic Mutations and Target Modification; Binding affinity is changed by point mutations in the genes encoding pharmacological targets (De Koning, 2020). For instance, Eimeria tenella is resistant to triazines (toltrazuril and diclazuril) due to changes in cytochrome b (Kheirandish et al., 2014). Sulfonamide resistance in Eimeria species is caused by altered dihydropteroate synthase (DHPS) (Jeffers, 1974). It has been documented that Trypanosoma brucei amplifies resistance genes, which decreases the efficacy of diamidines (De Koning, 2001). Reduced Drug Uptake and Increased Efflux; Protozoa may enhance efflux pump function or reduce drug-permeability of membranes. Metronidazole resistance in Giardia lamblia has been linked to ATP-binding cassette (ABC) transporters (Ansell et al., 2015; Leitsch, 2015). The resistance of closely related protozoa, Leishmania, to diamidines is mediated by similar efflux mechanisms (De Koning, 2001).

Drug Inactivation and Metabolic Bypass: Enzymes that detoxify or deactivate medications can be produced by parasites. They might also upregulate other metabolic pathways to get around blocked ones (De Koning, 2001). Example: *Eimeria* spp. exposed to amprolium may upregulate secondary thiamine transporters (Chapman, 2014). Stage-Specific Resistance: Many medications only work against particular stages of the life cycle. In order to survive, parasites can change the dynamics of their life cycle or increase the percentage of stages that are resistant to treatment (e.g., early schizonts in Eimeria) (Blake & Tomley, 2014). Epigenetic and Adaptive Mechanisms: Without undergoing irreversible genetic alteration, protozoa can display phenotypic plasticity. Parasites can withstand transient pharmacological pressure through epigenetic regulation (chromatin remodelling, RNA interference) (Resende et al., 2020).

**Resistance in Specific Drug Classes**

**Triazine resistance (Toltrazuril, Diclazuril)**

Following extensive preventive use (Peek & Landman, 2011b), resistance was initially observed in poultry coccidiosis. Reduced triazine binding due to mutations in the mitochondrial electron transport chain's cytochrome b gene (Kheirandish et al., 2014). Incomplete Eimeria clearance results in subclinical infections and decreased poultry weight gain (Blake et al., 2020). There was evidence of cross-resistance between diclazuril and toltrazuril.

**Nitroimidazole resistance (Metronidazole)**

Resistance in Histomonas meleagridis, Trichomonas foetus, and Giardia lamblia is described (Leitsch, 2015). The pyruvate: ferredoxin oxidoreductase (PFOR) pathway, which is required to convert metronidazole into its harmful radical form (Leitsch, 2015). The clinical impact is on dogs with recurring giardiasis in spite of frequent treatment (Ballweber et al., 2010).

**Diamidine resistance (Diminazene Aceturate)**

Widespread resistance in ***Babesia bovis*** and ***Trypanosoma congolense*** (Giordani et al., 2016). The mechanism is that diminazene cannot be absorbed by the parasite if the P2 adenosine transporter is not functioning (De Koning, 2001). Resistance is often stable and cross-resistant to pentamidine (Giordani et al., 2016).

**Amprolium resistance**

*Eimeria spp.* frequently exhibit resistance to amprolium (Chapman, 2014). The mechanism is due to elevated expression of high-affinity thiamine transporters, which allow parasites to scavenge thiamine in spite of competitive inhibition (Chapman, 2014). This occurs particularly in poultry that get continuous feed medication (Peek & Landman, 2011b).

**Sulfonamide resistance**

In chicken coccidiosis, resistance to sulfaquinoxaline, sulfadimethoxine, and similar medicines is common (Jeffers, 1974). The mechanism involves DHPS gene mutations which decrease sulfonamide binding affinity (Jeffers, 1974). This is a long-standing issue due to the fact that sulfonamides are utilised for both prevention and treatment (Chapman, 2014).

