International Journal of Advanced Multidisciplinary Research
ISSN: 2393-8870
www.ijarm.com
DOI: 10.22192/ijamr Volume 6, Issue 3-2019

Review Article

DOI: http://dx.doi.org/10.22192/ijamr.2019.06.03.006

An Overview of Role of Immunity on Parasitic Infections

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Keywords

Parasitic infection,
Role of immunity,
Vaccine development

Abstract

Parasitic infections are caused by protozoa, helminthes and arthropods. Most of the parasites go through complex life cycles, occurring partly in definitive host and partly in intermediate host. In addition, parasites are structurally and antigenically diversified. This structural and antigenic diversity of pathogenic parasites reflected in the heterogeneity of the adaptive immune responses that they elicit. Both the innate and adaptive/acquired immune responses are co-evolving to allow hosts to identify and eliminate parasites as non-self antigens. The principal innate immunity to protozoa is phagocytosis, and the natural killer cells pathway of interferon gamma production is another innate immune response to protozoa; whereas acquired immunity encompasses both cell-mediated through helper T cells (Th1) response (for intracellular) and antibody-mediated (for extracellular). Helminthes are eliminated by immunoglobulin E (IgE) antibody, helper T cells (Th2) response and eosinophil mediated killing as well as by other leukocytes. The third groups of parasites, arthropods, are combated by delayed hypersensitivity reaction, cutaneous basophil hypersensitivity and Th2 response. However, parasites have evolved the ability to evade immune system by varying their antigens; by acquiring resistance to immune effector mechanisms; by masking their surface antigens; and by suppressing the host immunity. Understanding of these parasite-host interactions contributes for the vaccine production as a solution to growing antiparasitic drugs resistance.

1. Introduction

In infectious disease terminology, parasitic infection refers to infection with parasites such as protozoa, helminthes and ectoparasites (e.g. ticks and mites). Such parasites currently account for greater morbidity and mortality than any other class of infectious organisms, particularly in developing countries. About ten years back, it is estimated that about 30% of world's human population suffers from parasitic infections [1].

Parasites infect their hosts through penetrating the hosts' skin; being ingested by their hosts; carried by vectors and so on [2]. Once parasitic pathogens encountered their hosts, they are considered as antigens by the immune system of the host. These antigens are the body components of parasites, and are generally classified as "natural" and "hidden" antigens [3].

It is the immune system that plays a central role in determining the outcome of parasitic infection by establishing a critical balance to ensure both host and pathogen survival [4]. The development of immunity is complex process arising from the activation of both innate and adaptive immune responses and the switching-on of many different kinds of cells over a

period of time. Innate immune recognition relies on a growing number of receptors, termed pattern recognition receptors (PRRs) that have evolved to recognize pathogen associated molecular patterns (PAMPs), whereas adaptive immunity is initiated through APCs [5].

The field of immunoparasitology is focused on developing a basic understanding of this important host-parasite interface for the ultimate purpose of intervention. Indeed, because of their years of close encounter with and adaptation to the vertebrate immune system, parasites can be thought of as the "ultimate immunologists" and there is much to be learned from them about the fundamental nature of immune responses [4].

Therefore, the objectives of this seminar paper are:-

- To highlight the role of immunity in parasitic infections
- To indicate the gaps in the understanding of immunity roles in parasitic infections for future studies

2. Parasites

2.1 Definition and Classification

Parasite is an organism that lives and/or infests in or on another and takes its nourishment from other organism by harming the organism. Although used loosely to describe all infectious agents, for historical reasons the term "parasite" has been formally reserved as a designation for eukaryotic single-cell and metazoan pathogens, the most highly evolved and biologically sophisticated invaders encountered by the vertebrate immune system (Paul, 2003). Parasitic diseases include infections that are due to protozoa, helminthes or arthropods [6].

Under kingdom animalia, parasites are scientifically classified in to three phyla: Helminthes (Nemathelminthes, Platyhelminthes), Protozoa and Arthropoda [7]. Parasites are also classified based on their interactions with their hosts and on their life cycles. Parasites that live on the surface of the host are called ectoparasites (e.g. some mites). Those that live inside the host are called endoparasites (including all parasitic worms). Endoparasites can exist in one of two forms: intercellular parasites (inhabiting spaces in the host's body) or intracellular parasites (inhabiting cells in the host's body). Intracellular parasites, such as protozoa, tend to rely on a third organism, which is generally known as the carrier or vector to be transmitted to other host. Those parasites living in an intermediate position, being half ectoparasites and half-endoparasites, are sometimes called mesoparasite [5].

2.2 Host-Parasite Interactions

For the parasites the host is the total environment. The larval and other productive stages may live in the outside world for longer or shorter periods but this represents merely a necessary phase in the environment from host to host. Particular parasites occupy particular niches in the major habitats provided by the host environment and adapted to the conditions present in those niches in exactly the same way as free-living organisms are adapted to their environment [2]. Some endoparasites infect their host by penetrating its external surface, for example, Hookworms and Schistosoma larvae invade their hosts by penetrating the skin, while others like tapeworms, pinworms and roundworms must be ingested [5]. Among protozoan endoparasites, such as the malarial parasites and trypanosomes, infective stages in the host's blood are transported to new hosts by biting-insects, or vectors [2; 5].

Some ectoparasites, such as monogenean worms, rely on direct contact between hosts. Ectoparasitic arthropods may rely on host-host contact (e.g. many lice), shed eggs that survive off the host (e.g. fleas), or wait in the external environment for an encounter with a host (e.g. ticks). Some aquatic leeches locate hosts by sensing movement and only attach when certain temperature and chemical cues are present [2].

2.3 Parasites as Pathogens

If we examine the list of invaders that the immune system encounter, it will be seen that these fall in to two major categories. One category consists of the invaders that originate from outside of the body (most bacteria, many protozoa and invading helminthes), whereas the other category consists of the invaders that originate or live inside the body's own cells (viruses, intracellular bacteria or protozoa and cancer cells). Therefore, parasites are involved in the two categories of pathogens [8]. Parasitic pathogens enter into the host body as antigens. These parasites have many different structures composed of proteins, carbohydrates, lipids and nucleic acids, which serve as antigens and trigger an immune response [4].

In general, parasite molecules have been divided in to two categories. Those termed 'natural antigens' or 'conventional antigens' are recognized by the host during an infection and are the targets of the natural acquired immune response. On the other hand, molecules which are normally not recognized, or which do not induce an immune response during a natural infection but which may serve as targets of the immune response generated against them, are termed 'concealed' or 'hidden' antigens [3].

Natural antigens are constituted mainly of worm surface/cuticular antigens, substances released during moulting processes and excretion/secretion products [9]. For example, nematode cuticle is generally composed of highly cross-linked structural proteins (mainly collagen), lipids and carbohydrates. The moulting of the cuticle anchoring proteins during ecdysis is aided by protease enzymes such as cysteine proteases [10]. These cuticular materials and proteases are one of the candidates for vaccine production as they are highly immunogenic [11]. The immunological attack directed against the surface antigen is more apparent with tissue dwelling parasites (worms such as filarial nematodes) than extracellular (intestinal) parasites or worms. In the later, the immunity seems more dependent up on antigens released during feeding, excretion, moulting reproduction [12]. Similarly, antigens such as EG95 and 45W can be produced from onchospheres of cestode parasites such as *Taenia* and *Echinococcus* species for use as immunogens [13].

