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Review Article

Effect of Helminth Infections on the Immunogenicity and Efficacy of Vaccines: A Classical Review

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Abstract: Vaccines are responsible for the reduced cases of mortality caused by infections worldwide. However a number of studies have shown that helminth infections have strong immune modulatory effects. Due to this, they have been considered as one of the contributing causes of lowered immune responses induced by vaccines observed in developing areas, where these infections are endemic. This is often due to the host's inability to mount an effective protective immune response once receiving the vaccine. Nevertheless, it has been shown that elimination of the helminth infections, with the use of antihelminthic treatment, would improve recipients' immune responses to vaccines. These helminth infections such as Ascariasis, hookworm and schistosomiasis are rampant in developing countries, especially Sub-Saharan Africa. This remains a major health concern as helminth infections, especially those that remain untreated, would reduce efficacy of vaccines thus posing a serious risk of increased infections leading to outbreaks in these areas. The effects helminths have on the immune responses elicited by vaccines still remain unclear as relatively little information is available. This could be due to lack of controlled experiments involving animal models, especially the Non-human primates. This review compiles information from a number of peer reviewed articles and aims to explain the host-parasite interaction, the immune response generated and summarizes how helminth infections affects the immune responses of various vaccines. This may provide a greater understanding of the strategies helminths use to evade the immune system which in turn affect the immune responses elicited by vaccines.

Keywords: Vaccines, Helminths, Immunomodulatory

1. Introduction

Helminth infections are caused by a diverse group of metazoan organisms which pose a public health concern. According to WHO, Schistosomiasis and soil-transmitted helminths affect approximately 1.5 billion people, of which 300 million suffer from severe morbidity associated with the infection. These infections are also highly prevalent in livestock which result in reduced production of meat and milk leading to economic losses [1]. There are numerous types of helmiths that infect both human and animals. However the most prevalent are the soil-transmitted helminths (*Ascaris lumbricoides, Trichuris trichiura, Ancylostoma duodenale, Enterobius vermicularis*) and Schistosome (*Schistosoma mansoni, S. haematobium, S. japonicum, S. intercalatum, S. mekongi*) [2]. These helminthes are common in the developing countries, especially in Sub-Saharan Africa [3]. One of the major challenges faced in the helminth endemic areas is the unavailability of effective vaccines against these helminths and the infections may be asymptomatic thus persisting in the host for long periods of time causing severe morbidity.

The ability of helminths to evade or even modulate the host's immune system serves in parasite protection [4]. This skewing of the immune response to a TH2-type response during a chronic infection has been shown to interfere with the antibody and cellular responses of certain available vaccines, as a number of these vaccines require an efficient TH1 response to be effective [5]. Reduced responses to vaccines observed in developing countries, where helminth are highly endemic, could be attributed to individuals harboring chronic

helminth infections [6, 7]. This review aims to explain the immunology of helminths and the consequences they have on the efficacy of various vaccines.

2. Methodology

The information used for this review was obtained through systematic searches in Pub Med, NCBI and references from published journal articles. These sources were selected as they provide access to over 5000 peer reviewed journals. The searching system contained specified keywords such as "Vaccines", "Helminths", and "Schistosomiasis".

3. The Parasites

Helminths are worm-like parasites that are divided into 3 groups; Trematodes, Cestodes and Nematodes. Trematodes and Cestodes are characterized by their flat bodies while the Nematodes have thin tube-like forms [8]. These worms infect a wide range of hosts, many of which are zoonotic [4, 9]. These parasites undergo a number of larval stages before developing into an adult. The life cycle starts with eggs being passed out in feaces, urine or sputum into the environment. The egg hatches into the larva which infects their intermediate host where it undergoes asexual reproduction. After this stage the parasite will be released and will infect the definitive host through faecal-oral, transdermal, vector-borne or predator-prey transmission [8]. Within this host, the parasite will feed on blood and will undergo sexual development to produce more eggs which are then released from the host [10]. Many of the parasites are destroyed by the host's non-specific and specific immune responses. The ability to mount an effective immune response against these parasites highly depends on the host's genetics, age, sex, diet and overall health.

4. Immunology of Helminth Infections

Helminths have a complex life cycle which often involves the larval stage infecting a mammalian host where it will mature and reproduce [11]. The different stages of the infection cause the host to mount different immune responses. The infective larva may penetrate the host's skin. As the parasite migrate through the host's tissues and travel to different organs such as the lungs, heart, liver and gut [12], [13], there will be an activation of immune cells, such as macrophages which induce the production of nitric oxide which is toxic to the parasite.

