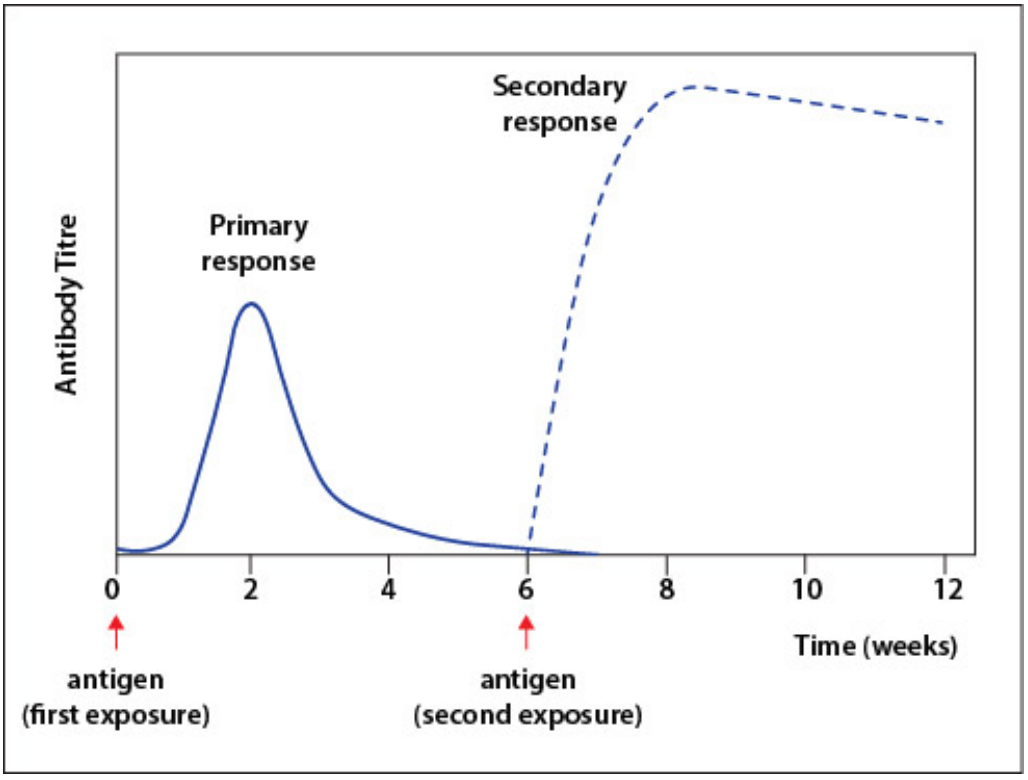
VACCINES

How do hosts survive the deprivations of the constant microbial onslaught incurred simply by living in a contaminated world? They can become more impervious to infection (resistant) or more able to tolerate or ameliorate disease (better defence or repair processes). To do so, hosts have evolved an array of immune responses to combat invading pathogens and provide protection against further infection.

Immune defences

Nonspecific defences such as the skin and inflammation provide general barriers to infection, but other immune responses are more specific, identifying and destroying particular invaders. Many consider there to be three lines of immunological defence to infection:

- The first line of defence involves nonspecific barriers to infections: both physical barriers (such as the skin and mucous membranes) and chemical barriers (such as mucus, lysozyme and gastric juices).
- The second line of defence involves nonspecific innate immunity, whereby inflammatory responses deliver cells (phagocytes and natural killer (NK) cells) and antimicrobial proteins (complement (C'), interferon (IFN)) to the site of infection to combat invading organisms. The four cardinal signs of inflammation involve rubor (redness), calor (heat), tumor (swelling), and dolor (pain) due to the increased blood flow at the site of infection.
- The third line of defence involves specific adaptive (or acquired) immunity, whereby cytotoxic cells and antibodies are produced to specifically attack the invading pathogens. These specific responses involve effector and memory cells, the latter facilitating more efficient responses when the host is exposed to secondary challenge infections. Vaccination aims to prime the adaptive immune system to antigens of a particular microbe so that a first infection induces a secondary response.