The majority of concealed antigens of parasites described so far are components of the epithelial cell surface membranes of the digestive tract parasites. For example, *Boophilus microplus* 86 (Bm86) is expressed in the tick gut and is not recognized by antibody arising from natural infestation. Antigens with this property have been termed "hidden" or "concealed" and immunity stimulated referred to as "artificial" [14]. The rationale behind the use of hidden antigens is the presumable absence of natural selection pressure due to the lack of recognition of the immunizing antigens during natural infections. Antibodies directed against these molecules following immunization and ingestion of blood by the parasites, have proven to be effective in reducing worm burdens [15].

3. Immunity

The term 'immunity' is derived from the Latin word *'immunitas'*, which refers to the protection from legal prosecution offered to Roman senators during their tenures in office. Historically, immunity meant protection from disease and more specifically, infectious disease. The cells and molecules responsible for immunity constitute the immune system, and their collective and coordinated response to the introduction of foreign substances is called the immune response. Therefore, the more inclusive definition of immunity is a reaction to foreign substances including microbes, as well as to macromolecules such as proteins and polysaccharides, regardless of the physiologic or pathologic consequence of such reaction [1]. In medical and veterinary literatures written in English dealing with host defense mechanisms, differentiation is made between acquired and inherited immunity. In order to differentiate between these, host defense mechanisms are divided in to two [8].

The first defense comes from innate immunity, which is a medical and hereditary trait of the organism used for defending itself against infectious, toxic, allergic and neoplastic antigens, and composed of many clearly definable mechanisms [8]. It includes species resistance, age resistance and in some cases, breeds resistances which, by and large, are not immunological in origin [7]. This innate immunity provides the first line of defense by detecting the immediate presence and nature of infection. The epithelial surfaces of the body keep pathogens out by preventing pathogen adherence, secreting mucus that may contain antimicrobial enzymes and peptides, increasing intestinal propulsive activity [16]. The innate response also consists of humoral factors (cytokines and complement) and cellular components (natural killer cells, macrophages, dendritic cells, eosinophils, mast cells, etc) [17]. The innate response can be initiated by the nonspecific degranulation of tissue mast cells and the activation of complement that subsequently results in binding of eosinophils to parasite surfaces. Innate mechanisms provide rapid protection that keeps microbial invaders at bay until acquired immunity develops [18].

The second defense comes from adaptive or acquired immunity, which is acquired either actively or passively which can combat only that particular antigen against which it was formed [8]. It is dependent on antigenic stimulation and subsequent humoral and cellular responses [7]. The adaptive or acquired immunity is initiated when an innate immune response fails to eliminate a new infection and antigens and activated antigen presenting cells (APC) are delivered to the draining lymphoid tissues [2].

While the mechanism by which viral, bacterial or protozoan pathogens interact with and activate APCs are increasingly understood, much less is known about how these cells react to more complex organisms such as helminthes. It takes several days or weeks for acquired immunity to become effective [19].

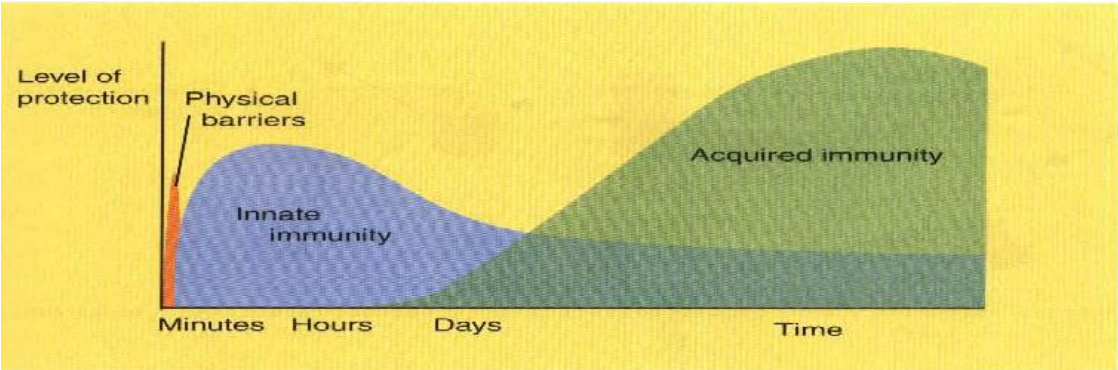

Figure 1: The time course of innate and acquired immunity
Source: [8]

4. Host Immune Response to Parasitic Infections

4.1 Recognition and Presentation of Parasitic antigens

It is becoming increasingly clear that events occurring during the early contact of parasites with the immune system can play a critical role in determining the character of the ensuing host-parasite relationship. Thus, innate immune defenses must be overcome for infections to establish, while the nature of the initial contact of parasites with APCs can dictate both the magnitude and class of adaptive immune responses that emerge [4]. Antigen presentation is an essential step in the initiation of clonal immune responses against parasitic invasions [8]. APCs are major sentinels in this process and their ability to recognize and discriminate among pathogens is thought to be determined by pathogen recognition receptors (PRRs) that recognize pathogen associated molecular patterns (PAMPs) shared by different groups of parasites [20].

APCs are heterogeneous populations that include Langerhans cells, macrophages, dendritic cells and B cells; and is found in the skin, bone marrow, lymph nodes, spleen and thymus. B lymphocytes found in spleen and lymph nodes are also efficient APCs, especially when they recognize antigens. In this case, B cells can capture even minute quantities of antigens compared to other APCs [21]. Besides the APCs found in the lymphoid tissues, there are a large number of potential APCs in the body. These include Kupffer cells in the liver, microglias in brain, follicular cells in thyroid and fibroblasts in connective tissues and endothelial cells. Depending on the nature of the antigen and the mode of antigen presentation, APCs function to activate immunologically competent T cells, and delete or anergize self-reactive T cells [22].

A unifying feature of the targets (Pathogen Associated Molecular Patterns) is their highly conserved structures, which are invariant between parasites of a given class. Although many parasites are known to activate the immune system in a non-specific manner shortly after infection, it is only recently that attention has been given to the mechanisms involved. While major advances are being achieved in the area of microbial recognition by PRRs, a small but growing number of studies show that parasites also possess specific molecular patterns capable of engaging Pattern Recognition Receptors [5; 20].

