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Vaccination Against Parasitic Infection

From Past to Current Approaches in the Development of a Vaccine

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14.1 Introduction

Infections with parasites are the root cause of one of the most serious and widespread diseases that can affect both humans and animals. Significant economic losses are connected with infections. These losses can be broken down into two categories: losses in productivity and losses arising from infertility. The management of animal parasitic diseases should have as their primary objective the enhancement of animal productivity and overall mass. As a result, it is necessary to implement control measures that are not only efficient but also cheap and long-lasting. Even though there are many effective treatments available for the treatment of the majority of important diseases, there is still a pressing need for the development of efficient vaccines. The problem of drug resistance among parasites is getting worse, there are no newly developed drugs that are effective, and there are drug residues in milk, goods made from milk, and meat. The invention of immunisations is largely attributable to these circumstances.

In many regions of the world, parasite illnesses provide a substantial challenge to the efficient production of cattle. For the past 55–60 years, antiparasitic drugs have been utilised extensively in an effort to restrict the spread of these illnesses. However, there are some diseases for which there are no effective antiparasitic treatments, and there are others for which chemotherapy is only partially

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effective due to the relatively late onset of clinical signs and diagnosis following infection. Both of these situations are caused by the parasites that cause the diseases. On the other hand, parasites like ticks, mites, enteric nematodes, and avian coccidia that rapidly multiply, recycle, and disseminate across host populations call for additional continual mass medicine administration through food, drink, or spraying.

Vaccination has long been recognised as the strategy that has proven to be the most effective in lowering the number of illnesses caused by parasites in both humans and animals. Despite the years of study that have gone into it, the few vaccines for parasites that are presently available on the market all have licences to be used against parasites that affect veterinary animals.

Because of the biological complexity of parasites, the creation of vaccines can be a particularly challenging endeavor. Unlike viruses and bacteria, parasites progress through a variety of growth phases, each of which presents the host with a distinct antigenic profile. There are very few instances in which sustaining parasite populations does not necessitate passing through or creating chronic infections in their particular animal host. A significant obstacle to progress is the lack of in vitro methods for the growth of the appropriate stages of many different parasites. The ability of many parasites to alter the immune responses of their hosts in order to prevent or delay the clearance of parasites further complicates the process of vaccine development [1].

Vaccines have had a significant impact on the improvement of public health, particularly since the 1960s when national immunisation programmes were successfully established and structured for the first time. In countries where there is a high level of vaccination programme coverage, many of the diseases that were once responsible for the majority of fatalities have almost completely disappeared. According to the World Health Organization (WHO), the current vaccination schedule saves between two and three million lives annually, which contributes to a reduction in the overall mortality rate among children under the age of five across the globe [2]. The purpose of this chapter is to investigate the methods used in the creation of vaccinations against parasitic infections from the beginning of time up until the present day.

For this reason, it is recommended that a multidisciplinary approach be utilised to tackle parasitic infections. This approach should include chemotherapy, grazing management, biological control, genetic host resistance, and parasite vaccinations. Because so many parasites have developed sophisticated immune evasion mechanisms, it is currently difficult to imagine the development of vaccinations that are actually effective. However, given the rapid advances being made in immunology and cell genetics, these predictions may soon be rendered obsolete [3].

14. ifferent Vaccines against Parasites

14.2.1 Protozoan Vaccines

Because protozoan infections in animals are linked to considerable production losses and because many of these organisms either cause zoonotic diseases or have close ties to human parasites, the importance of protozoa as infection reservoirs for human diseases is increased. Protozoan infections in animals are linked to considerable production losses. Vaccines against protozoa are not yet available for humans, although there are several that are in the process of being developed for animals [4].

14.2.1.1 Live Protozoan Vaccines

In live vaccinations, living organisms are administered to their hosts in the hope of eliciting an immune response and thereby replicating the effects of a disease. Since the immunological processes that are involved in protection and the stages of protozoan parasites that are involved in infections are mostly unknown, the majority of vaccines use live organisms themselves to trigger the necessary protective immune response in protozoan infections. This is because live organisms can trigger the necessary protective immune response in protozoan infections. T-cell driven immune responses can be induced using a live vaccine technique by ensuring that antigens are properly processed and presented within cells, as well as combining these antigens with major histocompatibility complex Class I and Class II antigens. Live vaccination methods more precisely resemble the development of both the innate and adaptive immune responses that would occur in a natural infection. As a result, live immunisation will induce the appropriate inflammatory and regulatory immunological responses in the host animals [5]. It is believed that T-cell responses are necessary to provide adequate protection against intracellular infections (Table 14.1).

14.2.1.2 Killed and Subunit Protozoan Vaccines

Several inactivated vaccines made of indeterminate antigenic structures or, more recently, crude whole organisms have been registered for use on the market for companion animals. These vaccines come in a variety of different formulations. Vaccines like these have the potential to lessen the severity of an illness or stop its transmission, but in general, their efficacy is inferior to that of living organisms. They have the potential to act as the building blocks for the development of recombinant vaccines. The selection of a sufficient parasite antigen and the delivery of that antigen to the immune system in a manner that will allow it to properly trigger innate and adaptive immune responses are two of the most challenging aspects in developing a dead vaccination that is effective [6].

Table 14.1 Different types of vaccine with their advantages, disadvantages and mechanisms.

Type of Vaccine	Invention	Advantages	Disadvantages	Vaccine using current technology	Mechanisms/ property of vaccine	Refences
Live vaccines	Edward Jenner	Single dose, long-term immunity Stimulates immune system naturally Produces strong immunity Elicits both humoral and cellular immune response Multiplication in the host Induces innate and adaptive immune responses Induces CD4+ and CD8+ T cells	Not safe Has side effects Uses whole pathogen Generation of unfavorable immune response	Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster	Live vaccinations include living, weakened germs that can still reproduce in the host. By inducing a wider variety of immune responses, both humoral (B cells) and cellular (CD8+ and CD4+ T cells), genuine infection is replicated almost precisely.	[46]
Killed vaccines	Almroth Edward Wright	No risk and safer than live vaccines Inexpensive No amplification in the host	Less powerful than live vaccines Requires multiple doses to have significant reactogenicity Increased risk of allergic reactions	Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies	Vaccine action is induction of both CD^{4+} and CD^{8+} T-cell responses, which require both endogenous as well as exogenous antigen processing and presentation of antigens with MHC class I and II molecules	[5]
Toxoid	Ramon	Diphtheria, which can be very serious and even deadly, as well as tetanus, and whooping cough . Prevents your child from developing a thick coating in the back of the nose or throat from diphtheria that can make it hard to breathe or swallow.	Vaccines do have some risk of an adverse reaction, the most common being redness and soreness at the injection site or fever and allergic reactions.	Diphtheria, tetanus	The diphtheria vaccine is made by taking the diphtheria toxin and inactivating it with a chemical. The inactivated toxin is called a “toxoid”. Once injected, the toxoid causes an immune response to the toxin, but unlike the toxin	[2]