**Veterinary Practice Factors Contributing to Resistance**

**Availability of OTC**: Farmers frequently purchase antiprotozoals without a veterinarian's oversight (FAO, 2021).
**Under-dosing**: As a result of poor compliance, improper feed/water mixing, or cost-cutting measures (FAO, 2021).
**Preventive abuse**: Consistent drug pressure is exerted by routine feed inclusion (Peek & Landman, 2011b).
**Lack of rotation**: Resistance emergence is accelerated when the same drug class is used consistently (Peek & Landman, 2011a).
**Insufficient biosecurity**: Selective pressure for resistance is increased by a high parasite load (Peek & Landman, 2011b).

**Case Studies**

Nearly every class of anticoccidials had decreased efficacy by the 1990s (Chapman, 2014). Field isolates continue to exhibit multidrug resistance despite the use of rotation and shuttle programs to reduce resistance (Peek & Landman, 2011a). There have been reports of *Babesia bovis* that are resistant to diminazene in South America and Africa (Mshelia et al., 2019). Recurring mass treatment initiatives are associated with treatment failures. Similarly, Resistance to many drug strains of *Trypanosoma congolense* is widely dispersed. Control programs are compromised by resistance to diminazene, isometamidium, and homidium (Giordani et al., 2016). *Giardia* that is resistant to metronidazole has been reported in Europe, the United States, and Australia

(Ballweber et al., 2010). May cause zoonotic overflow and chronic or frequent diarrhoea in pets (Ballweber et al., 2010).

**Broader Implications**

**Animal health**: Resistance increases mortality, decreases productivity, and increases costs (Blake et al., 2020).
**Public health**: *Giardia* and *Cryptosporidium* are examples of resistant protozoa that humans can get (Thompson & Ash, 2016; Ballweber et al., 2010).
**Economic impact**: Reduced success in reproduction, milk output, feed efficiency, and weight gain (Blake et al., 2020).
**Food safety**: Meat, milk, and eggs may have medication residues when higher dosages are used to overcome resistance (FAO, 2021).

**Strategies to Delay Resistance**

**Rotation and combination therapy** refer to the use of different pharmacological classes either sequentially or in combination (Peek & Landman, 2011a).
**Alternative control**: vaccinations (Blake & Tomley, 2014), probiotics (Czarnecki-Maulden, 1999), and phytotherapy (Dhama et al., 2015).
**Surveillance**: Monitoring resistance patterns with molecular technology (Thompson & Ash, 2016).
**Education**: Educating farmers and veterinarians on the appropriate dosage and withdrawal periods (FAO, 2021).
**Regulation**: restricting the sale of over-the-counter drugs and promoting veterinary oversight (FAO, 2021).

## VETERINARY PRACTICE ISSUES

Protozoal infections in veterinary medicine have significant clinical and financial repercussions (Blake et al., 2020). Globally, veterinary services are under a lot of strain from diseases, including trypanosomiasis in equids and ruminants (Giordani et al., 2016), babesiosis in cattle and dogs (Mshelia et al., 2019), giardiasis in companion animals (Ballweber et al., 2010), and coccidiosis in poultry (Chapman, 2014). Antiprotozoal medications have long been the mainstay of treatment, but their efficacy is being threatened by the pervasive development of resistance (De Koning, 2020). This section discusses antiprotozoal resistance's effects on veterinary practice, with particular attention paid to diagnostic issues, treatment failures, farm-level management, and worldwide differences in drug access and regulation.

**Diagnostic Challenges**

Veterinarians frequently struggle to differentiate between relapses brought on by inadequate administration or reinfection and treatment failures caused by drug resistance (Thompson & Ash, 2016). Diarrhoea, weight loss, and anaemia are common nonspecific symptoms of protozoal infections (Ballweber et al., 2010). It is uncommon to find molecular assays (PCR, resistance marker sequencing) outside of research or reference labs (Thompson & Ash, 2016).

Resistance is often assumed based on a post-treatment infection that persists, which can be complicated by medication degradation or underdosing (FAO, 2021).