For example, in the case of protozoa, an important set of PAMPs are glycosylphosphatidylinositols (GPI) lipid anchors present on many parasite surface proteins. Thus, GPIs from *Leishmania mexicana* can stimulate macrophages to up-regulate inducible nitrogen oxide synthase (iNOS) and produce tumor necrosis factor (TNF) and interleukin-1 (IL-1). Similarly, the GPI anchor fraction of mucin-like molecules from *Trypanosoma cruzi* trypomastigotes stimulates macrophage production of IL-12 and TNF [23; 24]. Such a unique pattern recognition system is

also most likely to be directed at helminthes because many worm proteins are heavily glycosylated and these carbohydrate side chains could provide unique patterns of initiation of the innate response [24; 25]. Examples of some parasites PAMPs along with their receptors are given in table 1 below:

Table 1: Innate immune receptors involved in parasite recognition

Receptor family	Member	Parasite ligand(s)
Collectins	MBL	Mannose rich sugars from numerous protozoans and helminthes
Pentaxins	CRP	Phospholipids and phosphosugars
		Leishmania species LPG
C-type lectins	Macrophage mannose receptor, DC-SIGN	*Trypanosoma cruzi*
		Schistosoma species (Lewis x)
Scavenger receptors	SR-B (CD36)	*Plasmodium falciparum* (PfEMP1)
Complement receptors	CR_1/CR_3	Leishmania species LPG
		Necator NIF
		Plasmodium falciparum (PfEMP1)
Toll-like receptors	TLR_2 (withTLR_1/TLR_6)	GPI anchors from many protozoa
	TLR_3	Lyso-PS From Schistosoma species
	TLR_4 (with CD14)	Double stranded RNA from Schistosoma species
		LPS-like molecules from the filarial endosymbiont Wolbanchia species

Source: [5]

4.1.1 *Presentation to T Cells*

T cells can be divided into two major populations: a subset carrying the CD4 antigen, known as helper T cells, and a subset carrying the CD8 antigen, termed cytotoxic T cells (CTLs) [26]. Cell mediated immunity against intracellular parasites (nearly all protozoa) often involves succession of both $CD4^+$ and $CD8^+$ T cell responses [4]. $CD8^+$ CTLs recognize peptide fragments bound to class I MHC molecules; whereas $CD4^+$ helper T cells recognize them in association with class II MHC molecules. Activation of cytotoxic and helper T cells, therefore, depends upon whether antigenic peptides are presented by class I or class II MHC molecules [27]. It has been generally accepted that antigens derived from pathogens that reside intracellularly (endogenously) are usually presented to $CD8^+$ CTLs in the context of class I MHC molecules. Activation of $CD8^+$ T cells results in cell mediated immunity which is associated with the activation of CTLs that kill pathogen-infected cells [28]. On the other hand, extracellular antigens are usually taken up by endocytolytic pathways of APCs and presented to $CD4^+$ helper T cells by class II MHC molecules. Activation of $CD4^+$ helper T cells in general results in humoral immune responses which are associated with the production of specific antibodies against pathogens by B cells [29].

4.1.2 *Presentation to B Cells*

In general, B cells can directly recognize native antigens either in solution or on cell surfaces and therefore need no specific antigen-presenting cells to be activated. Antigen presentation to B cells by FDCs and macrophages, however, augments the immune response and is critical in the selection of high-affinity antigen-specific B cells [30; 31]. In contrast to T cells, which recognize antigen-derived peptides bound to MHC molecules, B-cell recognition of native antigen or antigen epitopes is MHC-unrestricted. Antigen presentation by FDCs localized in the B-cell compartment of primary follicles of lymphoid tissues plays an essential role in the activation, differentiation and apoptosis of B lymphocytes [31].

4.2 Mechanisms of Immune response to Parasitic Infections

4.2.1 *Immunity to Protozoa*

The principal innate immune response to protozoa is phagocytosis, which is the process by which cells like macrophages and neutrophils bind, ingest and destroy or eliminate parasites [8]. The process of phagocytosis involves four discrete stages: chemotaxis, adherence and opsonization, ingestion and destruction [1].

In contrast to phagocytes, most innate cellular defenses do not eliminate parasites directly but instead trigger other effector cells to do so. Perhaps the best studied example of this form of innate immunity is the NK cells pathway of IFN-γ production, which is triggered by monokines (IL-1, IL-12 and TNF) produced by adherent cells in response to parasitic components (e.g. *Leishmania* promastigotes). In addition, activation of complements in response to infection results in formation of the potentially lytic membrane attack complex (MAC) as well as opsonic recognition by C3 receptors on phagocytes [4].

Acquired immunity to protozoa encompasses both antibody and cell-mediated immune responses. In general, antibodies control the numbers of parasites in blood and tissue fluids, whereas cell-mediated responses are directed largely against intracellular parasites [8]. Serum antibodies directed against protozoan surface antigens may opsonize, agglutinate, or immobilize them. Antibodies together with complement and cytotoxic cells may kill them, and some antibodies (called ablastins) may inhibit their division. In genital infections of humans due to *Trichomonas vaginalis*, a local IgE response is stimulated. The allergic reaction that ensues provokes intense discomfort; more importantly by increasing vascular permeability, this reaction permits IgG antibodies to reach the site of infection and immobilize and eliminate the organisms [29].

Protective immunity against apicompexan protozoa such as *Cryptosporidia, Eimeria, Neospora, Plasmodia* and *Toxoplasma* is generally mediated by Th1 responses [8]. For example, *T. gondii* (Figure 2) is an obligate intracellular parasite whose tachyzoites grow with in cells. Eventually, the infected cell ruptures and the tachyzoites are released to invade other cells. They penetrate these cells by squeezing through a molecular junction in the cell membrane and so do not trigger proper phagosome formation and maturation. Normally, both Th1 and Th2 immune responses occur on exposure to *Toxoplasma* [32]. The Th2 response involving antibodies together with complement destroys extracellular organisms and reduces the spread of organisms between cells. The intracellular organisms are destroyed by, an IL-12-dependent Th1 cell-mediated response. Sensitized Th1 cells secrete IFN-γ in response to *Toxoplasma* ribonucleoproteins. This IFN-γ activates macrophages, enabling them to kill the intracellular organism by permitting lysosome-phagosome fusion [4]. Some T cells may also secrete cytokines that interfere directly with *Toxoplasma* replication. In addition, cytotoxic T cells can destroy *Toxoplasma* tachyzoites and *Toxoplasma* infected cells. In these ways, both Thl and Th2 immune responses act together to ensure the elimination of the tachyzoite stage of this organism [29].

Th1-mediated responses involving activation of macrophages are important in many protozoan diseases in which organisms are resistant to intracellular destruction. One of the most significant destructive pathways in these activated cells is the production of nitric oxide. Nitrogen radicals formed by the interaction of NO with reactive oxidants are lethal for many intracellular protozoa [8; 29].

