PARASITE CONTROL

Parasitic infections have deleterious effects on many human and animal populations, being responsible for significant host morbidity and mortality. The impact of many parasitic infections has been quantified in economic terms by estimating the cost of the morbidity burden (YLD = years of life lost due to disability) and the mortality burden (YLL = years of life lost due to premature death), cumulatively contributing to the disease burden (DALY = disability adjusted life years = YLL + YLD). These estimates are used by health agencies to allocate finite resources on a priority basis (those diseases causing the greatest losses having more resources allocated). Animal industries also calculate the burden of subclinical production losses due to depressed growth and fertility, as well as the cost of control programmes. It is therefore advantageous on moral, ethical and economic grounds to try and control parasitic infections, especially those resulting in disease.

Three main strategies are utilized to control infectious diseases:

- drugs (to cure/curb/prevent infection);
- vaccines (to protect against infection/disease); and
- environmental management (to prevent transmission).

DRUGS

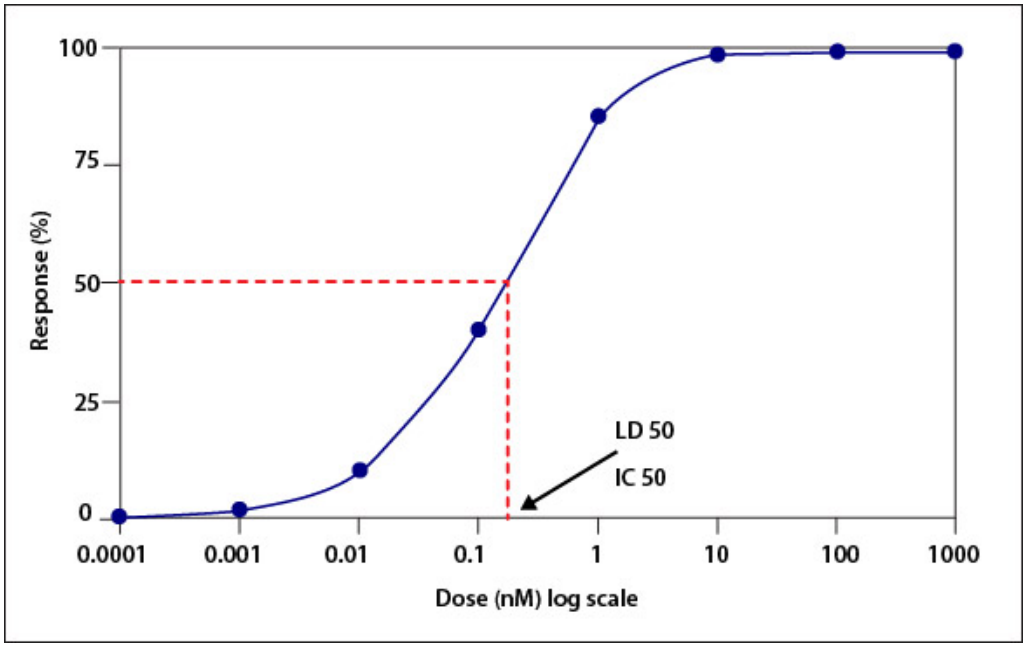
Throughout history, various substances have been endowed with medicinal qualities and folklore herbal remedies have long been used by humans (and even by some animal populations). Many drugs come from plants, particularly those species that have developed chemical defenses against pests, pathogens and disease. Scientists are continuing to identify the active ingredients in herbal remedies and they are constantly attempting to create synthetic analogues to overcome problems in supply and demand. Drugs may kill parasites ('-cidal' activity) or inhibit their growth or reproduction ('-static' activity). However, because parasites are eukaryotic organisms just like their hosts, the drugs may also act on the hosts. Anti-parasitic drugs must therefore exhibit a selective toxicity for the parasite many times greater than that for the host (selectivity index ≥ 30). Drugs may be used therapeutically to treat infections (chemotherapy), or prophylactically to prevent infection (chemoprophylaxis).