**Treatment Failures**

Reports of reduced drug efficacy are increasingly common in veterinary settings:

**Poultry coccidiosis**: Few farms globally remain completely susceptible to anticoccidial resistance, which is almost widespread (Chapman, 2014; Peek & Landman, 2011b).
**Dog babesiosis**: Treatment for both working and companion dogs is made more difficult by proven resistance to imidocarb and diminazene (Mshelia et al., 2019).
**Giardiasis in dogs and cats**: Despite repeated treatments, isolates that are resistant to metronidazole cause recurrent diarrhoea and weight loss (Leitsch, 2015; Ballweber et al., 2010). Significant expenses result from treatment failures, including retreatments, more veterinary visits, lost production, and, in the case of poultry mortality spikes during epidemics, lost productivity (Blake et al., 2020).

**Farm-Level Management Issues**

At the farm level, several practices contribute to both the development and persistence of resistance:

**Preventive use**: Drugs are frequently added to water or feed, which results in ongoing selective pressure (Peek & Landman, 2011b).
**Inappropriate dosing**: Resistance is accelerated by under- or overdosing brought on by mixing mistakes, farmer misinterpretations, or deliberate cost-cutting (FAO, 2021).
**Inadequate biosecurity**: In crowded, unsanitary environments, resistant parasites can spread quickly (Peek & Landman, 2011b).
**Limited drug rotation**: Because many smallholders do not have access to a variety of drug classes, they tend to take the same chemical for extended periods of time (Peek & Landman, 2011a).
**Economic incentives**: Anticoccidial regimens for commercial poultry must strike a compromise between cost-effectiveness and efficacy. Resistance drives a shift towards more costly options, such as immunisation (Blake & Tomley, 2014).

**Economic Implications**

**Poultry industry**: The yearly cost of coccidiosis to the worldwide poultry business is estimated to be between USD 14 and $15 billion and resistance increases the financial burden (Blake et al., 2020).

**Cattle industry**: *Trypanosoma* and *Babesia* resistance lowers draught capacity, fertility, and milk output (Mshelia et al., 2019).

**Pet care industry**: Owners' veterinary expenses are raised by recurring **giardiasis**, which frequently results in treatment discontinuation (Ballweber et al., 2010).

**Global Disparities in Veterinary Practice**

Veterinary drug resistance reflects regional inequities e.g., Antiprotozoals are widely available without a prescription in low- and middle-income countries (LMICs) due to lax regulation (FAO, 2021). Although metronidazole resistance is still a problem in companion animal care, stricter regulations

and increased vaccination availability help to reduce resistance in high-income nations (Blake & Tomley, 2014). But, the prevalence of resistance is probably underreported since many LMICs do not have surveillance systems (Thompson & Ash, 2016).

### Regulatory and Stewardship Issues

Veterinary practitioners deal with competing demands: Farmers want protozoal infections to be controlled at a reasonable cost. However, to maintain efficacy, global health guidelines recommend reducing drug use (FAO/OIE/WHO, 2022). Effective stewardship programs that inform farmers, encourage diagnostics, and implement rotation techniques are necessary to strike a balance between these (FAO, 2021).

### One Health Perspective

Human and environmental health are inextricably linked to veterinary practices (Loken & Owen, 2021). Antimicrobial resistance in human gut flora may be indirectly caused by antiprotozoal residues found in meat, milk, and eggs (FAO, 2021). *Cryptosporidium* and *Giardia* are resistant zoonotic protozoa that emphasise the problem's commonality (Thompson & Ash, 2016). Veterinary medicine is in the forefront of the crisis caused by antiprotozoal resistance. The need for concerted action is underscored by treatment failures, diagnostic gaps, economic losses, and global disparities. To ensure medication efficacy for both animal and human populations, veterinarians must embrace integrated parasite control, improve stewardship, and participate in One Health partnership (FAO/OIE/WHO, 2022).

## MITIGATION AND FUTURE DIRECTIONS

Stewardship principles, adapted from antimicrobial stewardship, are critical for protozoal diseases:

**Use drugs responsibly**: Steer clear of preventative mass treatments unless epidemiologically warranted (FAO, 2021).
**Rotation and combination therapy**: The danger of resistance selection is decreased by switching up or combining medications (Peek & Landman, 2011a).
**Evidence-based dosing**: To avoid subtherapeutic exposure, therapeutic medication monitoring and pharmacokinetics are used (FAO, 2021).
**Educating farmers and veterinarians**: Making sure all parties involved are aware of the dangers of abuse (FAO, 2021).