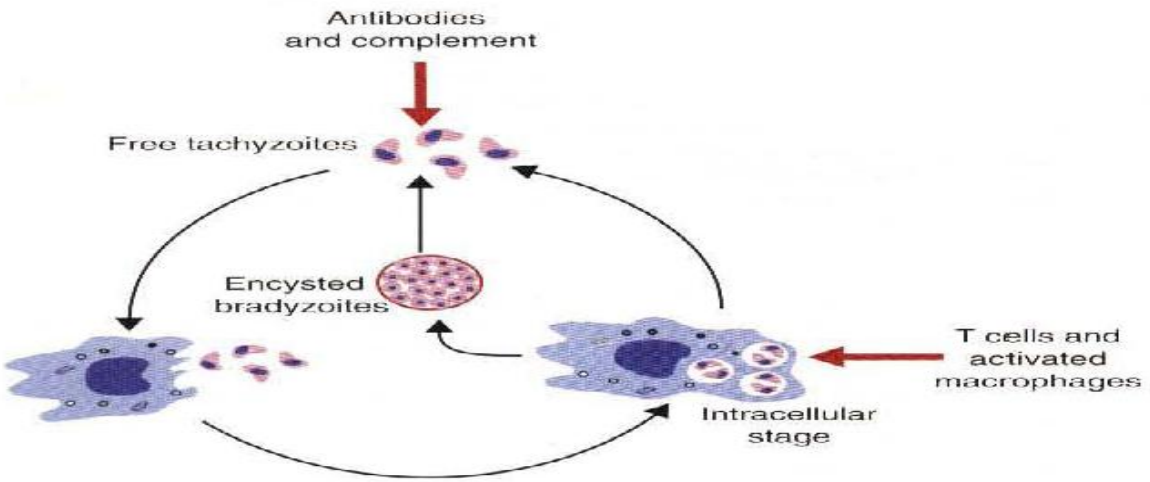

Figure 2: The points in the life cycle of *Toxoplasma gondii* at which the immune system can exert a controlling influence
Source: [8]

4.2.2 *Immunity to Helminthes*

Helminthes are multicellular organisms capable of elaborating plethora of surface and excretion/secretion (ES) antigenic products, and it is not yet clear which of its antigens are taken by Antigen Presenting Cells and which one of them elicit protective immune responses. The infections of helmenthes are typically associated with hyper-eosinophilia, considerable immunoglobulin E production, mucuous mastocytosis and goblet cells hyperplasia. These responses are attributed to the property of helminthes to stimulate the Th2 the subset of CD4+ helper T cells, which secret IL-4 and IL-5. The IL-4 stimulates production of IgE, and IL-5 stimulates the development and activation of eosinophils. These immune parameters are involved in different effector mechanisms highly depending on where the helminthes are localized [33].

In connection to this, several mechanisms against tissue-dwelling parasites have been described. These parasites are mainly larval stages, for example, of trematodes (*Schistosoma spp., Fasciola spp.*) or nematodes, which migrate through tissue [5]. Antibody Dependent Cellular Cytotoxicity (ADCC) is dependent on eosinophils, neutrophils, macrophages, or platelets as effector cells and IgE, IgG, or IgA as antibodies. The parasitic structures covered by antibodies are destroyed by cells carrying receptors to the Fc fragment (RFc). When these cells are activated by fixation of the antibodies to the RFc, they release products that are toxic to the worm (major basic protein/MBPs/, eosinophil cationic protein, eosinophil-derived neurotoxin, reactive nitrogen intermediates, etc). ADCCs are also able to immobilize nematode larval stages as they migrate through the gut mucosa [18].

In addition, a granuloma can occur around the parasite in the tissue which stops the worm migration and development. This phenomenon has been well investigated for *Schistosoma mansoni*. The granuloma is composed of eosinophils, macrophages, and lymphocytes with an increasingly fibrotic extracellular matrix [34], which surrounds and segregates the eggs from the hepatic tissue. In the long term, fibrosis may develop as the eggs die and the granuloma is resolved [35]. Finally, nitric oxide (NO), toxic to the worm, is released by the macrophages classically activated by IFNγ and TNFα. This mechanism has been described mainly against trematodes (*Schistosoma sp., Fasciola sp.*) during acute infection, before egg production in *Schistosoma mansoni*. The following figure shows the discussed idea with some modifications for *Fasciola hepatica* as an example.

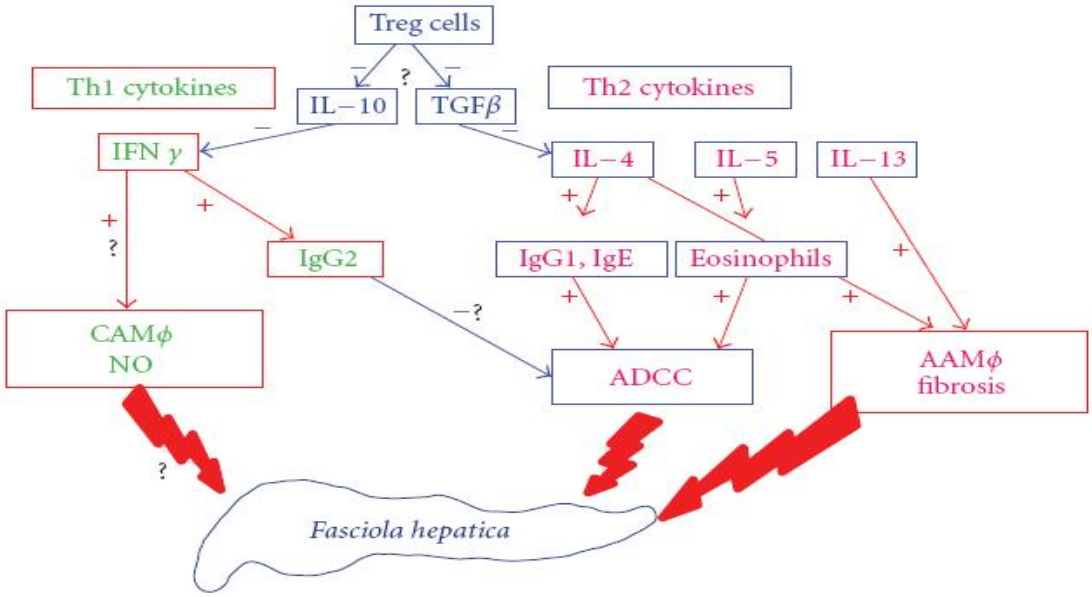

Figure 3: Immune mechanisms and regulation induced against *Fasciola hepatica*
Source: [36]

Because they have Fc receptors, eosinophils can bind to antibody coated parasites, degranulate, and release their granule contents directly on to the worm cuticle (Figure 4). These contents include oxidants and nitric oxide generated by eosinophil peroxidase, lytic enzymes such as lysophospholipase and phospholipase D [8]. Eosinophils may be more effective than other leukocytes in killing helminthes are because the major basic protein of eosinophil granules may be more toxic for helminthes than the proteolytic enzymes and reactive oxygen intermediates produced by neutrophils and macrophages [1].