A huge range of prescription and nonprescription drugs are produced by multinational companies under a staggering number of names (one international non-proprietary name, but with several regional non-proprietary names and many proprietary brand names). Drugs come in a vast array of topical preparations (liniments, lotions, ointments, dips, shampoos, washes, pour-ons, spot-ons, collars, creams, sprays, powders, aerosols), oral formulations (tablets, pills, capsules, bolus, liquids, emulsions) or parenteral formulations (liquids in ampoules/vials, or solid implants, for subcutaneous, intramuscular, intravenous or intraperitoneal administration). Pharmacological modes of action may involve selective activity on parasite:

- DNA synthesis (alkylation, purine, cofactor);
- protein synthesis (inhibition, translation);
- energy metabolism (electron transport, reduction);
- neurotransmission (blockers, inhibition);
- membrane function (vacuoles, permeability);
- microtubule function (paralysis);
- haem(oglobin) interaction (disruption); or
- growth regulation (insect hormones).

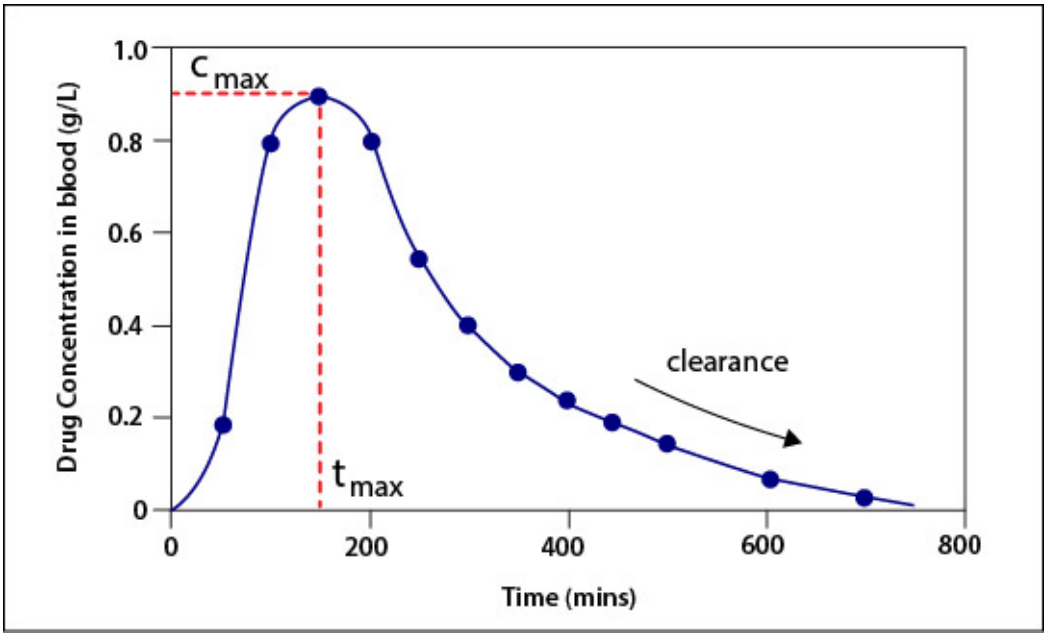
Pharmacodynamics (PD)

PD is the study of the biochemical and physiological effects of drugs on the body (or on infective microorganisms within the body) and the mechanisms of drug action and the relationship between drug concentration and effect. The majority of drugs either mimic or inhibit normal physiological/biochemical processes or inhibit pathological processes. Drugs may act as stimulants, depressants, toxins or substitutes in their chemical interactions with enzymes, structural proteins, carrier proteins, ion channels, hormones, neuromodulators or neurotransmitters. Many drugs act as ligands which bind to receptors influencing cellular processes, either resulting in enhanced action (agonist), blocked action (antagonist), or even opposite action (inverse agonist). For drugs to work, they must reach specific target concentrations. Many factors affect drug concentrations; such as patient size, age, genetic disposition, physiology, metabolism, etc. There may also be undesirable side-effects including: cell mutation (carcinogenic activity); metabolic disturbances, physiological damage and abnormalities. Plots of drug quantity (dose) against efficacy frequently yield sigmoidal (S-shaped) curves, conveniently modelled as logistic functions. The middle portion of the graph is close to linear and allows the accurate calculation of the LD_{50} (50% of lethal dose) or IC_{50} (50% of total inhibitory concentration).