(Continued)

Table 14.1 (Continued)

Type of Vaccine	Invention	Advantages	Disadvantages	Vaccine using current technology	Mechanisms/ property of vaccine	Refences
Recombinant protein vaccine	William Rutter	No risk No interference with the maternal immunity and/or other vaccines Induces strong immune response	Needs cold chain for transportation Expensive, no biological activity Needs adjuvant to enhance immunogenicity Contamination with bacteria substances Large-scale preparation is difficult	Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A	CD^{4+}T cell and humoral responses. Poor induction of cellular responses, particularly of CD8+ T cells	[5, 59]
DNA vaccines	Enzo Paoletti and Dennis Panicali	Safe to use, no adjuvant needed Stable at room temperature and shipment is inexpensive Easy for manipulation and production Elicits antigen-specific immune responses	Low potency in humans Often weak immunogenicity	Hepatitis B vaccine, HPV vaccine	Induces both CD4+ and CD8+ T cells Elicits both humoral and cellular immune response Due to CpG motifs, are immunomodulators Prime antigen-specific memory T cells	[58]

Live genetically modified vaccines	Maurice Hilleman	Stable Safer than general live vaccines Stimulate immune system as in natural infection Multiplication in the host	Risk of reversion to virulent state Needs cold chain for transportation Unknown memory formation and duration Stimulates a weaker immune system response	Rotavirus vaccine MMR vaccine BCG vaccine against TB	Live vaccines use a weakened form of the germ that causes a disease. Because these vaccines are so similar to the natural infection that they help prevent, they create a strong and long-lasting immune response.	[50]
Live non-pathogenic vaccines	Edward Jenner	Safe to use Life-long immunity No reversion to virulent state	Unknown memory formation and duration Need cold chain for transportation	SARS-CoV-2	Stimulates immune system similar to natural infection Multiplication in the host Live vaccines induce T-cell mediated immune responses and mimic natural infection through correct processing and presentation of antigens in association with MHC class I and II antigens	[5, 59]

Neospora caninum is a common factor in the occurrence of abortions in cattle. A crude *N. caninum* vaccine is available in the United States of America. This vaccine combines inactivated *N. caninum* tachyzoites with an adjuvant in order to help reduce the number of abortions caused by the parasite in healthy pregnant cattle and to prevent it from spreading to calves while they are in gestation. Neogaurd is the brand name of this particular immunisation [7, 8]. *Giardia intestinalis* is a type of enteric parasite that affects a wide variety of animal species and has the potential to cause significant damage to the immune systems of young children and humans. Giardia Vax®, a commercially available vaccination, has been granted authorisation by the government of the United States for use in canines and felines so that it can significantly cut down on the frequency, intensity, and length of cyst shedding. An unprocessed mixture of *G. intestinalis* trophozoites that have been disturbed and artificially produced is contained within the vaccine [9].

Vaccination has been recognised for a very long time as the most effective and long-lasting technique for managing parasite disease in both humans and animals. (Table 14.1) Despite years of research, the few parasite vaccines that are now on the market are all licenced for use against parasites in veterinary species. This is the case despite the fact that there are no vaccines against human parasites. *Toxoplasma gondii*, *Babesia bovis*, *Eimeria* species, *Theileria annulata*, and other live parasites that are often attenuated or partially disabled by irradiation or concurrent antibiotic administration were the only effective vaccinations. Because the bulk of these live vaccines have to be created using parasites that have been extracted from animal hosts, there are significant challenges associated with standardisation, quality control, shelf life, and the costs of production. Despite the fact that live vaccines have traditionally been regarded as unacceptable for use in humans, a recent initiative has been instigated to investigate the use of *Plasmodium falciparum* sporozoites for vaccination. This initiative was motivated by the well-documented challenges encountered in developing subunit vaccines for malaria [1].

14.3 Administration Route

With one important exception, all routinely administered vaccines continue to rely on the injection route as the principal means of presenting the vaccine antigen to the recipient's immune system.

The challenge of meeting the demand for sterile syringes and needles in less developed countries is a primary focus of the work made by the EPI. Even if the pain from the injections is slight, it is something to keep in mind, particularly in light of the numerous vaccines that infants receive frequently. This is especially important to keep in mind in light of the fact that the immunisations

can be repeated several times. A basic approach to reducing the total number of injections required is to incorporate multiple antigens into a single vaccination. Consequently, the live vaccines for measles, rubella, and mumps as well as the combination vaccines for diphtheria, tetanus, and pertussis are the kind of vaccines that are utilised most commonly. Additional combinations – of which there are many available on the market – raise concerns about the possibility of decreased immune responses when several antigens are competing for the same piece of equipment as well as the expense. Each new combination will need to go through a series of rigorous clinical tests, which will drive up the overall price of the finished product. This raises significant problems because immunisations should be administered to every child in the world, including and especially the poorest of those children.

The immunisation against live poliovirus, which is given orally, constitutes the exemption that was just discussed. Due to the fact that it replicates in the intestinal epithelium, the attenuated form of the polio virus is able to enter the body on its own. It is believed to have the additional benefit of activating the immune system of the intestinal mucosa, which is the body's natural first line of defence, and creating a defence that is more effective than a vaccine that is administered via injection. However, the vast majority of infections are naturally obtained through mucosae, whether in the respiratory system, the bowels, or the genital tract; as a consequence, local mucosal defences may be the most efficient type of resistance. In point of fact, the mucosae have a highly developed immune surveillance system, which is comprised of specialised cells that assess the antigens that are loading onto them and then convey the information to antigen-presenting dendritic cells and the lymphocytes that lie beneath them. It is a mystery how the various components of food and the microorganisms found in the environment are able to circumvent the immune activation pathway. One explanation for this phenomenon is self-tolerance, which is also sometimes referred to as "oral tolerance". However, it is unknown whether an immune response or the formation of tolerance is responsible for determining which channel is taken [10].