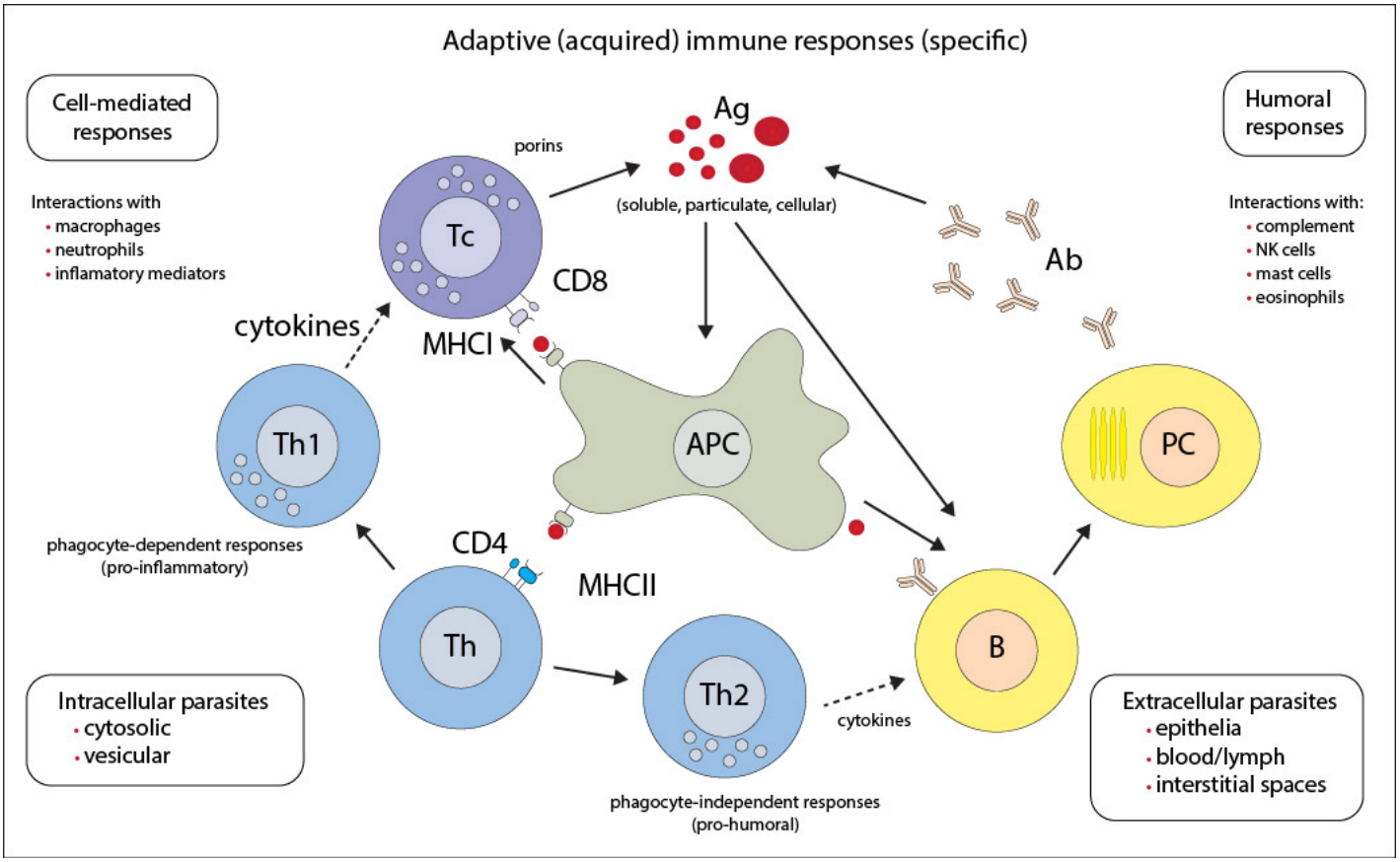


Adaptive (acquired) immunity

Adaptive immune responses are highly specific and are reliant on lymphocytes. These cells circulate throughout the blood and lymph and are found in high numbers in lymphatic tissues. They develop from pluripotent stem cells in the bone marrow; B cells mature in marrow and T cells mature in the thymus. B and T cells recognize antigens via specific surface antigen receptors; B cell membrane antibodies and T cell receptors. Self tolerance develops as cells bearing receptors for native molecules are destroyed or rendered nonresponsive. Major histocompatibility complex (MHC) molecules are crucial to antigen presentation (via antigen-presenting cells (APC)). Class I MHC molecules located on all nucleated cells present antigens to cytotoxic T cells while class II

MHC on macrophages and B cells present antigens to helper T cells. When an antigen binds to a particular lymphocyte, it is activated to produce numerous identical copies (clonal selection). The primary immune response (first exposure to an antigen) results in clones of short-lived infection-fighting effector cells as well as clones of long-lived memory cells. Subsequent exposure to the same antigen activates the memory cells and the resultant secondary immune responses are faster, stronger and often protective (providing the basis for vaccination).