The immune response elicited by the host in the initial stages of the infection is dependent on the niche the parasite occupies. For instance Schistosoma and filarial worms, which are present in the host tissue, blood and lymphatics, would stimulates a strong TH1 immune response [12], [14]. This results in the release of proinflammatory cytokines such as IFN-γ, TNF-α, IL-6. Once eggs get deposited and get carried to the sinusoids of the liver. Antigens present on the egg surface, such as the Soluble Egg Antigen (SEA) present on Schistosoma eggs, are toxic and they interact with the dendritic cells causing a dramatic shift to a TH2 response [14]. This results in the release of anti-inflammatory cytokines such as IL-4, IL-5, IL-9, IL-10, and IL-13. These cytokines stimulate the B cells to proliferate to Plasma cells which produce antibodies. These specific antibodies such as IgG1, IgG4, IgM, IgD, IgA and IgE are produced against the parasite antigens [15]. Early in the infection, IgG4 antibodies are produced with low levels of IgE. This creates a 'modified Th-2 immune response'. As the infection persists, IgE production builds up creating a protective response against the parasite. [16]. Cytokines also activate the eosinophils and mast cells [11] which play a vital role in fibrosis and activation of Antibody-dependent cellular cytotoxicity (ADCC) resulting in the release of toxic mediators further contributing to the clearance of the infection [1].

Along with the TH2-response, the T regulatory cells produce IL-10 and TGF-β which down regulates the TH1 response, further enhancing the TH2 response. It has been indicated that the TH2 immune response serves to protect the host against severe egg induced morbidity [17]. IL-13, IL-10 and T regulatory cells plays a crucial role in the formation of the granuloma surrounding the eggs in the liver, as well as fibrosis [14, 18]. Granulomas that develop around the parasite, prevents further migration within the host tissue, and around the eggs protecting the surrounding hepatic tissues from their toxicity. Eventually the parasite or the eggs die and the granuloma resolves [11]. Helminths' ability to evade the host's immune system by skewing the immune response to a Th2 response, enables the parasites to survive in the host.

Gastrointestinal helminths, such as the cestodes, which spend the majority of their life cycle in the host's gut elicit a strong Th2-type immune response. This results in the production of an array of cytokines such as IL-4, IL-5, IL-13 and production of the IgE antibody which contribute to their expulsion from the host. Individuals who are infected repeatedly often show a mixed Th1/Th2 immune response which is characterized by high levels of IFN-γ, IL-5 and IL-13 [19].

A protective immunity against these parasites develops over time especially once the parasites begin to die either naturally or through treatment with antihelmithic drugs such as Praziquantel. Therefore elimination of the helminth infection through treatment may be aid in reversing the Th1-Th2 shift.

5. Effect of Helminths on Vaccine Efficacy

Vaccines are able to confer protective immunity by eliciting strong cellular and antibody responses. These induced immunity may provide protection for several years on a single immunization, or may require booster vaccination to maintain this protection [20]. Due to the immunomodulatory effects of helminth infections, individuals living in helminth endemic regions are at risk of reduced immune responses to vaccines especially if these vaccines rely on a strong TH1 immune

response. Several studies have shown that parasitic infections, such as chronic trematode, nematode and protozoan infections, impair the long-term responses of certain vaccines. While elimination of these helminth infections through antihelminthic treatment may be a cost-effective method for improving vaccine efficacy [21].

A comparison study involving mice infected with *S. mansoni* and those that were not infected were vaccinated with the BCG vaccine. The results showed that the mice infected with *S. mansoni* had significantly higher number of colony forming units of TB bacilli in their lungs thus they had reduced protection against Tuberculosis compared to those that were not infected. Splenocytes from infected mice produced lower levels of IFN-γ and nitric oxide when stimulated in vitro with Purified Protein Derivative (PPD) while stimulation with SEA and ConA resulted in the production of high levels of IL-4 and IL-5 [22]. An investigation on the effects of *Schistosoma mansoni* on the immunogenicity of the candidate TB vaccine MVA85A showed that there was no significant difference in IgG4 levels between the *S. mansoni* infected group and uninfected group. However there was increased cellular response as well as increased IFN-γ levels after immunization [23]. Peripheral blood mononuclear cells (PBMCs) obtained from individuals infected with helminths prior to receiving the BCG vaccine were shown to produce lower levels of IFN-γ and IL-12 cytokines compared to those collected from individuals who received anti-helminthic treatment prior to the BCG vaccination. The infected group also produced lower PBMCs when stimulated with the mycobacterial antigen compared with the treated group. Though, it was also shown that the helminth infected group had a high levels of TGF-β, IL-4 and IL-5 was produced when stimulated with PPD or ConA [24]. Another study by Elias et al. showed that elimination or reduction of the helminth infection using Albendazole treatment resulted in significantly improved T cell proliferation along with IFN-γ production [25].