14.4 Trematodes and Helminths Spread through Soil

14.4. Schistosomiasis

Schistosoma haematobium and *S. mansoni*, both of which are dimorphic parasitic flatworms that are transmitted by freshwater snails and circulate in the bloodstream of mammalian hosts, are the primary etiological agents of schistosomiasis. *S. haematobium* and *S. mansoni* cause schistosomiasis. At the moment, there are 52 countries that are home to 219 million people who have been exposed to schistosomes, with Africa accounting for 90% of the disease's expected cases in 2003.

Several studies that have been conducted up to this point have uncovered proteins that have the potential to be used in the development of novel diagnostic tools and vaccinations [11].

Proof of concept for a vaccination against *Schistosoma* trematodes was provided by mice and non-human primates inoculated with natural, irradiated cercariae. This vaccine offered about 80% protection against schistosomula challenge [12, 13, 14]. In light of the fact that attenuated preparations were deemed unsuitable for use as a human cercarial vaccine, efforts were made to produce a subunit vaccine [15]. The majority of the targets for the existing lead subunit vaccines were found by using traditional biochemical methods on parasite protein fractions (for instance, *S. mansoni* glutathione S-transferase antigens of 28 kDa and 14 kDa). These methods were used to isolate the target proteins from the parasites [14]. These compounds originate predominantly from the tegumental membranes of migrating schistosomulum stages (which have an effect on parasite invasion) and adult females (which have an effect on parasite survival and fecundity), which are the objectives of the treatment. Recent advancements in high-throughput technology have helped to speed up the process of identifying antigens for important schistosome species. Despite this, there is still a lack of translation from basic research to clinical and field studies. At the moment, there are just a handful of recombinant targets that are in various stages of clinical and commercial development [11] (Figure 14.2).

14.4.2 Hookworm Disease: Helminths that Spread Through Soil

Soil-transmitted helminths include medically significant endoparasites such as hookworms, roundworms, and whipworms. Some examples of these endoparasites include *Necator americanus* and *Ancylostoma duodenale*. Roundworms include *Ascaris lumbricoides*. Whipworms include *Trichuris trichiura*. Hookworms include *Necator americanus* [16]. Since hookworm infections presently account for around two-thirds of the global human illness burden from soil-transmitted nematode infections, a significant amount of work has been put into the search for a vaccine. Approximately 440 million people across Asia, sub-Saharan Africa, the Caribbean, and Latin America are afflicted with human hookworm disease, which is mostly brought on by the parasites *N. americanus* and *A. duodenale*. This condition is a global health concern [17, 18].

14.4.3 Helminthiases: Endoparasite Vaccines

The bulk of disease-causing parasites that are of relevance to medicine and veterinary science are endo-parasites, with helminthiasis being a major contributor to the problem [19]. These parasites are responsible for a range of disorders that can

be chronic and/or debilitating, which can interfere with normal physical and cognitive development. Children are particularly sensitive to these diseases because of their developing bodies and brains [19, 20]. Mass anti-helminthic drug administrations (MDAs), such as praziquantel for schistosomiasis and albendazole or mebendazole for soil-transmitted helminthiases, are the primary public health interventions that are recommended to control morbidity in endemic countries. These are the types of helminthiases that are transmitted from the soil to humans (STH). However, because of the risk of developing chemical resistance, treatment is made more difficult [21–23].

14.5 Arthropods that Act as Parasites

14.5. Ectoparasite Vaccines

The ectoparasitic arthropods make up the most numerous animal phylum and are becoming increasingly important in the fields of veterinary and medical research [24, 25]. More than twenty percent of all newly discovered infectious diseases that occurred between the years 1940 and 2004 were caused by arthropod-borne illnesses [26] (Figure 14.2).

14.5.2 Flies That Carry Parasites

The haematophagous biting flies, the non-biting annoyance flies, and the flies that induce myiasis, are the three primary groups of flies that are significant to veterinary medicine [27]. Important biting flies for veterinarians include the *Haematobia irritans* (also known as the horn fly), *H. irritansexigua* (also known as the buffalo fly), and *Stomoxys calcitrans* (also known as the stable fly) [28]. (Figure 14.2). Cattle horn flies are a nuisance that can be financially devastating since they cause severe itching, a reduction in milk production, lower body weight, considerable blood loss, and damage to hides [29]. In addition, horn flies are capable of transmitting a variety of illnesses, including several species of *Staphylococcus* that can cause mastitis in dairy heifers [30].

14.6 The Protector Immune Response

The creation of vaccines has been hampered by a lack of knowledge regarding the specific immune effectors that are responsible for the attrition of parasites and the antigens that trigger them. According to [31], the effective development of a schistosomiasis vaccine had been hampered by disagreements over the necessary immune response as well as a lack of understanding of the effector mechanisms

that mediate immunity. This was one of the reasons why the disease is so difficult to treat. For natural immunity to be maintained, it is often necessary to have recurrent infections, stage-specific immunological responses, as well as a wide array of antibody classes and T-cell responses. Even though the technology necessary to produce recombinant proteins has been available for around 30 years, it is still rather uncommon to find proteins that have the required level of effectiveness. The most prominent and groundbreaking exceptions are the advances that have been made in tick and cestode vaccines. These are successes that have set a new standard [32, 33].

14.7 ntigenic Differences and Their Relation to Stage-Specific Antigen Expression

When a host is infected with protozoan or metazoan parasites, the immune system of the host is subjected to a wide variety of antigens that are stage-specific and temporally expressed. There will be a connection established between some of them and immune responses that are protective, while for others there will not. The greatest challenge for the vaccine researcher is to identify the components that are essential for the production of protective immunity. An illustration of the enormous antigenic variation that all parasites display is provided by the variant surface glycoprotein (VSG) of trypanosomes. Trypanosomes are the pathogens responsible for sleeping sickness, which is transmitted by tsetse flies and is seen in high prevalence in Africa. The surface of the parasite is covered in VSGs, which act as a physical barrier to protect the underlying proteins from the effectors of the immune system [34]. This surface coat is responsible for inducing a one-of-a-kind trypanocidal immune response, which is then neutralised by antigenic variation. During this process, the trypanosomes switch to the production of a separate VSG, which, if it is antigenically novel, promotes the clonal growth of the switched cells and creates a new parasitaemia peak. Although only one VSG gene is expressed by each trypanosome, these cells have the ability to flip between hundreds of thousands of different VSG genes [35] (Figure 14.2).