Specific acquired immunity involves both cell-mediated (T-cell) and humoral (B-cell) responses. Cell-mediated responses provide excellent defence against intracellular pathogens because infected cells are identified and destroyed, while humoral responses are effective by tagging extracellular pathogens for destruction. Helper T cells (T_h) interact with antigen-class II MHC complexes on macrophages through T cell receptors and the cell surface protein CD4. Contact stimulates T_h cells to grow and divide as does the cytokine interleukin-1 (IL-1) secreted by macrophages. T_h cells secrete IL-2 which activates other cells in the immune system; including cytotoxic T cells (T_c) (stimulated to become active killer cells), B cells (stimulated to become antibody-producing plasma cells (PC)) as well as additional T_h cells (stimulated to divide more rapidly and increase cytokine production). T_h cells stimulated to proliferate first become T_h0 cells that secrete IL-2, IL-4 and interferon-gamma (IFN-γ). They then differentiate into T_h1 or T_h2 cells depending on the cytokine environment. IFN-γ drives T_h1 cell production and inhibits T_h2 cells, while IL-10 and IL-4 drive T_h2 cell production and inhibit T_h1 cells. T_h1 cells produce IFN- γ, IL-2 and tumour necrosis factor (TNF)-β, which activate macrophages and are responsible for cell-mediated immune and phagocyte-dependent protective responses. T_h2 cells produce IL-4, IL-5, IL-10 and IL-13, which are responsible for strong antibody production, eosinophil activation and inhibition of several macrophage functions, thus providing phagocyte-independent protective responses. Antigens from intracellular pathogens are also gathered in nucleated cells of the body and presented on the surface by class I MHC proteins. They are recognized by T_c cell receptors and the cell surface protein CD8. T_c cells are stimulated by contact and by IL-2 to release the protein perforin which punctures the target cell, allowing water and ions to rush in causing swelling and lysis. Humoral responses are effective against extracellular pathogens. B cells have antibody receptors in their plasma membranes specific for particular antigens. Successful binding stimulates B cell proliferation producing clones of plasma cells and memory cells. Plasma cells secrete antibodies in increasing amounts peaking 10-17 days after activation. Antibodies flow through the body's fluids and tag foreign cells and molecules for destruction via neutralization, agglutination, precipitation and complement fixation.



Immunity to parasites

The efficacies of the different types of immune responses against parasites depend largely on where the parasites are found in the hosts, and thus their accessibility to different effector systems.

- Intracellular parasites located in the host cell cytoplasm (such as coccidia, haemosporidia, piroplasms, microsporidia) or in vesicles (such as leishmanias and toxoplasms) often elicit strong protective responses afforded by cell-mediated mechanisms involving T_c and T_h cells. T_h1 cell responses are effective against intracellular bacteria and protozoa. These responses are triggered by IL-12 and IL-2, their effector cytokine is IFN-γ, and their main effector cells are macrophages as well as CD8 T cells, IgG B cells and IFN-γ CD4 T cells.

- Extracellular parasites located within interstitial spaces, blood or lymph (such as filarial worms, schistosomes and trypanosomes) or on epithelial surfaces (such as gastro-intestinal nematodes, flukes, flagellates, amoebae or ciliates) generally elicit weaker protective responses afforded by humoral immune responses involving antibody opsonization, then macrophages, natural killer cells and eosinophils. In particular, T_h2 cell responses act against extracellular helminths. The responses are triggered by IL-4, their effector cytokines are IL-4, IL-5, IL-9, IL-10 and IL-13, and their main effector cells are eosinophils, basophils and mast cells as well as B cells and IL-4/IL-5 CD4 T cells. IL-4 stimulates B-cells to produce IgE antibodies, which in turn stimulate mast cells to release histamine, serotonin, and leukotriene to cause broncho-constriction, intestinal peristalsis, gastric fluid acidification to expel helminths. IL-5 from CD4 T cells also activates eosinophils to attack helminths.

Hypersensitivity

A critical aspect in immunity is the proper regulation of host responses: hypo-responsiveness is insufficient to control the infection, while hyper-responsiveness may control the infection but go on to cause immunopathology. Excessive or exaggerated immune responses have been found to cause four types of hypersensitivity:

- Type I (immediate or anaphylactic) hypersensitivity occurs within 15-30 minutes of exposure to antigens (often allergens) and may involve the skin (urticaria, eczema), eyes (conjunctivitis), nasopharynx (rhinorrhoea, rhinitis), bronchopulmonary tissues (asthma) or gastrointestinal tract (gastroenteritis). It is mediated by IgE and the primary cellular components are mast cells and basophils. Reactions are amplified by neutrophils, eosinophils and platelets. Examples include weal and flare reactions to insect venoms and pollens, urticaria to some helminths (roundworms), and there appears to be a genetic disposition to particular atopic diseases.

- Type II (cytotoxic) hypersensitivity occurs within minutes to hours of exposure to endogenous antigens (sometimes exogenous haptens) and may affect a variety of organs and tissues (with lysis and necrosis). It is mediated by antibodies (IgG or IgM) and complement; and phagocytes and NK cells may be involved. Examples include reactions sometimes associated with haemolytic anaemia, granulocytopenia and thrombocytopenia.