Pharmacokinetics (PK)

PK is a branch of pharmacology dedicated to the determination of the fate of substances administered externally to a living organism (applies mainly to drugs, but in principle concerns other substances such as nutrients, metabolites, hormones, toxins, etc.). PK considers four main areas: the extent and rate of absorption, distribution, metabolism and excretion (ADME scheme). Pharmacokinetic analyses are performed by noncompartmental or compartmental methods. Noncompartmental methods estimate the exposure to a drug by estimating the area under the curve (AUC) of a concentration-time graph while compartmental methods use kinetic models to describe and predict the concentration-time curve. Such curves can often be modelled by surge functions (power function multiplied by exponential decay function) which yield maximum concentration (C_{max}), time of maximum concentration (t_{max}), clearance rate, clearance time, drug half-life as well as total exposure to drug (AUC); most parameters being compulsory prerequisites for drug registration.



Anti-parasitic drugs

Ideally, all drugs should have registered "terms of use", including chemical composition, generic and trade names, intended application (spectrum of efficacy), target species (pathogen and host), dosages, course and route of administration, pharmacodynamics, mode of action (depressant, stimulant, toxin, substitute), pharmacokinetics (absorption, distribution, metabolism, excretion), toxicity, contra-indications, side effects, storage and disposal information (usually detailed on product inserts). These days, there are many web resources providing a structured approach to pharmacology (e.g. pharmacopoeia). Parasites belong to several disparate assemblages, so no single formulation exhibits broad-spectrum activity against all parasites. Indeed, anti-protozoal drugs generally do not work against helminths or arthropods, anthelmintics often do not work against protozoa or some arthropods, and acaricides and insecticides do not work against protozoa or most helminths.

Drugs used to treat parasitic protozoan infections

Drug class (generic exemplars)	Spectrum of efficacy	Mode of action
sulfonamides (sulfachloropyrazine, sulfadiazine, sulfadimethoxine, sulfadimidine, sulfadoxine, sulfaguanidine, sulfaisoxazole, sulfalene, sulfamerazine, sulfamethazine, sulfamethoxazole, sulfametoxypyridazine, sulfanilamide, sulfanitran, sulfathiazole, sulfaquinoxaline); sulfones (dapsone)	coccidia, haemosporidia	enzyme inhibition
diaminopyrimidines (diaveridine, epiroprim, ormetoprim, pirithrexim, pyrimethamine, trimethoprim)	coccidia, haemosporidia	enzyme inhibition
hydroxynaphthoquinones (atovaquone, buparvaquone, menoctone, parvaquone)	haematozoa	enzyme inhibition
aminobenzoic methyl esters (ethopabate)	coccidia	enzyme inhibition
quinazolinones (febrifugine, halofuginone)	coccidia, theileriids	enzyme inhibition
asymmertic triazines (clazuril, diclazuril)	coccidia	enzyme inhibition
symmetric triazines (toltrazuril)	coccidia	enzyme inhibition
nitrofurilidene derivative (nifurtimox)	trypanosomes	enzyme inhibition
biguanide derivatives (chlorproguanil, proguanil)	haemosporidia	enzyme inhibition
substitued amino acid (eflornithine, ornidyl)	trypanosomes	enzyme inhibition
azonaphthalene dyes (trypan blue)	babesiids	enzyme inhibition
aminoquinaldines (antrycide, quinapyramine, triguin, trypacide)	trypanosomes	protein inhibition
aminoglycoside antibiotics (paromomycin)	amoebae, leishmanias, diplomonads	protein inhibition
tetracyclines (doxycycline, chlortetracycline, minocycline, oxytetracycline, tetracycline)	haematozoa, diplomonads, ciliates	protein inhibition
cyclic undecapeptide (cyclosporin A)	kinetoplastids, coccidia	protein inhibition
alkaloids (emetine, dehydroemetine)	amoebae, leishmanias	protein inhibition
4-hydroxyquinolones (amquinate, buquinolate, decoquinate, methylbenzoquate)	coccidia	energy inhibition
arsenicals (arsanilic acid, carbasone, glycobiarsol, melarsoprol, roxarsone, tryparsamide)	kinetoplastids, trichomonads, coccidia	energy inhibition
polyether ionophorous antibiotics (laslocid, maduramicin, monensin, narasin, salinomycin, semduramicin)	coccidia	energy inhibition
guanidine derivatives (cycostat, robenidine, robenz, robenzidene)	coccidia	energy inhibition
pyridinoles (clopidol, clopindol, coyden, meticlorpindol)	coccidia	energy inhibition
naphthoquinones (atovaquone)	haemosporidia	energy inhibition
thiamine analogues (amprol, amprolium, amprovine, beclotiamine, corid)	coccidia	anti-metabolite
hydroxyquinoline derivatives (iodoquinol)	amoebae, ciliates	anti-metabolite
nitrobenzamides (aklomide, dinitolamide, nitromide, zoalene)	coccidia	anti-metabolite
nitrofurans (furaltadone, furazolidone, nifurtimox, nitrofurazone)	coccidia	anti-metabolite
purine analogues (aprinocid, glycarbylamide)	coccidia	anti-metabolite
naphthyridines (pyronaridine)	haemosporidia	anti-metabolite
bis-nitrophenols (nitrophenide)	coccidia	anti-metabolite
phenyl ureas (fluorophenylurea, nitrophenylurea)	coccidia	anti-metabolite
sulphated naphthylamines (antrypol, germanin, moranyl, naganol, naganin, naphuride, suramin)	trypanosomes	anti-metabolite
alkyl phospholipid compounds (miltefosine)	leishmanias, amoebae	lipid interference
antimonials: trivalent (antimony tartrate); pentavalent (meglumine antimoniate, sodium stibogluconate, stibophen)	kinetoplastids	DNA interference
diamidines (amicarbalide, carbesia, imidocarb, imixol, imizol, imizocarb)	piroplasms, trypanosomes	DNA interference
aromatic diamidines (azidin, berenil, diminazene, ganasag, isometamidium, pentamidine, phenamidine, samorin, trypamidium, trypan, veriben)	piroplasms, trypanosomes	DNA interference
nitroimidazoles (benznidazole, carnidizole, dimetronidazole, furazolidone, metronidazole, nimorazole, nitrofuratoin, ornidazole, radanil, rochagan, ronidazole, tinidazole)	flagellates, amoebae, ciliates	DNA interference
phenanthride derivatives (babidium, ethidium, dromilac, homidium, novidium, pyrithidium)	trypanosomes	DNA interference
dichloroacetamide derivatives (diloxanide, entamide, furamide)	luminal amoebae	DNA interference
urea derivatives (nicarbazin, quinuronium sulfate)	babesiids, coccidia	DNA interference