Mice infected with *S. japonicum* were shown to have a reduced immune response to the Hepatitis B vaccine. This was indicated by low levels of anti-Hepatitis B antibodies as well as low production of certain cytokines such as IFN-γ and IL-2. The mice were then treated with Praziquantel (PZQ) resulting in a gradual increase of the anti-HB antibodies and the TH1/TH2 cytokine balance was restored. Significantly lower levels of hepatitis B surface antibodies after the first boost of the Hepatitis B vaccine has also been observed in clinical trials [26].

Mice infected with *Trichinella spiralis* have presented with lowered splenocyte proliferation responses when stimulated in vitro with the hepatitis B surface antigen. Lower levels of Anti-hepatitis B surface antigen antibodies, IFN-γ and IL-2 cytokines were also observed along with high levels of IL-4 and IL-5 cytokines. However reduced immune response was only seen in the enteric stage of the parasitic infection and not in the muscle stage. This is due to the production of TH-2 cytokines during the enteric stage which, in turn results in an insufficient Hepatitis-B antigen specific TH1 response [27], [28]. The muscle phase has a Th1/Th2 mixed response [29].

Schistosome infected individuals have similarly shown to have reduced immune responses to the tetanus toxoid (TT) vaccine [26]. The *S. mansoni* infected individuals who received the tetanus toxoid vaccine had significantly lower anti tetanus toxoid antibodies after vaccination and these levels decline faster than the control group hence indicating short lived vaccine induced protection and these individuals may require frequent boosters [30].

Previous studies have documented that maternal helminth infections may also have an impact on the vaccine induced immune responses of infants. For instance a group of children aged 13 months were enrolled in the ECUAVIDA birth cohort study where the mothers tested positive for helminth infections in their last trimester showed higher plasma IgA levels after receiving the oral polio and rotavirus vaccines compared to children with uninfected mothers. However there was no significant difference in IgG levels between these two groups [31]. Another study showed that infants from mothers infected with Schistosomiasis or filariasis showed a significant elevation of IgE, IL-4, IL-5 and IL-10 levels and lower levels of IFN-γ and IL-2 cytokines. The study concluded that maternal helminth infections reduced efficacy to the BCG vaccine in infants [32]. Mothers treated with a single dose of albendazole, to eliminate hookworm infections, have shown to be associated with infants with reduced T-helper 2 cytokine responses to tetanus toxoid vaccine and increased IFN-γ response to mycobacterium antigen [33].

It has been reported that elimination of worms by praziquantel treatment in mice prior to receiving the HIV-1 C vaccine resulted in restored T cell responses and significantly increased levels of IFN-γ produced by splenocytes stimulated with ConA compared to the untreated mice. It was indicated that restoration of HIV-1C vaccine specific T cell responses after antihelminthic treatment was time dependent [34].

A number of studies have been done to investigate whether treatment of helminth infections prior to vaccinations may improve the vaccine immunogenicity. A clinical trial involving antihelminthic treatment of children aged between 6-10 years one month prior to immunization with the influenza vaccine showed that the memory B cell response was slightly elevated in the group that received the albendazole antihelmith treatment compared to the placebo group. However there was no significant difference between these two groups, thus it was concluded that antihelminthic treatment had no significant effect on the influenza vaccine induce immune responses [21]. This same effect was seen in a study involving the meningococcal and cholera vaccine which showed that the B-cell response and the antibody production was not significantly different between the subjects with the helminth infection and those that received the anti-helminth treatment [35].

Numerous studies have concluded that vaccine impairment could be due to helminth infection shifting the balance of the immune system from a TH1 to the TH2 type while a number vaccine induced immunity rely on the TH1 responses [36]. Studies have shown that early anti-parasite treatment can

prevent immunomodulation caused by these parasite antigens thereby improving vaccine efficacy [7].

6. Conclusion

The helminths' ability to persist in a host and their immunomodulatory effects still remains a great concern in vaccine efficacy and development of new vaccines in endemic regions. There is growing evidence that the immunomodulation during helminth infection may interfere with immune responses of vaccines. However it seems likely that treatment of these helminth infection may improve vaccine immunogenicity. Therefore if treatment and control measures are put in place in helminth endemic regions, the possibility of lowered vaccine efficacy may not be a concern. Few studies have been conducted to determine the effects these helminths have on available vaccines. Insufficient studies have been conducted under controlled experimental conditions involving animal models therefore there is a need for further studies, preferably using non-primate primates due to their anatomical, physiological and genetic similarities. This can be conducted to garner more information on how helminth infections affect vaccine induced immune responses.

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