- Type III (immune complex) hypersensitivity occurs within 3-8 hours and may be general (e.g. serum sickness) or involve individual organs including skin (systemic lupus erythematosus, Arthus reaction), kidneys (lupus nephritis), lungs (aspergillosis), blood vessels (polyarteritis), joints (rheumatoid arthritis) or other organs. It is mediated by soluble immune complexes comprising antibodies (mostly IgG) and antigens (exogenous microbial or endogenous non-organ-specific autoimmunity antigens) and sometimes complement. The damage is caused by platelets and neutrophils with erythema, oedema and necrosis. Immune complex disease may be seen in malarial nephritis, trypanosomiasis or schistosomiasis.

- Type IV (cell-mediated or delayed) hypersensitivity occurs within 2-3 days (sometimes up to 3 weeks) and involves the skin (eczema, erythema, induration, fibrosis) as well as a variety of organs and tissues. It has been implicated in many autoimmune and infectious diseases (tuberculosis, leprosy, blastomycosis, histoplasmosis, toxoplasmosis, leishmaniasis, filarial elephantiasis, swimmer's itch, etc.), granulomas (due to infections and foreign antigens) and contact dermatitis (poison ivy, chemicals, heavy metals, etc.). It is mediated by T cells, monocytes and/or macrophages. T_c cells cause direct damage whereas T_h1 cells secrete cytokines which activate T_c cells and recruit more monocytes and macrophages.

Specific vaccination

While adaptive/acquired immune responses may provide protection against re-infection, they only do so against the particular parasite species (or strain) that elicited the initial response. This high specificity means that no single vaccine will give broad-spectrum protection because separate vaccines will have to be developed against each individual parasite species/strain. The degree of immunity may also vary, ranging from sterile immunity (pathogens eliminated) to partial immunity (clinical disease prevented) to concomitant (premunitive) immunity (some pathogens persist but hosts are protected against super-infection). The duration of protection may also vary, with protection lasting for years or waning after months.

Many vaccination strategies have been proposed for infectious diseases, including anti-infection (prevent infection); anti-disease (prevent disease if not infection); and anti-transmission (prevent further dissemination). Most parasites have complex life-cycles involving sequential developmental stages which may be quite different from each other, may infect different tissues, and may elicit different immune responses. This complicates the process of finding parasite immunogens (antigens that also provoke protective responses). Vaccines may be developed from live organisms (drug-truncated infections, attenuated strains), whole killed organisms (fixed, frozen), subcellular fragments (excretory-secretory products, lysates, extracts, fractions), toxoids (inactivated toxins that still induce protective antibodies) or artificially synthesized antigens (recombinant proteins or DNA-encoding regions) used alone, in cocktail mixtures or with adjuvant formulations. Vaccines need to be monitored for reversion to virulence (in the case of live organisms), allergic or hypersensitivity reactions (particularly those involving adjuvants), and contamination (by non-target microbes or genes). Vaccines must also be extensively tested *in vitro* (in tissue culture) and *in vivo* (in laboratory animal models) before they undergo clinical trials (often using double-blind placebo-control protocols). The moral and ethical dilemmas involved in confirming vaccine efficacy by challenging vaccine recipients with clinical infections are numerous, particularly for virulent diseases with compromised treatment options.

Considerable work has been conducted on the development of vaccines against parasites, but with few successes. Because many infections are self-limiting and/or provoke protective responses in naturally-infected hosts, there are ample reasons to think that effective vaccines could be developed against eukaryotic parasites. However, it has proven difficult to unravel the complexities of most host-parasite immunological interactions to identify immunogens stimulating protective responses. Early studies using whole parasites (and a few fractions) elicited good protection, but the logistics involved in large scale parasite production limited their development and commercialization. Despite the promise of modern technology to produce recombinant and/or DNA vaccines, most studies on individual products have failed to provide adequate protection. There is growing evidence that cocktail vaccines are required to simultaneously stimulate different types of immune responses which collectively contribute to protection.

In addition to research designed to stimulate active immunity against parasites by natural infection or vaccination, studies have also been conducted on the acquisition of passive immunity through the transfer of effectors cells/molecules from resistant to susceptible hosts. In particular, studies have centred on the adoptive transfer of maternal antibodies from mothers to offspring by feeding natural or artificial colostrum (first few days breast milk). Colostrum is naturally enriched in antibodies and high titres against particular pathogens may be found in previously-infected mothers. High titres can also be generated in dairy cattle by experimentally inoculating cows before or during pregnancy and then harvesting the hyperimmune bovine colostrum (HIBC) post-partum. The enriched colostrum has demonstrated variable success in the treatment (immunotherapy) of gastro-intestinal infections in neonates (including rotavirus, cryptosporidiosis and giardiasis).