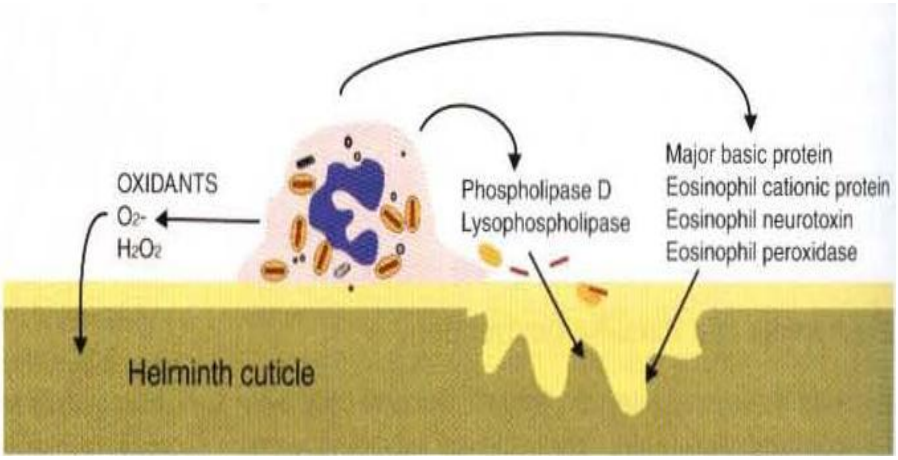

Figure 4: Some of the molecules released from eosinophils that cause damage to parasitic helminthes **Source**: [8]

For the parasites localizing lumen of the gut (Figure 5), intestinal anaphylaxis, with IgE-induced mast cells degranulation, is responsible for changes in the intestine physiology as well as architecture and chemistry of the gut epithelium, including stimulation of fluid, electrolyte and mucus secretion, smooth muscle contractility, increased vascular and epithelial permeability, and recruitment of immune cells such as eosinophil or mast cells. This can lead to rapid elimination of the gastrointestinal larvae, before they reach their tissue niche and to expulsion of the adult. Furthermore, IgA on the surface of the gut mucosa helps to neutralize the metabolic enzymes released by digestive strongyles and interfere with the worm's ability to feed [18].

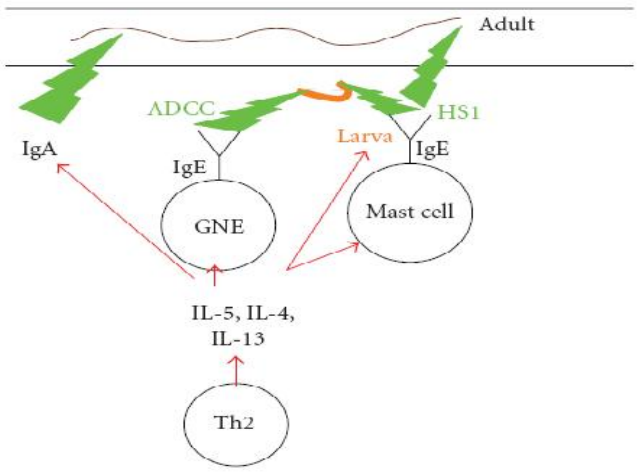

Figure 5: Immune response against gastrointestinal nematodes
Source: [36]

4.2.3 *Immunity to Arthropods*

When arthropods such as ticks or mosquitoes bite an animal, they inject saliva, which has molecules that assist the parasite in obtaining its blood meal. For example, the arthropod saliva contains kininases that destroy bradykinin, which mediates pain and itch, histamine-binding and proteins that block complement activation [2]. As a result, host scratching and grooming responses are minimized. Because some salivary molecules are antigenic, they induce immune responses. Host responses to arthropods saliva are of three types. These include: first, delayed type hypersensitivity reaction; some saliva components are of low molecular weight and cannot function as normal antigens. They may, however, bind to skin proteins such as collagen and then act as haptens, stimulating a Th1 response. On subsequent exposure, these haptens induce a delayed type hypersensitivity reaction. Second, cutaneous basophil hypersensitivity; other salivary antigens may bind to epidermal Langerhans cells and induce cutaneous basophil hypersensitivity, a Th1 response associated with the production of IgG antibodies and basophil infiltration. If the basophils are destroyed by anti-basophil serum, resistance to biting arthropods is reduced. The third type of response to arthropod saliva is a Th2 response, leading to IgE production and type I hypersensitivity. Each of these three types of responses may modify the skin in such a way that the feeding of the offending arthropod is impaired and the animal becomes a less attractive source of food [8].

4.3 Evasion of immunity by parasites

The success of any parasite is measured not by the disturbances it imposes on a host but by its ability to adapt and integrate itself with in host's internal environment. From immunological point of view, parasite can be considered as success if it integrates itself into the host in such a way that it is not regarded as foreign [8]. The survival and transmission of pathogenic protozoa depends on their ability to evade or subvert host's innate and adaptive immune responses. A great challenge to research in immunology and parasitology is the development of strategies that favor immunity against protozoan parasites and prevent their evasion, chronic, or recurrent infections and associated pathologies [29]. And helminthes have also developed several means of escaping these immune responses. Recently, Maizels and coworkers in 2004 [37] called them "masters of immunomodulation". These immunomodulatory abilities enable the worm to persist in the host and can lead to interactions with inflammatory and immune mechanisms involved in other infections or to vaccines or in allergic and autoimmune diseases. Generally, parasites evade protective immunity by reducing their immunogenicity and by inhibiting host immune responses. For this regard, different parasites have developed remarkably different effective ways of resisting immunity [1], described as follows:

Antigenic variation: - Parasites change their surface antigens during their life cycle in vertebrate hosts [1]. This antigenic variation is an important mechanism of immune evasion shared by diverse classes of pathogenic protozoa, including African trypanosomes, Giardia and malaria. Two forms of antigenic variation are well defined. The first is stage specific change in antigen expression, such that the mature tissue stages of parasites produce different antigens than the infective stages do. For example, the infective sporozoite stage of malaria parasites is antigenically distinct from the merozoites that reside in the host and are responsible for chronic infection. By the time that the immune system has responded to infection by sporozoites, the parasite has differentiated, expresses new antigens, and is no longer a target for immune elimination. The second and most remarkable example of antigenic variation in parasites is the continuous variation of surface antigens as seen in African trypanosomes such as *Trypanosoma brucei* and *Trypanosoma rhodiense* [1]. Variant surface glycoproteins (VSGs) are the major surface antigens of these trypanosomes. The VSGs produced early in trypanosome infections tend to develop in a predictable sequence. However, as the infection progresses, the production of VSGs becomes more random. Trypanosomes grown in tissue culture also show spontaneous antigenic variation demonstrating that the change in surface VSGs is not induced by antibodies [24].

Resistance to immune effector mechanisms: -

Parasites become resistant to immune effector mechanisms during their residence in vertebrate hosts. Perhaps the best examples are *Schistosoma* larvae, which travel to the lungs of infected animal and during this migration, develop a tegument that is resistant to be damaged by complement and CTLs [1]. Intracellular parasites that live inside macrophages have evolved different ways of avoiding being killed by oxygen metabolites and lysosomal enzymes: *T. gondii* penetrates macrophages by a non phagocytic pathway and so avoids triggering the oxidative burst;

and *Leishmania* spp. can enter by binding to complement receptors, another way of avoiding respiratory burst [5]. Similarly, *Fasciola sp.* escapes from the immune responses by: production of superoxide dismutase which neutralizes superoxide radicals toxic for juveniles [38]; releasing cathepsin L-protease which cleaves IgE and IgG involved in the ADCC [39]; and IgM deposition on fluke tegument to inhibit eosinophil adhesion [40].

Hiding: - Protozoan parasites may conceal themselves from the immune system either by living inside the host cells or developing cysts that are resistant to immune effectors. Some helminthic parasites reside in intestinal lumen and are sheltered from cell-mediated immune effector mechanisms; and their very thick cuticle has the role of hiding them [8].