14.8 Vaccination as a Preventative

Vaccines are the most efficient, trustworthy, and long-term method of controlling parasite disease, and they are also beneficial in reducing reliance on pharmaceutical drugs and pesticides. Vaccines are also a sustainable method [36]. The use of vaccines has many benefits, some of which include improving animal health and welfare by lowering the incidence of animal infections; improving public health by lowering the incidence of zoonoses and other food-borne pathogens in

animals; resolving problems with acaricide, antibiotic, and anthelmintic resistance; preventing the use of chemicals on animals and in the environment; and preserving biodiversity (Figure 14.2). All of these features should raise the economic advantage of animal production and improve its long-term viability [5].

14.8.1 Malaria

Malaria is the most significant tropical parasite sickness that can be found anywhere in the world. The disease is widespread with an estimated yearly mortality toll of approximately 1.1 million deaths. Each year, there are between 350 and 500 million clinical cases of the disease. The costs associated with treatment as well as days missed from work might be significant. The life cycle of the parasite is quite complex, and it all begins when female mosquitoes feed on blood and release sporozoites into the bloodstream. The sporozoites then make their way to the liver and enter hepatocytes there. As they develop into merozoites over the course of about two weeks, tens of thousands of new ones are produced at this location. After leaving the hepatocytes, the merozoites continue their journey through the circulation to infect the erythrocytes (RBCs). There, they multiply and mature within twenty-four to seventy-two hours, until the RBCs lyse and release the merozoites, which then infect new RBCs to finish the cycle. The acute fever episodes and rigors that are characteristic of malaria, which happen every 48 to 72 hours, occur at the same time as the synchronised lysis of infected RBCs, which releases the newly matured merozoites. This is because the synchronised lysis of infected RBCs is triggered by the synchronised release of newly matured merozoites. Some of the merozoites will develop into gametocytes, which is the sexual stage of development. These gametocytes have the ability to reproduce sexually and create new sporozoites if they are swallowed by an anopheline mosquito, which in turn restarts the cycle [37].

The fact that human participants who were given irradiated sporozoites were protected against experimental infection to a high degree (about 90%), showing the feasibility of vaccination. [38] People who live in regions where malaria is common can build a natural immunity to the disease, but it is a slow process that requires constant antigenic stimulation and has an effect on how severely they are affected by the disease. Hyperimmunoglobulins derived from malaria-resistant individuals have been passively transplanted into healthy human volunteers who have never been infected with the disease [38].

There are three different approaches to creating a vaccine against malaria. 1) To provoke potent immune responses that will prevent merozoites from entering the bloodstream; 2) vaccination results in the development of disease-limiting immunity; and 3) transmission of the virus by mosquitoes is prevented by means of population-based immunisation.

Techniques for administering pre-erythrocytic vaccines make an effort to either elicit a cell-mediated immune response that will limit intra-hepatic parasites or

an antibody response that will destroy sporozoites and prevent them from penetrating the hepatocyte. Both of these immune responses are intended to limit the number of parasites that can be found within the liver. If a vaccination of this nature existed, it would prevent the spread of clinical sickness. The most promising pre-erythrocytic vaccine option comes from the circumsporozoite protein (CSP), which is an essential part of the surface of the sporozoite. The first evidence that people may be protected from malaria infection with a subunit vaccination was provided by prototype vaccines. These vaccines were created to stimulate antibody responses against the repetitive epitopes of the circumsporozoite protein [39, 40]. This was the first proof that people may be protected from malaria infection with a subunit vaccination. Because the immunogenicity of the prospective vaccines was low, an amalgam of circumsporozoite protein synthesised with unfused hepatitis B surface antigen (HBsAg) was constructed as a vaccine. This vaccine is now in use [41].

Asexual blood-stage (erythrocytic) vaccine techniques are designed to elicit T-cell responses that will prevent the establishment of the parasite in RBCs as well as antibodies that will inactivate merozoites and/or target malarial antigens expressed on the surface of RBCs. Additionally, these techniques are intended to elicit antibody responses that will target malarial antigens expressed on the surface of RBCs. This type of immunisation would primarily serve as a disease-reduction vaccine in endemic nations by slowing down the exponential growth of merozoites, which is the infectious stage of the parasite. Recently, there was a publication of an in-depth analysis of the development of MSP-1 as a potential vaccine candidate [42]. To summarize, MSP1 provided protection against challenge infection with *Plasmodium yoelii* in laboratory mice. Passive vaccination with monoclonal antibodies (mAbs) also provided protection against challenge infection in the same model, highlighting the importance of antibodies for providing protection. Extensive structural research made feasible by gene sequence analysis led to the discovery of a disulphide-rich region of approximately 100 amino acids at the C-terminus of the gene that encodes two epidermal growth factor (EGF) domains. This area is located at the end of the gene [37].

14.8.2 Leishmania

Leishmaniasis is a widespread disease that affects people in many parts of the world, including Africa, Latin America, south and central Asia, the Mediterranean basin, and the Middle East. It is caused by a wide variety of species of flagellated protozoan parasites that belong to the *Leishmania* genus. There are an estimated 12 million new instances of the disease worldwide every year. It can lead to severe disfigurement as well as death . Although the parasite can be passed on to healthy humans, the vast majority of infections are contracted from wild animals who

serve as a reservoir for the parasite (small rodents, dogs). Visceral symptoms, mucocutaneous manifestations, and cutaneous manifestations are all possible for this condition. Cases of visceral leishmaniasis occur on a yearly basis at a rate ranging from 1.5 million to 2 million, and epidemics can emerge with high rates of death. In order to treat it, chemotherapy is administered, which is both expensive and risky due to the development of drug resistance. After recovering from an infection, a person develops a resistance to subsequent infections; this demonstrates that it is possible to create an effective vaccine [43]. Vaccines against attenuated parasites have a good chance of producing the same immune response as genuine infections and replicating such infections. However, there are concerns with transitory infections that only deliver moderate amounts of antigen, which elevates the possibility of an inappropriate skew in the Th1 response's bias. This can be a problem for people who suffer from allergies. This method of immunisation will also provide a high number of parasite antigens, which is a potential benefit. This is in contrast to the few parasite antigens that can be obtained by employing subunit or recombinant antigens [44].