Commercially-available vaccines against parasites

Genus/species	Vaccine composition*	Utility
Protozoan parasites		
Leishmania major	whole mastigotes (live and killed)	two vaccines used for leishmanization in eastern Europe, largely discontinued
Leishmania infantum	recombinant fucose mannose ligand (FML) antigen	Leishmune developed for disease in dogs
Tritrichomonas foetus	killed trophozoites	TrichGuard developed to prevent reproductive failure in cattle
Giardia duodenalis	killed disrupted trophozoites	GiardiaVax developed to prevent giardiasis in dogs and cats
Eimeria spp.	live attenuated, precocious or non-attenuated heterologous strains	many (Advent, Coccivac, Eimeriavax, Embrex, Hipracox, Immucox, Inovocox,Livacox, NobilisCox, Paracaox, Viracox, etc.) developed to prevent coccidiosis in layer and broiler chickens, turkeys
Eimeria spp.	antigens from wall-forming bodies in macrogametocytes	CoxAbic developed to prevent coccidiosis in broiler chickens (via maternal immunization)
Toxoplasma gondii	live attenuated strain (S48)	Toxovax developed to prevent congenital infection in ewes
Neospora caninum	killed tachyzoites	NeoGuard developed to prevent abortion in cattle
Babesia bovis, B. bigemina	live attenuated merozoites	several (Anabasan, Combavac, Embravac, Eritrovac, Hemovac, Redwater, Trivalent, Vacuna) developed to prevent tick fever in cattle
Babesia canis, B. rossi	soluble parasite antigens (SPA)	Nobivac Piro developed to prevent babesiosis in dogs
Theileria parva, T. annulata	live wild-type parasites (infections drug-truncated), and live attenuated parasites	local stocks used to prevent theileriosis in cattle
Helminth parasites		
Dictyocaulus viviparus	irradiated larvae	Dictol and Huskvac developed to prevent parasitic bronchitis in cattle
Haemonchus contortus	proteins from worm intestines	Barbervax developed to prevent gastroenteritis in sheep
Ancylostoma caninum	irradiated larvae (L3)	irL3 vaccine developed to prevent disease in dogs (discontinued as commercial failure)
Arthropod parasites		
Rhipicephalus microplus	tick midgut membrane-bound recombinant protein (Bm86)	TickGuard and Gavac developed to reduce infestations on cattle
Caligus spp.	recombinant proteins (my32, Ls4D8)	Aquatec Sea Lice developed to reduce infestations on farmed fish (salmonids)

Experimental studies on vaccine development against protozoan parasites

Genus/species	Vaccine composition*	Vaccine efficacy
Amoebae		
Entamoeba histolytica	serine-rich protein	protective in gerbils, monkeys
Entamoeba histolytica	n-acetylgalactosamine-inhibitable lectin (GAL / GALNAC)	protective in animals
Entamoeba histolytica	cysteine-rich protein (peroxiredoxin), lipophosphoglycan, lectins	under development
Flagellates		
Histomonas meleagridis	live attenuated parasites	protective in turkeys
Trypanosoma brucei	invariant antigen in flagellar pocket (FP), invariant surface glycoproteins (ISG), membrane-associated sialidase, glycosylphosphatidylinositol (GPI) anchor	protective in mice
Trypanosoma brucei	congopain cysteine protease (CP)	protective in cattle
Trypanosoma evansi	recombinant cytoskeletal proteins (actin, tubulin)	protective in mice
Trypanosoma cruzi	live attenuated parasites	protective in dogs
Trypanosoma cruzi	recombinant proteins (Tc24, TSA-1)	under development
Trypanosoma cruzi	DNA and recombinant proteins (TcG2, TcG4)	protective in mice
Leishmania spp.	whole killed mastigotes (incl. ALM)	protective in humans
Leishmania spp.	recombinant surface-expressed glycoprotein (gp63)	protective in mice, monkeys
Leishmania spp.	hydrophilic acylated surface proteins (HASP)	protective in mice
Leishmania spp.	naked DNA (heterologous prime-boost, HPB)	protective in mice, dogs
Leishmania spp.	cysteine protease antigens	protective in mice, dogs
Leishmania spp.	live attenuated mastigotes (dihydrofolate reductase thymidylate synthase (dhfr-ts) knockout (KO))	protective in mice
Leishmania donovani	promastigote membrane antigens (LAg)	protective in mice
Leishmania donovani	recombinant fucose mannose ligand (FML) antigen	protective in mice, rabbits, dogs
Leishmania donovani	live attenuated mastigotes (centrin null (LdCEN-/-) mutants)	protection in mice
Leishmania major	*Leishmania* activated C kinase (LACK)	protective in mice
Leishmania major, L. braziliensis	*Leishmania* derived recombinant polyprotein (Leish-111f)	protection in mice, humans
Leishmania infantum	live attenuated parasites (ΔHSP70-II deletion mutant)	protective in hamsters
Apicomplexans		
Eimeria spp.	sporozoite fractions	protective in chickens
Eimeria spp.	recombinant merozoite antigens	protective in chickens, cattle
Eimeria spp.	gametocyte antigens	protective in chickens
Eimeria spp.	recombinant proteins (EtMic, GPI, LDH, SOD)	protective in chickens
Cryptosporidium parvum	irradiated oocysts	protective in calves
Cryptosporidium parvum	sporozoite surface antigens (Cp15/17, Cp23/27, Muc4/5)	protective in mice, calves
Cryptosporidium parvum	DNA encoding Cp15/60, Cp23, Cp15+Cp23	protective in mice
Sarcocystis neurona	killed merogonic stages	protective in horses
Toxoplasma gondii	DNA encoding dense granule antigens and SAG1	protective in mice
Toxoplasma gondii	bradyzoite mutant (T263) deficient in sexual reproduction	protective in cats
Neospora caninum	tachyzoites from low virulence (Nowra) strain	protective in cattle
Neospora caninum	recombinant antigens (SRS2, SAG1, DG1, DG2)	protective in rodents
Plasmodium berghei	irradiated sporozoites	protective in mice
Plasmodium falciparum, P. vivax	irradiated sporozoites	protective in humans, but discontinued (logistics)
Plasmodium falciparum, P. vivax	genetically attenuated sporozoites (PfGAP gene deletion)	protective in humans
Plasmodium falciparum	whole blood-stage parasites (low doses)	protective in animals, humans
Plasmodium falciparum	recombinant circumsporozoite protein (RTS,S)	protective in humans
Plasmodium falciparum	recombinant blood-stage antigens: apical membrane antigens (AMA), merozoite surface proteins (MSP), glutamate rich protein (GLURP), ring-infected erythrocyte surface antigens (RESA), serine repeat antigens (SERA),	some protective in mice, monkeys, humans