### Vaccination Strategies

Vaccines offer a sustainable solution by reducing reliance on chemotherapeutics (Blake & Tomley, 2014).

**Vaccines against coccidiosis**: **Live attenuated vaccines**: such as Coccivac® and Paracox®, are frequently administered to chickens (Chapman, 2014).
**Babesia vaccinations**: Attenuated live vaccines against bovine babesiosis have been produced in Latin America, although production and distribution issues still exist (Mshelia et al., 2019; Vial & Gorenflot, 2006).
**Toxoplasmosis**: Toxovax® vaccination lowers the risk of congenital toxoplasmosis in sheep (Blake & Tomley, 2014).
**Future direction**: vaccines based on DNA, vectors, and epitopes may offer durable protection with few safety issues (Blake & Tomley, 2014).

### Alternatives to Conventional Drugs

Several novel approaches are emerging as adjuncts or replacements for classical antiprotozoals (Giovanoli et al., 2022): Phytochemicals and plant-derived compounds: Compounds of artemisinin are effective against coccidia (Abbas et al., 2012). Probiotics and competitive exclusion: Using good bacteria to lessen protozoan colonization in the intestines (Czarnecki-Maulden, 1999). Nanotechnology: Nanocarriers circumvent resistance mechanisms, lower dosage, and enhance drug delivery (Giovanoli et al., 2022). Host-directed therapies: Changing host immunity instead of going against protozoa directly (Giovanoli et al., 2022).

### Environmental and Management Interventions

Various environmental and managemental interventions could help in overcoming the problem of drug resistance, like;

**Increased biosecurity**: clean water, regulated animal density, and good hygiene lower the risk of parasite exposure (Peek & Landman, 2011b).
**Nutritional strategies**: immunomodulatory supplements combined with balanced meals increase host resilience (Gupta et al., 2019).
**Integrated parasite management (IPM)**: combines chemical and non-chemical methods to reduce drug dependence, is comparable to integrated pest management (Peek & Landman, 2011a).

### Policy and Regulation

National and international policies play a pivotal role in mitigating resistance. Limiting the selling of essential antiprotozoals over-the-counter is one way to regulate medicine availability. Similarly, for residue monitoring to guarantee adherence to withdrawal periods, food safety procedures were reinforced (FAO, 2021). By cooperation for One Health-driven guidelines between WHO, OIE, and FAO (FAO/OIE/WHO, 2022) and promoting public-private collaborations to create safer medications, vaccines and diagnostics is one way to encourage innovation (Giovanoli et al., 2022).

### Future Outlook

The veterinary industry may serve as a paradigm for integrated resistance management if these tactics are used in concert. A multimodal approach that strikes a balance between short-term therapeutic requirements and long-term sustainability is needed to mitigate antiprotozoal resistance. The One Health viewpoint guarantees that actions safeguard ecological balance, public health, and animal productivity (Loken & Owen, 2021). The international community can ensure efficient protozoal control for upcoming generations by

coordinating science, policy, and practice (FAO/OIE/WHO, 2022).

## CONCLUSION

Protozoal infections remain a problem for veterinary medicine. While a variety of antiprotozoal drugs have greatly improved the control of diseases caused by protozoa, their long-term overuse has fueled the rise of drug-resistant protozoa. This increases risks not only in reduced efficacy of treatment but also in zoonotic transmission and economic loss. Protozoa develop resistance through smart survival strategies, such as mutation of drug target enzymes, activation of efflux pumps that expel drugs out of the cell, rerouting metabolic pathways, and entry into dormant phases to evade therapy. These adaptive tactics signal that continuing to rely on conventional drugs is no longer effective. In this regard, protozoal resistance for veterinarians means higher production costs and food safety problems arising from drug residues. The way forward will depend on One Health–based strategies. Further reductions in drug dependence may be achieved with vaccines, genomic tools, probiotics, and phytochemicals. The future of parasite control will depend not only on new drugs but also on smarter management, balancing pharmacology with biotechnology, genetics, and ecology. Only by cooperating can we ensure sustainable control of protozoal diseases.

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