Immunosuppression:- Generalized immuno depression, which is a feature of many chronic parasitic infections, including malaria, African trypanosomosis, visceral leishmaniasis, appears in most instances to be secondary to other immune evasion strategies, results from a varieties of immune dysfunctions that high systemic parasite burdens can produce [5; 8]. These include: disruption of normal lymphoid architecture, or the accumulation of parasite-derived metabolic products that are directly inhibitory to lymphocyte function, or that induce suppressor cell activities such as prostaglandin production by macrophages [8].

5. Parasitic Vaccine Development

5.1 Parasitic Vaccines

Limiting the impact of parasitism in both human and livestock relies almost exclusively on the use of antiparasitic drugs. However, available drugs have often been in use for decades and drug resistance in the target parasites is now prevalent, and particularly in the case of livestock, threatening sustainable controls [41]. The issue surrounding drug resistance in the major human parasites is extensively discussed in Trends in Parasitology (2003), and [42; 43]. In livestock, drug resistance has been reported to every antihelminthic class in every livestock host [41; 44]. In some regions, multi-drug resistant nematodes are becoming prevalent and threaten the viability of small-ruminant production units [45].

Furthermore, for some parasitic diseases, prevalence should eventually decrease with improved health education, water supply and sanitation. For vector-borne diseases this is not necessarily so. In many areas, malaria is out of control and there is increasing drug resistance, particularly in sub-Saharan Africa. It affects all socio-economic groups [46]. The only practical control measures are protection against mosquitoes, such as with insecticide impregnated bed-nets [46]. Epidemic leishmaniasis and trypanosomiasis affect the most vulnerable members of society unable to protect themselves [48].

For these reasons, there had been an urgent need to develop novel, sustainable control procedures with vaccination to the fore. For example, major efforts coordinated by WHO, other international organizations and philanthropic charity activity were in the process of seeking novel methods to control if not eradicate several of the major parasites of man and animals [49]. Accordingly, the ability to produce recombinant parasite proteins in the early 1980's (e.g. [50]) was heralded as a major breakthrough for vaccine development yet, 25 years on, only a few recombinant vaccines against parasitic diseases of livestock have reached the point of being marketed. The first recombinant vaccine against a human parasite continues to remain elusive [51].

Even though, it is an important factor in disease control and prevention, vaccine development has been hampered by a lack of definition of the precise immune effectors of parasite attrition and the antigens which stimulate them. Wynn & Hoffmann [52] noted that successful vaccine development for schistosomiasis had been hindered by a lack of consensus on the type of immune response required and an incomplete knowledge of the effectors mechanisms which mediate immunity. The maintenance of natural immunity is often dependent on repeated infection, may be stage-specific and will be dependent on different antibody classes and T-cell responses. Despite it being almost 30 years since the technology to produce recombinant proteins became available, recombinant proteins with the required efficacy are rare [51], spectacular exceptions being vaccine developments in ticks and cestodes, these developments constituting land mark achievements [53; 54].

5.2 Current status of parasitic vaccines

After having some knowledge of immune response to parasitic infection, vaccine development originally focused on a fractionate and vaccinate approach. Antigens are purified from parasite extracts or are harvested following *in vitro* culture using a variety of protein fractionation procedures [29; 55] and then evaluated for protective efficacy in control trials in the target host, or frequently, in a laboratory infection model. Antigens can be selected on the basis of presumed functional importance to parasite survival such as enzymes required for feeding/migration, immunomodulatory molecules or on the basis of immune recognition by hosts rendered immune to infection by repeated exposure. In the case of helminth infection, Excretory/Secretory *in vitro* released proteins have been prime targets because they are readily accessible to the host immune response, are immunogenic and many are functionally important [51]. The table 2 below highlights some real success towards parasites vaccine development.

Table 2: Antiparasitic vaccines manufactured by governmental organizations

Parasite	Host	Type of vaccine	Comments	References
Eimeria spp.	Poultry	Non-attenuated	Low (nonpathogenic) dose Infection immunity	[56]
Eimeria spp.	Poultry	Attenuated for precocity	Infection immunity	[56]
Eimeria maxima	Poultry	Sub-unit vaccine of gametocyte antigen	Induction of maternal immunity	[57]
Toxoplasma gondii	Sheep	Attenuated for truncated life cycle	Reduces abortion	[58]
Neospora caninum	Cattle	Killed tachyzoites	Reduces abortion	[6]
Babesia bovis and B. bigemina	Cattle	Attenuated by repeated passage through splenectomized calves	Live infection immunity Manufactured locally	[59]
Theileria parva	Cattle	Non-attenuated wild type	Chemotherapeutically controlled infection Manufactured locally	[37]
Theileria annulata	Cattle	Attenuated by *in vitro* culture	Manufactured locally	[60]
Babesia canis	Canine	Antigens from *in vitro* culture	Reduces diseases	[61]
Giardia duodenalis	Canine	Disrupted axenically cultured whole trophozoites	Reduces diseases and cyst shedding Commercially available in the USA	[62]
Leishmania infantum	Canine	Sub-unit vaccine (FML)	Antiparasitic activity and possibly therapeutic	[63]
Taenia ovis	Sheep	Recombinant antigen	Registered but not marketed	[53]
Dictyocaulus viviparous	Cattle	Irradiated L3 larvae	Limited to Europe	[64]
Boophilus microplus	Cattle	Recombinant tick gut antigen (Bm86)	Limited to Australia, Cuba and South America	[65]

Source: [66]

5.3 Challenges to parasitic vaccine development

Apart from the fact that vaccines began to be developed much later than chemotherapeutic drugs, a number of additional factors have affected the progress of parasitic vaccine development. Not least was the implementation in the 1990s of legislation on the authorization of veterinary medicinal products in Europe [67]. Moreover, in contrast to viruses and bacteria, even the simplest parasites and their life cycles are highly complex, and there is a general lack of precise understanding of the host/parasite interaction [4].

Owing to the complex nature of parasites, the immune system is confronted with a highly diverse and plastic antigen repertoire. A number of biological characteristics perpetuate this diversity. First, many parasites go through a phase of sexual reproduction, with the associated exchange of genetic material from the parent strains (e.g. crossing-over). This results in progeny with a different genetic and phenotypic make-up. Secondly, there is a differential expression of genes during the successive life cycle stages, as if the host has been infected with a number of different parasites. Finally, a number of species can express antigenically distinct variants of stage-specific molecules. This ability allows them to avoid the defensive responses of the host. These factors impose considerable challenges in screening for potential vaccine antigens [66].

In addition, the site of infection affects the nature of the protective immune response and may constrain research on vaccine development. For instance, many gastrointestinal parasites are not invasive and dwell only in the gastrointestinal tract, the interface with the host being the epithelial lining of the gut lumen. Since little is known about the immune effector mechanisms that function in immune hosts, there are few immunological tools to aid in selecting potential vaccine antigens [5].