	erythrocyte-binding antigens (EBA), combinations (GMZ, BSAM)	
Plasmodium falciparum	surface protein antigens (Pfs25, Pvs25, Pfs28, Pvs28), some with transmission-blocking activity in mosquitoes	under development
Plasmodium falciparum	GPI toxin	protective in mice
Plasmodium falciparum	sexual stage specific antigens (Pfs48/45, Pfs230)	under development
Plasmodium falciparum	adhesion ligands, erythrocyte membrane proteins (PfEMP1), some sequestered in placenta (VAR2CSA)	protective in humans
Plasmodium falciparum	polyepitope plasmid DNA vaccine (EP1300)	protective in humans
Plasmodium falciparum	viral vectors encoding thrombospondin-related adhesion protein (TRAP) pre-erythrocytic antigen, circumsporozoite protein (CSP), AMA1, MSP, merozoite surface protein (PEV), combinations (NMRC), multi-stage, multi-antigen (NYVAC)	some protective in animals, humans
Babesia bovis, B. divergens	killed parasites	protective in cattle
Babesia bovis, B. bigemina	culture supernatant (exoantigens)	some protective in cattle
Babesia bovis, B. bigemina	parasite fractions (lipids, rhoptries, rhoptry-associated protein (RAP), GPI-anchored proteins)	protective in animals
Babesia bovis	recombinant proteins (immunodominant antigens)	protective in cattle
Babesia bigemina	recombinant proteins (RAP)	protective in cattle
Babesia divergens	live attenuated parasites (rapid passage in splenectomized calves, passage in gerbils, irradiation, low dose)	protective in cattle, mostly discontinued
Babesia divergens	recombinant protein (Bd37)	protective in animals
Babesia divergens	purified merozoite polypeptides	protective in gerbils
Theileria parva	recombinant sporozoite surface antigen (p67)	protective in cattle
Theileria annulata	attenuated live zoites	protective in cattle
Ciliates		
Ichthyophthirius multifiliis	purified cell surface immobilization antigens (I-ags)	protective in catfish
Ichthyophthirius multifiliis	DNA encoding I-ags and cysteine protease	protective in trout
Philasterides dicentrarchi	whole fixed scuticociliate trophozoites	protective in turbot