According to research conducted on mice, the genetics of the host may have an effect on the protective immune responses elicited by vaccination [43].

DNA vaccination is regarded as a potentially fruitful avenue for the advancement of vaccine research because it often results in Th1 responses [45]. The results of the testing of several DNA vaccine designs have yielded a wide range of outcomes. Sand flies are the insect vectors for the parasite, and a 15kDa protein found in sand flies has showed promise as a means of triggering some defensive response. Despite the many advances that have been made, it is instructive to refer back to the concept of the ideal antileishmanial vaccine that was presented by [43].

14.8.3 Contemporary Approaches to Leishmaniasis Vaccination

Leishmania and the recent discovery of the DNA sequence of the human genome have lately opened up new possibilities for the development of innovative vaccine techniques. Vaccines that are created using recombinant DNA techniques include recombinant subunit vaccines, recombinant DNA vaccines, genetically modified live vaccines, recombinant viral-based vaccines, and recombinant vaccines based on epitopes or peptides. Other types of recombinant vaccines include genetically modified live vaccines.

Prior to the creation of recombinant vaccines, susceptible individuals were protected against leishmaniasis by being immunized with crude antigens. After the development of recombinant DNA technology, numerous components of the parasite, in particular genes that are essential for the parasite's continued existence, were targeted, and the immunological response that was elicited in the host has been characterized. A separate strategy was utilized to generate genetically

attenuated live vaccines, and it involved silencing a number of important genes. Vaccines against *Leishmania* can be developed using recombinant techniques with the use of essential information on the genes involved in the parasite's structure, metabolism, and virulence. There is no risk of sickness due to the presence of unfavorable pathogenic qualities when using individual or multiple proteins from one or more species of an organism instead of the entire parasite cell antigens. This is the primary benefit of using individual or multiple proteins from one or more organisms. Since there may be a synergistic effect on the immune response, utilising multiple antigens rather than just one may produce better results than using just one antigen. This is the conclusion drawn from a number of studies. As a direct consequence of this, these vaccinations have a lower risk than the conventional immunisations.

Numerous antigens derived from different species of *Leishmania* have been studied for their potential use as recombinant proteins and DNA vaccines. However, none of them were able to establish a complete level of long-term immunity; rather, they only produced a partial level of protection against the infection. Researchers have created novel methods, such as cocktail vaccines and heterologous prime-boost vaccination, in order to lengthen the duration of the immune response in the host. Specifically, this was done in order to combat the challenge of chronic infections [46]

14.9 The Zoonotic Consequences of Parasitism

There are a wide variety of zoonotic diseases that are brought on by parasites and can affect both metazoan and protozoan organisms. Public health is threatened in many parts of the world by a condition known as hydrated illness, which is brought on by an infection with tapeworms belonging to the *Echinococcus* genus. People become ill from the disease when they swallow the eggs of the organism that causes it, which hatch in the intestines of dogs and other canids. This makes proper sanitation a concern for the disease. The sickness caused by the digenetic trematode *S. japonicum*, which is also a major cause of mortality in sub-Saharan Africa, affects more than 250 million people throughout Southeast Asia [47]. More than 40 million individuals in China's tropical and subtropical regions are affected by this disease [48, 49]. The disease known as fascioliasis is brought on by the liver fluke *Fasciola hepatica*. This widespread infection often strikes bovines and sheep first, but it also has the potential to strike humans. Infection can occur in people when they consume unwashed and raw aquatic plants that are contaminated with encysted larvae. In humans, *Fasciola* spp. can cause severe diseases that can even be fatal; nevertheless, animals can carry enormous worm burdens without becoming ill from the infestation. In most

cases, fasciolosis in humans is linked to locally endemic cases of fasciolosis in animals. People, dogs, and cats can all become infected with the protozoan parasite known as *Giardia*, which is responsible for severe gastrointestinal sickness. People whose immune systems are impaired are especially at risk for developing a severe gastrointestinal sickness caused by *Cryptosporidium parvum* [37].

14.10 Current Spectacular Technical Advancements in Vaccines Development

14.10.1 Recombinant Protein Vaccines

Recombinant vaccines rely on the ability of one or more specific antigens to generate immunity against the disease when they are given with additives, when they are created by plasmids, or when they are delivered by non-harmful bacterial or viral vectors during administration. When compared to vaccines that are based on purified macromolecules, recombinant protein vaccines allow for the avoidance of a number of potential problems. These problems include the risk of co-purification of undesirable contaminants and the reversal of the toxoids to their toxigenic forms, for instance, when thinking about diphtheria or tetanus toxoid vaccines. Another significant issue that is alleviated by the utilisation of this technology is the challenge posed by the acquisition of adequate quantities of purified antigenic components. The majority of the vaccines that are now under investigation are derived from highly purified recombinant proteins or components of infectious diseases [50] (Figure 14.2). One well-known example of a recombinant protein vaccine is the hepatitis B vaccination, which is currently administered to human patients. The infection caused by the hepatitis B virus (HBV) is a form of chronic liver disease that affects people all over the world. HBV has a very strong attraction for human liver cells, and part of what contributes to this affinity is a receptor that is produced on the surface of infected cells. In order to produce vaccines against hepatitis B, the hepatitis B surface antigen, often known as HBsAg, is first produced in yeast cells. The formation of virus-like particles (VLPs) by the HBsAg, which are highly immunogenic, contributes significantly to the remarkable efficacy of the HBV vaccination. It is possible that the yeast expression system will secrete the antigen into the culture supernatant, which will make its purification much simpler [51, 52]. In addition, because yeast cells are able to glycosylate proteins, these cells provide some of the eukaryotic cellular machinery that is required for the post-translational modification of proteins. The HBV vaccination is now within reach of the vast majority of developing countries as a direct result of price reductions brought about by increased market competition and the dissemination of production technology to a large number of manufacturers (Table 14.1).