6. Conclusion and Recommendations

Animal parasites such as protozoa and helminthes give rise to chronic and persistent infections, because innate immunity against them is weak and parasites have evolved multiple mechanisms for evading specific immunity. The structural and antigenic diversity of pathogenic parasites reflected in the heterogeneity of the adaptive immune responses that they elicit. In general, the host immune responses against parasites are innate and acquired immunities. The knowledge of these immunities is vital for the ultimate purpose of intervention through immunotherapy. Because of their evading mechanisms; extraordinary complexity as immunologic targets and their remarkable adaptability to immunologic pressure, there are inevitable difficulties in vaccine development against parasites. Even though, there have been few approaches in developed countries. Still, the striking situation reflected in data is the absence of effective vaccines for protecting human populations from parasitic infections.

In line with the above conclusion, the following recommendations are forwarded:

- ✓ Detailed studies and researches should be conducted on host-parasite interactions and related immune responses;
- ✓ As there is an increasing antiparasitic drugs resistance worldwide, further investigation on parasitic vaccine development should be conducted; and
- ✓ Careful identification of the parasitic immunogens should be performed for the understanding of antigen-antibody/parasite-immune response interaction.

References

[1] Abbas, A.K. and Lichtman, A.H. (2003): Cellular and Molecular Immunology, 5th Edition, Saunders, Philadelphia, pp 359-363.

[2] Wakelin, D. (1996): Immunity to parasites. How parasitic infections are controlled, 2nd Edition, Cambridge University press, United Kingdom, pp 1-15.

[3] Klei, T.R. (1997): Immunological control of gastrointestinal nematode infections. *Veterinary Parasitology*, **72**: 507-523.

[4] Paul, W.E. (2003): Fundamental Immunology, 5th Edition, Lippincott Williams and Wilkins, Philadelphia, pp 1171-1194.

[5] Male, D., Brostoff, J., Roth, D. and Ivan, R. (2006): Immunology, 7th Edition, International edition, Milton Keynes, United Kingdom, pp 277-335.

[6] Schetters, T.P. (2004): Interveterinary symposium: bovine neosporosis. *Veterinary Parasitology*, **125**: 137-146.

[7] Urquhart GM, Armour J, Dunean JI, Dunn AM, Jennings FW (1996).Veterinary parasitology. 2nd Ed. Black Well Science. The University of Glaskow, Scotland, UK pp. 181-188.

[8] Tizard, I.R. (2004): Veterinary Immunology: Introduction, 7th Edition, Saunders, Philadelphia, pp 288-301.

[9] Wakelin, D. (1984): Immunological control of parasitic infection: Jarmuenty to parasite 1st Edition, EDio and Armold LTD, Great Britain, pp 28-31.

[10] Page, A.P. (2001): The nematode cuticle: synthesis, modification and mutants. In parasitic Nematodes-Molecular Biology, Biochemistry and Immunology. W.CAB International, pp 167-193.

[11] Bakker, N., Vervelde, L., Kanobona, K., Knox, D., Cornelissen, A., Vries, E. and Yatsuda, A. (2004): Vaccination against nematode *Haemonchus contortus* with a thiol binding fraction from the excretory secretory products (ESp). *Vaccine*, **22**: 618-628.

[12] Liod, S. (1981): Progress in immunization against parasitic helminthes. *Parasitology*, **83**: 225-242.

[13] Dalton, J. and Mulcahy, G. (2001): Parasites vaccines a reality? *Veterinary parasitology*, **98**: 147-167.

[14] Gough, J.M. and Kemp, D.H. (1993): Localization of a low abundance membrane protein (Bm86) on the gut cells of the cattle tick *B. microplus* by immunological labeling. *Journal of Parasitology*, **79**: 900-907.

[15] Knox, D. P. and Smith, W. D. (2001): Vaccination against gastrointestinal nematode parasites of ruminants using gut-expressed antigens. *Veterinary Parasitology*, **100**: 21-32.

[16] Castro, G.A. and C.J. Arntzen (1993): Immunophysiology of gut: a research frontier for integrative studies of the common mucosal immune system. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, **265**: 599-610.

[17] Biron, C.A., Nguyen, K.B., Pien, G. C., Cousen, L.P. and Salazar-Mather, T.P. (1999): Natural killer cells in antiviral defense: function and regulation by innate cytokines. *Annu.Rev.Immunology*, 17: 189-220.

[18] Balic, A., Bowles, V. and Meeusen, E. (2002): Mechanisms of immunity to *Haemonchus contortus* infection in sheep. *Parasite Immunology*, **24**: 39–46.

[19] Perona-Wright G., Rachel, J.L., Stephen, J.J., Lauren, M.W., Richard, K.G. and Andrew, S.M. (2012): Concurrent bacterial stimulation alters the function of helminth-activated dendritic cells, resulting in IL-17 induction. *J Immunol*., **188**: 2350–2358.

[20] Janeway, C.A. (1989): Approaching asymptote? Evolution and revolution in immunology. *Cold Spring Harbor Symposia on Quantitative Biology*, **54**: 1-13.

[21] Townsend, S.E. and Goodnow, C.C. (1998): Abortive proliferation of rare T cells induced by direct or indirect presentation by rare B cells *in vivo*. *Journal of Experimental Medicine* **187**: 1611–1621.

[22] Van Kooten, C. and Banchereau, J. (1997): Functions of CD40 on B cells, dendritic cells and other cells. *Current Opinion in Immunology*, **9**: 330–337.

[23] Ropert, C. and Gazzinelli, R. (2000): Signaling of immune system cells by glycosylphosphatidylinosi tols (GPI) anchor and related structures derived from parasitic protozoa. *Current Opinion Microbiology*, **3**: 395-403.

[24] Almeida, I.C. and Gazzinelli, R.T. (2001): Proinfl ammatory activity of glycosylphosphatidylinositols anchors derived from *Trypanosoma cruzi*: structural and functional analyses. *Journal of Leukocyte Biology*, **70**: 467-477.

[25] Velupillai, P. and Harn, D. (1994): Oligosccharide-specific induction of interleukin 10 production by $B220^+$ cells from *Schistosoma* infected mice: a mechanism for regulation of $CD4^+$ T cell subsets. *Proceedings of the National Academy of Sciences in USA*, **91**: 18-22.

[26] Schnare, M., Barton, G. and Holt, A. (2001): Toll-like receptors control activation of adaptive immune responses. *National Immunology*, **2**: 947-950.

[27] Kimura, M. and Nakayama, T. (1999): The molecular mechanisms governing T cell development in the thymus. *Nippon Rinsho*, **57**: 267-272.

[28] Pietters, J. (1997): MHC class II restricted antigen presentation. *Current Opinion in Immunology*, **9**: 89–96.

[29] Lopes, M., Zamboni, D., Ludan, H. and Rodrigues, M. (2012): Immunity to protozoan parasites. *Journal of parasitology Research*, **2012**: 1-3.

[30] Koopmann, J.O., Hammerling, G.J. and Momburg, F. (1997): Generation, intracellular transport and loading of peptides associated with MHC class I molecules. *Current Opinion in immunology*, **9**: 80–88.

[31] Kosco, M.H. (1991): Antigen presentation to B cells. *Current Opinion in Immunology,* **3**: 336–339.

[32] Liu, Y., De Bouteiller, O. and Fugier-Vivier, I. (1997): Mechanisms of selection and differentiation in germinal centers. *Current Opinion in Immunology,* **9**: 256–262.