Experimental studies on vaccine development against helminth parasites

Genus/species	Vaccine composition*	Vaccine efficacy
Ascarid nematodes		
Ascaridia galli	irradiated larvae	protective in chickens
Toxocara canis	irradiated larvae; excretory-secretory (ES) proteins	protective in mice
Ascaris suum	irradiated eggs; recombinant proteins (As14, As16, As24)	protective in mice, pigs
Baylisascaris schroederi	recombinant proteins (As14 homologue)	protective in mice
Rhabditid nematodes		
Strongyloides spp.	irradiated larvae	protective in rats, sheep, chickens
Trichostrongyloid nematodes		
Nippostrongylus brasiliensis	irradiated larvae	protective in rats
Amidostomum anseris	irradiated larvae	protective in geese
Cooperia punctata	irradiated larvae	protective in cattle
Cooperia oncopora	irradiated larvae	protective in cattle
Dictyocaulus filaria	irradiated larvae	protective in sheep
Dictyocaulus viviparus	irradiated larvae; recombinant protein (paramyosin)	protective in cattle
Heligmosomoides polygyrus	irradiated larvae, ES antigens	protective in mice
Trichostrongylus vitrinus	irradiated larvae	protective in guinea pigs
Trichostrongylus tenuis	irradiated larvae	protective in grouse
Trichostrongylus colubriformis	irradiated larvae; recombinant proteins (MIF, APY, TGF, TGH, cathepsin, astacin metalloprotease, VAL/ASP protein, SSA)	protective in gerbils, guinea pigs, sheep
Haemonchus contortus	irradiated larvae; ES and hidden antigens (contortin, cysteine proteases, H11, P1, galactose-containing glycoprotein (H-gal-GP), thiol sepharose-binding protein (TSBP))	protective in sheep, goats
Ostertagia circumcincta	irradiated larvae	protective in sheep
Ostertagia ostertagi	irradiated larvae; hidden antigens (Oo-gal-GP, ES-thiol containing CP and ASP/VAL proteins, polyprotein allergen (OPA))	protective in cattle
Strongyloid nematodes		
Strongylus vulgaris	irradiated larvae	protective in horses
Oesophagostomum columbianum	irradiated larvae	protective in sheep
Syngamus trachea	irradiated larvae	protective in chickens, pheasant
Stephanurus dentatus	irradiated larvae	protective in pigs
Ancylostomatoid nematodes		
Bunostomum trigonocephalum	irradiated larvae	protective in sheep
Gaigeria pachyscelis	irradiated larvae	protective in sheep
Ancylostoma ceylanicum	irradiated larvae	protective in hamsters
Ancylostoma caninum	irradiated larvae; prominent antigen (Ac16); aspartyl haemoglobinases (Ac-APR-1)	protective in dogs
Necator americanus	larval secreted protein (Na-ASP-2); glutathione S-transferase (Na-GST-1); cysteine haemoglobinase (Ac-CP-2); aspartyl haemoglobinases (Na-APR-1)	protective in hamsters, dogs, humans
Metastrongyloid nematodes		
Metastrongylus apri	irradiated larvae	protective in guinea pigs
Filarioid nematodes		
Dirofilaria immitis	irradiated larvae	protective in dogs
Litomosoides carinii	irradiated larvae	protective in rats
Brugia pahangi	excretory-secretory (ES) larval products	protective in jirds
Brugia malayi	irradiated mosquito-borne larvae (L3); abundant larval transcripts (ALT-1, ALT-2)	protective in jirds
Onchocerca ochengi	attenuated larvae, then 8 recombinant proteins	protective in cattle
Onchocerca volvulus	microfilarial extracts, irradiated L3, recombinant proteins (ES, surface, ALT, RAL2, tropomyosin, CPI-2, FAR1)	protective in mice, jirds, cattle
Enoplid nematodes		
Capillaria obsignata	irradiated larvae	protective in chickens
Trichuris muris	ES products	protective in mice

Trichinella spiralis	irradiated larvae; ES products	protective in mice
Cyclophyllidean cestodes		
Taenia ovis	oncosphere ES material, recombinant antigen (GST-45W)	protective in sheep
Taenia saginata	recombinant oncosphere antigens (TSA9, TSA-18)	protective in cattle
Taenia solium	recombinant oncosphere antigen (TSOL18)	protective in pigs
Echinococcus granulosus	recombinant protoscolex proteins (egM4,egM9, egM123); recombinant oncosphere protein (EG95)	protective in dogs, sheep, cattle
Echinococcus multilocularis	recombinant oncosphere protein (Em95)	protective in mice
Digenean trematodes		
Schistosoma mattheei	irradiated cercariae	protective in mice
Schistosoma bovis	irradiated cercariae; GST	protective in mice, goats
Schistosoma haematobium	recombinant glutathione S-transferase (Sh-GST28); DNA encoding triose phosphate isomerase (TPI)	protective in rats, hamsters, monkeys, pigs, humans
Schistosoma mansoni	paramyosin, synthetic peptide construct with multiple antigen epitopes (MAP) from TPI, fatty acid binding protein (Sm14); GST, recombinant surface proteins (Sm23, Sm29, SmCD59-like, Sm200, SmTOR, SM-p80, Sm-TSP2)	protective in mice, rats, monkeys, humans
Schistosoma japonicum	paramyosin, recombinant protein (Sj23); GST, DNA plasmid comprising fusion of TPI, heat shock protein and IL-12	protective in mice, sheep, pigs, water buffaloes
Fasciola gigantica	fatty acid binding protein (FABP)	protective in cattle
Fasciola hepatica	leucine aminopeptidase (LAP), GST, cathepsin, FABP, hemoprotein	protective in mice, rabbits, sheep, cattle