pyrazolopyrimidines (allopurinol, zyloric)	kinetoplastids	DNA interference
adenosine analogues (arprinocid, benzyl purine)	coccidia	DNA interference
pyrimidone analog (flucytosine)	amoebic keratitis	DNA interference
uridine analogs (tiazuril, azauracils)	coccidia	DNA interference
fluoromethanols (benflumetol, lumefantrine)	haemosporidia	DNA interference
peroxides (artemisinin (qinghaosu), artemether, arteether, artesunate, artelinic acid, dihydroartemisinin)	haemosporidia, coccidia	heme interference
aryl amino alcohols (halofantrine, mefloquine, quinidine, quinine)	haemosporidia	heme interference
4-aminoquinolines (amodiaquine, chloroquine)	haematozoa, amoebae	heme interference
8-aminoquinolines (pamaquine, primaquine)	haematozoa	heme interference
azacrine (pyronaridine)	haemosporidia	heme interference
iron chelating agents (desferrioxamine)	haemosporidia	heme interference
benzimidazole-methylcarbamates (albendazole, mebendazole)	diplomonads, microspora	microtubules
probenzimidazoles (febantel)	diplomonads	microtubules
polyene macrolide (amphotericin, azithromycin, clarithromycin, erythromycin, spiramycin) and lincosamide (clindamycin) antibiotics	amoebae, coccidia, flagellates, babesiids	membranes
aminoacridine (acriflavine, mepacrine, quinacrine)	haematozoa, diplomonads	membranes
azole antifungals (itraconazole, ketoconazole, miconazole)	amoebae, leishmanias	growth inhibition

Drugs used to treat parasitic helminth infections (anthelmintics)