14.10.2 The Creation of Vaccines Using Recombinant DNA Technology

When beginning a new vaccination study, how do you choose which prokaryotic or eukaryotic vector to employ for the production of recombinant proteins? There are a wide variety of prokaryotic and eukaryotic vectors available. This choice will be affected by one's familiarity with the pertinent antigen. Does post-translational modification play a role in the activation of a protective response or is it simply necessary for efficient protein folding? Even if glycans from yeast and insect cells would not be suitable, bacterial cells do not glycosylate their proteins [53]. According to the results of the tests, the majority of the sheep's antibody response to the protective gut antigens from *Haemonchus contortus* was to the glycan component. However, these authors noted that current research suggested that this was unlikely to be a factor in the protection brought on by the vaccine. Since parasite-specific patterns of glycosylation, such as *H. contortus* H11 [54], have been found, the currently available commercial eukaryotic expression systems will not result in the appropriate glycosylation of recombinant antigens. This is because glycosylation is a process in which sugars are attached to proteins (Figure 14.2).

14.10.3 The Use of Monoclonal Antibodies in the Research of Parasitic Diseases

Because of the features of monoclonal antibodies, the utilisation of these reagents has resulted in the provision of a number of advantages during the course of the inquiry into parasite illnesses. Immunotherapy, vaccine development, and diagnosis are the three main application areas that can be generally classified under this umbrella term. The antigens from a parasite of interest, in addition to the antigens from parasites that are closely related to it, can all be screened using monoclonal antibodies as a library for diagnostics in order to identify those that are unique. This can be done in order to find the antigens that are specific to the parasite of interest (Table 14.1).

Using monoclonal antibodies, it is now possible to recognize specific coccidial antigens and analyse their contribution to the immunological regulation of parasitism in vitro. This is achievable thanks to recent advances in the field. In a further step, recombinant parasite antigens cloned into bacteriophage from cDNA libraries have been discovered with the help of monoclonal antibodies and polyclonal immunological serum [55]. Because of this, a protein that was produced by *E. coli* and selected in this manner has been utilized to partially protect chickens from *E. tenella* infection, which is a challenge infection [56].

14.10.4 Utilizing Monoclonal Antibodies

In 1975, Kohler and Milstein outlined a method for combining healthy B lymphocytes with cancerous myeloma cells in a procedure that they called fusion. The hybrids that were produced were endowed with the ability to continue growing in vitro indefinitely and possessed the capacity to secrete antibodies much like their B lymphocyte parent. Clones are characterized by their inherent similarity and their ability to produce IgG with a consistent molecular structure and antigen specificity. Clones can be generated from hybridized cell populations. This is due to the fact that every B cell produces its own immunoglobulin molecule, which has a predetermined level of specificity.

Because of their high level of specificity, monoclonal antibodies are among the most useful tools for research into the antigens of parasites. Parasites are complicated organisms that progress through numerous phases of development, and at each stage of their life cycle, they provide the host with a wide variety of antigens. The use of monoclonal antibodies makes it much simpler to recognize, separate, and examine the various antigens that are produced by these complex organisms.

Also, if the antigens do not contain any repetitive epitopes, the monoclonal antibodies' specificity for a single epitope may preclude their use in certain testing methods, such as precipitation reactions. This is because these methods require the antibodies to recognize multiple epitopes simultaneously. Because a hybrid cell line may only generate one kind of antibody, isotype-dependent properties such as complement fixation and protein A binding may have a restricted applicability for monoclonal antibodies that are otherwise valuable.

The only way to make hybrids is by fusing together cells from different rodents, which has slowed down the process of developing monoclonal antibodies (and recently human cells). In the field of animal illness research, the utilisation and investigation of murine monoclonal antibodies are subject to a number of different limitations [57].

14.10.5 DNA Vaccines

This technique involves delivering the genetically modified DNA of a particular antigen so that immune cells can come into direct contact with the antigen and trigger a variety of reactions to various defence mechanisms. This allows immune cells to better fight off infections. DNA vaccines may have a number of advantages over conventional immunisations, including the ability to evoke a wider spectrum of immune reactions. Vaccination is the most effective method of disease control in both humans and productive animals; however, the development of vaccines to prevent parasitic infections in animals is still in its early stages. Vaccination is the most effective method of disease control in both humans and productive animals [58] (Table 14.1).

Concurrently with the advent of protein vaccines, a new feasible delivery technology known as DNA vaccines that encode one or more immunogenic proteins has been developed and made available. In 1990, RNA and DNA expression vectors were successfully injected into the skeletal muscle of mice for the very first time. These vectors contained reporter genes [59]. DNA vaccines hold a great deal of potential for use in the prevention and treatment of a wide variety of diseases, including leishmaniasis and other conditions for which Th1 responses and cell-mediated immunity are necessary to provide protection. DNA vaccines have been developed over the past 20 years in order to combat infectious microorganisms. This method of immunisation elicits both humoral and cellular immune response against native forms of protein, and antigens are produced in the natural conformation of the host due to post-translational modifications of the expressed proteins inside the cells. Reduce the amount of DNA that is used in order to increase the level of protection produced. The magnitude of the immune response that is induced can, of course, be influenced by a wide range of parameters, including the immunogenicity of the gene that is sought to be expressed and the presence of synthetic oligodeoxynucleotides. By acting as an adjuvant, the immunomodulators that can be found in the CpG patterns of plasmid DNA cause a change in the immune response towards Th1 [60]. In addition, immunisation with DNA alone triggers a protein called TLR9, which results in a considerable amount of IL-12 production and, eventually, a Th1 immune response [45]. DNA vaccines also have the advantage of being more stable throughout shipment and transition than conventional immunisations.