[33] Jankovic, D., Sher, A. and Yap, G. (2001): Th1/Th2 effector choice in parasitic infection: decision making by committee. *Current Opinion Immunology,* **13**: 403-409.

[34] Anthony, R., Kreider, T., Urban, J. and Gause, W. (2007): Alternatively activated macrophages in helminth infections. *Current Opinion in Immunology*, **19**: 448–453.

[35] MacDonald, A. S., Araujo, M. I. and Pearce, E. J. (2002): Immunology of Parasitic Helminth Infections. *Infections and immunity*, **70**: 427-433.

[36] Emmanuelle, M. and Alain C. (2010): Immunity against helminthes: Interactions with the host and the intercurrent infections. *Journal of Biomedicine and Biotechnology*, **2010**: 1-9.

[37] Maizels, R.M., Balic, A., Gomez-Escobar N., Nair, M., Taylor, M.D. and Allen, J.E. (2004): Helminth parasites—masters of regulation. Immunol Rev., **201**: 89-116.

[38] Ganga, G., Varshney, J. and Patra, R. (2007): Activity of antioxidant enzymes in excretory-secretory fluid and somatic extracts of *Fasciola gigantic*. *Journal of Veterinary Parasitology*, **21**: 51–52.

[39] Smith, A. Dowd, A. Heffernan, M. Robertson, C. and Dalton, J. (1993): *Fasciola hepatica*: a secreted cathepsin L-like proteinase cleaves host immunoglobulin. *International Journal for Parasitology,* **23**: 977–983.

[40] Chauvin, A. and Boulard, C. (1996): Local immune response to experimental *Fasciola hepatica* infection in sheep. *Parasite*, **3**: 209–215.

[41] Kaplan, R. (2004): Drug resistance in nematodes of veterinary importance. A status report. *Trends Parasitology*, **20**: 477-81.

[42] Fallon, P.G., Sturrock, R.F., Niang, A.C. and Doenhoff, M.J. (1995): Short report on diminished susceptibility to praziquantel in a Senegal isolate of *Schistosoma mansoni*. *American Journal of Tropical Medicine and Hygiene*, **53**: 61-62.

[43] De Clercq, D., Sacko, M., Behnke, J., Gilbert, F., Dorny, P. and Vercruysse, J. (1997): Failure of mebendazole in treatment of human Hookworm infections in the southern region of Mali. *American Journal of Tropical Medicine and Hygiene*, **57**: 25-30.

[44] Barnes, E.H., Dobson, R.J. and Barger, I.A. (1995): Worm control and antihelminthic resistance: adventures with a model. *Parasitology Today*, **11**: 56-63.

[45] Ismail, M., Metwally, A., Farghaly, A., Bruce, J., Tao, L.F. and Bennet, J.L. (1996): Characterization of isolates of *Schistosoma mansoni* from Egyptian villagers that tolerate high doses of praziquantel. *American Journal of Tropical Medicine and Hygiene*, **55**: 214-218.

[46] Van der Werf, M.J., de Vlas, S.J. and Brooker, S.G. (2003): Quantification of clinical morbidity associated with *Schistosoma* infection in sub-Saharan Africa. *Acta Tropica*, **86**: 125-139.

[47] Hoffman, S.L., Goh, L.M. and Luke, T.C. (2002): Protection of humans against malaria by immunization with radiation-attenuated *Plasmodium falciparum* sporozoites. *Journal of Infectious Diseases*, **185**: 1155-64.

[48] Handman, E. (2001): Leishmaniasis; current status of vaccine development. *Clinical Microbiology Reviews*, **14**: 229-43.

[49] Knox, D.P. and Redmond, D.L. (2006): Parasite vaccines - recent progress and problems associated with their development. *Parasitology*, **133**: 1-8.

[50] Enea, V., Ellis, J. and Zavala, F. (1984): DNA clo ning of *Plasmodium falciparum* circumsporozoite gene: amino acid sequence of repetitive epitope. *Science*, **225**: 628-630.

[51] Knox, D.P. (2010): Parasite Vaccines: Recent Progress in, and problems associated with their development. *The Open Infectious Diseases Journal*, **4**: 63-73.

[52] Wynn, T.A. and Hoffman, K.F. (2000): Defining a schistosomiasis vaccination strategy; is it really Th1 versus Th2? *Parasitology Today*, **16**: 497-501.

[53] Lightowlers, M.W. (2006): Cestode vaccines; origin, current status and future prospects. *Parasitology*, **133**: 27-42.

[54] Willadsen, P. (2006): Vaccination against ectoparasites. *Parasitology*, **133**: 9-25.

[55] Knox, D.P. (2000): Development of vaccines against gastrointestinal nematodes. *Parasitology*, **120**: 43-61.

[56] Williams, R.B. (2002): Anticoccidial vaccines for broiler chickens: pathways to success. *Avian Pathology*, **31**: 317-353.

[57] Wallach, M., Smith, N., Petracca, M., Miller, C., Eckert, J. and Braun, R. (1995): *Eimeria maxima* gametocyte antigens: potential use in a subunit maternal vaccine against coccidiosis in chickens. *Vaccine*, **13**: 347-354.

[58] Buxton, D. (1993): Toxoplasmosis: the first commercial vaccine. *Parasitology Today*, **9**: 335-337.

[59] De Waal, D.T. and Combrink, M.P. (2006): Live vaccines against bovine babesiosis. *Veterinary Parasitology*, **138**: 88-96.

[60] Shkap, V. and Pipano, E. (2000): Culture-derived parasites in vaccination of cattle against tick-borne diseases. *Annals of the New York Academy of Science*, **916**: 154-171.

[61] Schetters, T.P. (2005): Vaccination against canine babesiosis. *Trends Parasitology*, **21**: 179-184.

[62] Olson, M., Ceri, H. and Morck, D. (2000): *Giardia* vaccination. *Parasitology Today*, **16**: 213-217.

[63] Dantas, F. (2006): Leishmania vaccine: the newest tool for prevention and control of canine visceral leishmaniasis and its potential as a transmission-blocking vaccine. *Veterinary Parasitology*, **141**: 1-8.

[64] Ploeger, H.W. (2002): *Dictyocaulus viviparus*: re-emerging or never been away? *Trends Parasitology*, **18**: 329-332.

[65] Willadsen, P., Bird, P., Cobon, G. and Hungerford, J. (1995): Commercialization of a recombinant vaccine against *Boophilus microplus.* *Parasitology*, **110**: 43-50.

[66] Vercruysse, J., Scheters, T., Knox, D., Willadsen, P. and Claerebout, E. (2007): Control of parasitic diseases using vaccines: an answer to drug resistance. *Rev. Sci. tech. Off. Int. Epiz.*, **26**: 105-115.

[67] Schetters, T.P. and Gravendyck, M. (2006): Regulations and procedures in parasite vaccine development. *Parasitology*, **133**: 1-7

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DOI:10.22192/ijamr.2019.06.03.006

How to cite this article:
Tariku Geinoro. (2019). An Overview of Role of Immunity on Parasitic Infections. Int. J. Adv. Multidiscip. Res. 6(3): 33-47.
DOI: http://dx.doi.org/10.22192/ijamr.2019.06.03.006