Drug class (generic exemplars)	Spectrum of efficacy	Mode of action
aminoacetonitriles (monepantel)	nematodes	neuro-interference
aminophenylamidine (amidantel)	nematodes, cestodes	neuro-interference
symmetrical diamidine derivative of amidantel (tribendimidine)	nematodes, cestodes, trematodes	neuro-interference
organophosphates (bromophenophos, coumaphos, crufomate, dichlorvos, diuredosan, haloxon, fospirate, metrifonate, naphthalophos, pyraclofos, trichlorphon)	nematodes, cestodes, trematodes	neuro-interference
diethylenediamines (diethylcarbamazine, piperazine)	nematodes	neuro-interference
depsipeptides (emodepside)	nematodes	neuro-interference
tetrahydropyrimidines (morantel, oxantel, pyrantel)	nematodes, cestodes	neuro-interference
imidazothiazoles (butamisole, levamisole, tetramisole)	nematodes, cestodes	neuro-interference
ethanolamines (bephenium, methyridine, thenium)	nematodes	neuro-interference
alkaloids (nicotine), largely discontinued	nematodes	neuro-interference
macrocyclic lactones: avermectins (abamectin, doramectin, eprinomectin, ivermectin, selamectin), milbemycins (milbemycin, moxidectin)	nematodes	muscle interference
spiroindoles (derquantel)	nematodes	muscle interference
isoquinolines (praziquantel)	cestodes, trematodes	muscle interference
chenopodium oil	nematodes	paralytic
cyanoacetic acid hydrazides (cyacetacide)	nematodes	immobilization
phenothiazine, now discontinued	nematodes	microtubules
benzimidazole-thiazolyls (cambendazole, thiabendazole)	nematodes, trematodes	microtubules
benzimidazole-methylcarbamates (albendazole, cyclobendazole, fenbendazole, flubendazole, luxabendazole, mebendazole, oxfendazole, oxibendazole, parbendazole, ricobendazole)	nematodes, cestodes, trematodes	microtubules
halogenated benzimidazole-thiole (triclabendazole)	trematodes	microtubules
probenzimidazoles (febantel, netobimin, thiophanate)	nematodes, cestodes	microtubules
arsenicals (acetarsone, arsanilic acid, melarsamine, thiacetarsamide)	cestodes, nematodes	energy inhibition
salicylanilides (bromosalans, bromoxanide, brotianide, clioxanide, closantel, niclosamide, niclofolan, oxyclozanide, rafoxanide, resorantel)	cestodes, trematodes	energy inhibition
halogenated phenols: monophenols (disophenol, nitroxynil); bisphenols (bithionol, dichlorophene, hexachlorophene, meniclopholan)	cestodes, trematodes, nematodes	energy inhibition
substituted diphenylethers/isothiocyanates (bitoscanate, nitroscanate)	cestodes, nematodes	energy inhibition
substituted dihydroxybenzene (hexylresorcinol)	trematodes	energy inhibition
cyanine dyes (dithiazanine iodide, pyrvinium)	nematodes	energy inhibition
alkaloids (emetine)	trematodes	protein inhibition
glutarimide antibiotics (axenomycin)	cestodes	protein inhibition
glycopeptide antibiotics (streptothricin)	cestodes	protein inhibition
phenoxyalkane derivatives (coriban, diamfenetide)	trematodes	protein inhibition
cyclic undecapeptide (cyclosporin A)	trematodes, cestodes	protein inhibition
benzene sulphonamides (clorsulon, curatrem)	trematodes	enzyme inhibition
sulphated naphthylamines (suramin), mostly discontinued	nematodes	anti-metabolite
antimonies: trivalent (antimony tartrate); terahydroquinoline (oxamniquine)	trematodes	anti-metabolite
thiazolidinedione derivatives (nitrodan)	nematodes	anti-metabolite
nitrothiazoles (niridazole)	trematodes	growth inhibition
hexyloxynaphthamidines (bunamidine)	cestodes	tegument damage
hydropyrazinobenzazepine (epsiprantel)	cestodes	tegument damage
aminoglycoside antibiotics (paromomycin)	cestodes	tegument damage
tin compounds (tinostat), largely discontinued	nematodes, cestodes	cuticle damage
halogenated hydrocarbons (butyl chloride, butynorate, carbon tetrachloride, hexachloroethane, hexachloroparaxylene, tetrachloroethylene, toluene)	cestodes, nematodes, trematodes	purgative
alkaloids (arecoline)	cestodes	purgative
lead arsenate, largely discontinued	nematodes, cestodes	toxin, purgative
mineral salts (copper sulphate), largely discontinued	nematodes	toxin

Drugs used to treat parasitic arthropod infestations (insecticides, acaricides)