Experimental studies on vaccine development against arthropod parasites

Genus/species	Vaccine composition*	Vaccine efficacy
Arachids (ticks)		
Rhipicephalus microplus	midgut membrane-bound recombinant protein (BA95)	protective in cattle
Rhipicephalus annulatus	midgut membrane-bound recombinant protein (BA86)	protective in cattle
Rhipicephalus microplus, Haemaphysalis longicornis	recombinant vitellin-degrading cysteine endopeptidase (VTDCE), yolk procathepsin (BYC), GST	protective in cattle
Hyalomma anatolicum	midgut membrane-bound recombinant protein (HAA86)	protective in cattle
Rhipicephalus appendiculatus	salivary cement protein (64TRP)	protective in hamsters, guinea pigs, rabbits
Rhipicephalus appendicularis	cocktail of serpins (serine protease inhibitors, RAS)	protective in cattle
Ixodes ricinus, Rhipicephalus microplus, R. annulatus	ferretin 2 recombinant protein (RmFER2)	protective in animals
Ixodes scapularis	histamine release factor (tHRF)	protective in mice
Ixodes scapularis	recombinant subolesin (SUB) protein [ortholog of insect akirins (AKR)]	protective against ticks, mosquitoes, sand flies in animals
Arachnids (mites)		
Psoroptes ovis, P. cunniculi	purified mite extracts (esp. soluble antigens)	protective in rabbits, sheep, cattle
Psoroptes ovis	recombinant scab mite allergens (Pso o I, Pso o II)	protective in sheep, cattle
Sarcoptes scabiei	recombinant paramyosin, apolipophorin-like protein (Ssag1)	recognised by immune sera, not protective in rabbits
Insects (fleas)		
Ctenocephalides spp.	hidden antigens from flea gut	protective in rabbits, dogs
Insects (flies)		
Haematobia irritans	fly tissue extracts, trypsin-like enzyme	*in vitro* anti-fly activity, protective in cattle
Hypoderma lineatum	fly larval serine proteases (hypodermins A, B, C)	protective in cattle
Lucilia cuprina	fly larval peritrophin extracts (55, 95), and recombinant homologues	*in vitro* larval growth inhibitory activity
Oestrus ovis	fly salivary gland extracts	protective in sheep
Phlebotomus spp.	sand fly salivary proteins (SGE, PpSP30)	protection against *Leishmania* in mice
Anopheles spp.	mosquito saliva	protection against malaria in mice
Culex spp.	recombinant mosquito salivary proteins (MSP)	variable success *in vitro* and in animal models

*cf. *Chaudhury A 2014 Human parasitic vaccines - an overview. J Clin Biomed Sci 4:216*

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Immuno-evasion

Hosts have evolved sophisticated immune defences to help survive parasitic infections, but how do parasites survive the immunological onslaught? Parasites have evolved a spectacular range of mechanisms to avoid host immune responses, thus taking part in the host-parasite evolutionary arms race between parasite aggressiveness (virulence) versus host defence (immunity). Theoretically, the objective would be to find a common middle ground ensuring mutual survival (= enzootic stability), but in reality, there appears to be episodic escalation by one side or the other (disease resulting from the rise of more virulent strains and/or more susceptible hosts). Parasites have adopted three basic strategies to avoid host immune mechanisms: hide, disguise, or suppress. Many parasites hide from the host immune system by developing in cryptic or immunologically inert sites, such as within cells (free in cytoplasm or membrane-bound in vesicles or parasitophorous vacuoles), within the lumen of tubular organs, behind the blood-brain barrier, or by encapsulating themselves within cysts. Other parasites disguise themselves to avoid immune surveillance by masking (coating themselves with host molecules), mimicry (copying host molecules) or changing their surface coats (antigen variation). A range of parasites have also been found to actively down-regulate or negate host immune responses by saturating effector mechanisms (antigen shedding), blocking responses (by inhibition, destruction or developing tolerance), or inducing host suppressor mechanisms (cells or cytokines). The sophistication of the immune evasion mechanisms exhibited by these eukaryotic parasites has frustrated most attempts to identify immunogens and protective responses suitable for vaccination programmes. By contrast, many vaccines have been developed against acellular pathogens (viruses) and prokaryotic organisms (bacteria). Hopefully, sustained research endeavours will one day produce effective vaccines against parasites.