14.11 The Effects of Parasitism on the Entire World

The consumption of antiparasitic drugs is, in all practical respects, the one and only method for mitigating the negative consequences of parasitism in both humans and livestock. Parasites that are drug-resistant are becoming increasingly common in both animal and human populations, which presents a challenge for parasite control. Vaccination being the primary means of disease prevention, it is critical to develop other long-term control strategies. Twenty-five years after the ability to create recombinant parasite proteins was hailed as a major success in vaccine development, only a few recombinant vaccines against livestock parasitic diseases have advanced to the point where they can be released. This is despite the fact that it was possible to create recombinant parasite proteins [37]. The development of the first recombinant vaccination against a parasite that can infect people has not yet been successful. It is anticipated that by the year 2050, more than half of all people living in poor nations would reside in urban and peri-urban regions, the majority of whom will reside in slums, which are ideal environments

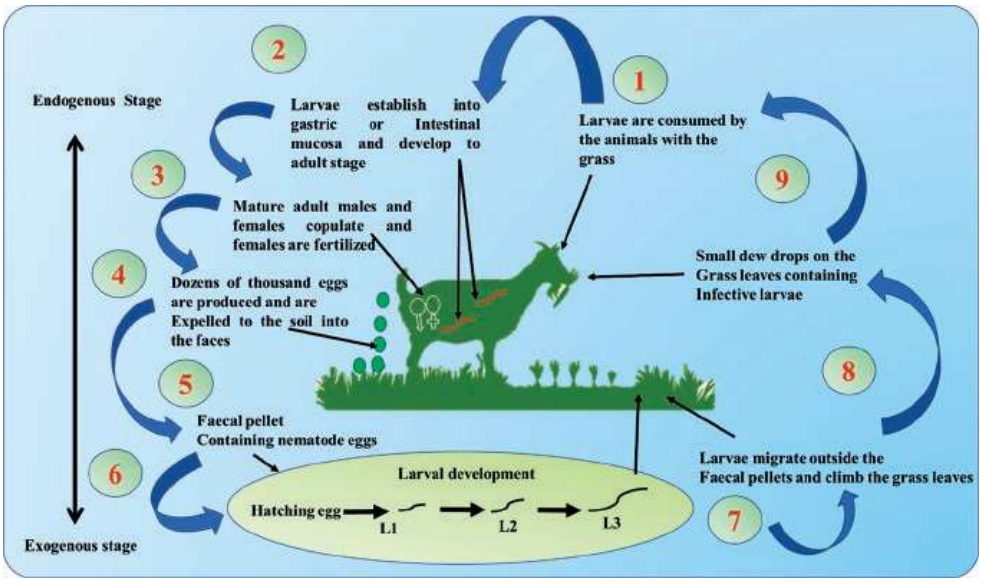

Figure 14.1 Development cycle of *Haemonchus contortus* in goat.

for the transmission of a wide variety of parasites [61]. Parasitic diseases, which can be transmitted by a wide variety of helminths, protozoan parasites, and ectoparasites, also have a substantial impact on the amount of cattle produced around the world. One of the most prominent is the *Haemonchus contortus* nematode, which is a pathogenic blood-feeding nematode parasite that affects sheep and goats. Both large-scale sheep and goat producers and, perhaps more significantly, resource-poor small holders, whose production directly affects family diet and, ultimately, survival, are directly affected by infection and its intensity. This parasite is especially common in tropical and subtropical regions (Figure 14.1).

14.12 cuity Control

Both for the treatment of clinical disease and for larger-scale programmes aimed at disease control, pharmaceuticals continue to be an indispensable tool. However, drug resistance in the target parasites is already quite common, which presents a challenge for sustainable management, most notably in the context of livestock. Many people have been successfully treating themselves with currently available medicines for years. The development of drug resistance in cattle hosts has been linked to the use of every type of anthelmintic [62]. Nematodes that are resistant to many treatments are becoming more prevalent in certain regions, which places the continued operation of production facilities for small ruminants at risk of

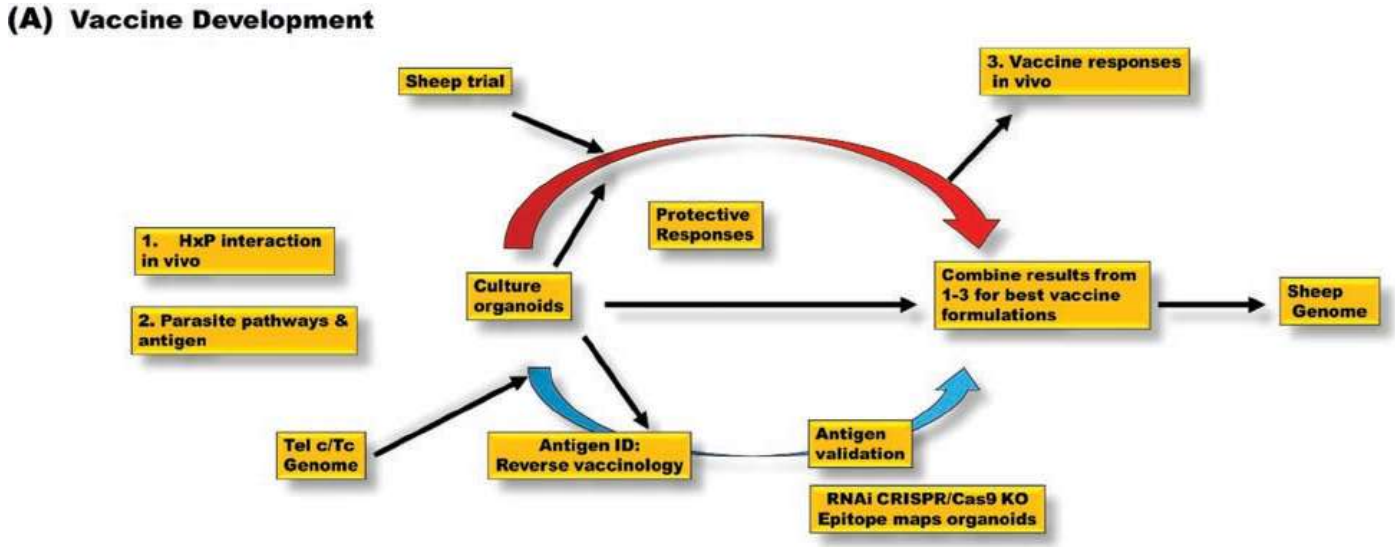

Figure 14.2 Different stages of vaccine development.