Drug class (generic exemplars)	Spectrum of efficacy	Mode of action
organochlorides (bromocyclen, bromopropylate, dichloro-diphenyl-trichloroethane (DDT), lindane, methoxychlor, toxaphene, cyclodiens (chlordane, dieldrin, endosulfan, heptachlor))	flies, lice, mites	neurotoxic
benzoic esters (benzyl benzoate)	mites, lice	neurotoxic
organophosphates (bendiocarb, dioxathion, fenchlorphos, haloxon, maldison, methomyl, metrifonate, naphthalofos, promacyl, propoxur), organophosphonates (chlorfenvinphos, dichlorvos, dicrotophos, heptenophos, naled, tetrachlorvinphos, trichlorfon), monothiophosphates (azamethiphos, chlorpyrifos, coumaphos, cythioate, diazinon, famphur, fenitrothion, fenthion, iodofenphos, pirimiphos, phoxim, propetamphos, temephos), dithiophosphates (dimethoate, ethion, malathion, phosmet)	flies, fleas, lice, ticks, mites	neuro-interference
carbamates (bendiocarb, carbaryl, methomyl, promacyl, propoxur)	flies, fleas, lice, ticks, mites	neuro-interference
chloronicotinyles (imidacloprid, nitenpyram)	fleas	neuro-interference
spinosyns (spinosad)	flies, fleas, lice	neuro-interference
arylpyrazoles (fipronil, pyriprole)	fleas, ticks, mites	neuro-interference
pyrethrins (cinerin, jasmolin, pyrethrin), type I pyrethroids (allethrin, bioallethrin, permethrin, phenothrin, resmethrin, tetramethrin), type II pyrethroids (alphamethrin, cypermethrin, cyfluthrin, cyhalothrin, deltamethrin, fenvalerate, flucythrinate, flumethrin, fluvalinate), non-ester pyrethroids (etofenprox)	flies, fleas, lice, ticks	neuro-interference
isoxazoline (afoxolaner)	fleas, ticks	neuro-interference
isoxazoline-substituted benzamide derivatives (fluralaner)	fleas, ticks	neuro-interference
alkaloids (nicotine), largely discontinued	ticks, mites, lice	neuro-interference
neonicotinoid (dinotefuran)	fleas, ticks	neuro-interference
semicarbazone (metaflumizone)	fleas, ticks	neuro-interference
oxadiazine (indoxacarb)	fleas	neuro-interference
macrocyclic lactones: avermectins (abamectin, doramectin, eprinomectin, ivermectin, selamectin); milbemycins (milbemycin, moxidectin)	flies, fleas, lice, ticks, mites	muscle interference
salicylanilides and substituted phenols (closantel)	flies (nasal bots)	energy depletion
amidines (amitraz, cymiazole)	mites, ticks, lice	anti-metabolite
natural product (deguelin, rotenone, tephrosine, toxicarol)	lice, flies, mites, ticks	anti-metabolite
anilides (crotamiton)	mites	unknown (antipruritic)
benzoylphenylureas (diflubenzuron, fluazuron, lufenuron, triflumuron)	fleas, lice, ticks	chitin inhibition
triazines (cyromazine, dicyclanil)	flies	growth inhibition
juvenile hormone mimetics (fenoxycarb, hydroprene, methoprene, pyriproxyfen)	flies, fleas	moult inhibition
sulphur (largely discontinued)	mites	toxic

The efficacies of many pharmacological interventions have been seriously compromised by the emergence of drug resistance in a wide range of parasites. Resistance is a consequence of evolution in response to environmental pressures. Individual parasites vary in their susceptibility to drugs and some with greater fitness survive drug treatment. Such traits are inherited by subsequent generations and can rapidly spread through parasite populations. Resistance problems are exacerbated when parasites are exposed to sub-lethal drug concentrations due to under-dosing and/or poor patient compliance (incomplete course of treatment). Widespread resistance has developed in parasites to many antimalarials, anticoccidials, anthelmintics and insecticides. Studies conducted on the possible mechanisms involved in the development of resistance have implicated a range of genetic mutations affecting drug accumulation (reduced influx, increased efflux, compartmentalization), drug activity (inactivation, modification, sequestration), drug metabolism (up/down regulation of antagonists/agonists) or target alteration (changes to binding sites). Drug residues may also accumulate in the food chain so most livestock industries mandate with-holding periods whereby drug application prior to slaughter is prohibited. Some drugs also persist in the environment and may exert deleterious effects on other organisms. The development of new drugs has assumed greater importance as drug resistance (especially multi-drug resistance) has severely challenged clinical care.

Successful chemotherapeutic treatment may cure the patient of current infection, but it does not impart any protection against re-infection. Patients go back to their homes and their old habits and often quickly become re-infected. To stop this from happening, patients require regular chemoprophylactic treatment, or vaccination, or re-education about parasite transmission.