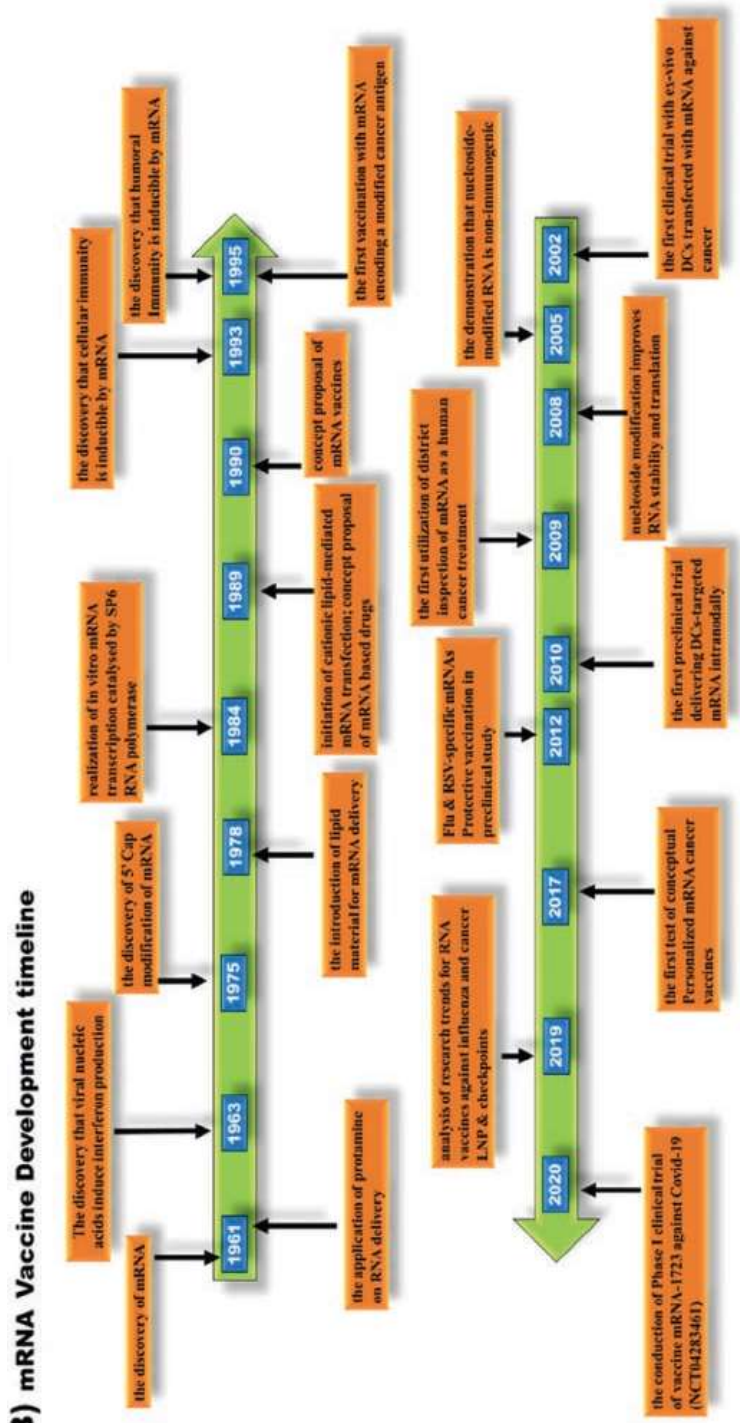

Figure 14.2 (ont'd)

extinction. In a review of this nature, it is imperative to discuss the widespread problem of ectoparasites, in particular the tick and mite infestations that are frequent in both humans and animals. Some parasitic diseases should become less common over time if public health education, access to clean water, and sanitary living conditions all continue to advance. However, this is not always the case with illnesses that are transmitted by vectors. Malaria is spreading unchecked in many parts of the world, and patients' resistance to treatment is increasing, particularly in sub-Saharan Africa. Every socioeconomic category will be affected by this. The only effective method of mosquito control is to protect oneself from bites by employing measures like using bed nets impregnated with insecticide. The most defenceless people of society are the ones who are affected when there is an outbreak of trypanosomiasis or leishmaniasis. The World Health Organization, along with other international organisations and charities, is coordinating significant efforts to find creative ways to control a number of the major parasites that affect both humans and animals, with the ultimate goal of eradicating as many of them as possible.

14.13 Conclusion

New insights into the immunobiology of the parasites have been provided as a result of the development of new vaccines. This has assisted in the concentration of efforts on the identification of new candidate antigens for vaccine testing and, in some instances, has provided new ideas for the design of vaccines. Vaccines should be able to achieve this goal without causing the disease to spread further since they stimulate an immune response in the animal host that afterwards identifies infectious microorganisms and helps the body fight sickness. Using recombinant DNA technologies, scientists have been able to create live genetically modified organisms, recombinant dead vaccines, and genetic immunisations that do not cause illness but still elicit a powerful immune response. These advancements have been made possible by the creation of genetically modified organisms that can replicate on their own. For the purpose of developing vaccines utilising rDNA technologies, a comprehensive understanding of the infectious agent, in particular the antigens that are absolutely necessary for providing protection and the factors that contribute to the development of the disease, is required.

There is good reason to assume that vaccinations will be developed against some or all of the most significant animal diseases as soon as the necessary financial and technical resources become available. Nevertheless, it is necessary to acknowledge the complexity of the problems that are being discussed at this time. Through immunisation, communities are protected from diseases that historically claimed the lives of millions of people each year, particularly children. According

to the United Nations Convention on the Rights of the Child, every child has the right to the highest attainable level of health, and as a direct consequence, every child has the right to get vaccines.

The creation of vaccinations as a method for preventing parasite infections in animals has a promising future and is the strategy that is both the most feasible and the most cost-effective. It is essential to preserve the synergy that exists between parasite vaccinations and anti-parasitic medications. Doing so will reduce the amount of anti-parasitic medication that must be taken in order to get the desired effect and will stop the development of drug resistance. Conventional methods of parasite control, such as chemotherapy, grazing management, and biological control of parasites, are not economically viable in many countries, including India, despite the fact that they can be used in an integrated pattern for effective control. This is true even though they can be employed individually for effective control. Vaccines give long-lasting immunity that can be periodically increased, which is beneficial in the event that animals are exposed to natural diseases.

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