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Review article

The double-sided effects of *Mycobacterium bovis* bacillus Calmette-Guérin vaccine on various parasite infections – current data and future prospects

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ABSTRACT. Bacillus Calmette–Guérin (BCG), a live attenuated strain derived from an isolate of *Mycobacterium bovis*, is one of the childhood vaccinations widely used against tuberculosis (TB). In addition to its effects on mycobacterial diseases, the information has shown the protection effect of BCG in helminthic diseases. In the current review, the role of BCG vaccine in non-specific protection helminthic infection is reviewed. In human alveolar echinococcosis (AE), treatment with BCG enhances host's innate immune response against the parasite via the number and activation of monocytes. In cysticercosis, despite the enhancement of Th1-biased immune responses by coadministration of rcC1 plus BCG-DNA, the level of induced protection did not increase compared to immunization with rcC1 antigen alone. Also, pretreatment of mice with live BCG vaccine induced a high level of protection against subsequent parasite infection with *Taenia taeniaeformis*. The reduction of the parasite burden in mice infected with *Mesocestoides corti* that received two doses of BCG post-infection demonstrated the therapeutic effect of BCG. The protective potential of the schistosomula/BCG vaccine against *Schistosoma japonicum* in sheep study showed a reduction in the number of adult worms and mean faecal egg counts post-challenge. In trichinellosis, BCG can induce hyperplasia of the reticuloendothelial system and activation of macrophages in mice. Therefore, these data revealed that BCG vaccination can exert non-specific protective effects for the prevention of diseases other than tuberculosis. Medicinal doses of BCG may be considered a new approach to the treatment of helminth infections.

Keywords: *Mycobacterium bovis* bacillus Calmette-Guérin, helminthic infections, alveolar echinococcosis, taeniosis, schistosomosis, trichinellosis

Introduction

Tuberculosis (TB) is a bacterial airborne infectious disease caused by *Mycobacterium tuberculosis* that in most cases affect the lungs at first, but sometimes spreads from the lungs to other parts of the body. TB may be regarded in two groups: active disease or latent infection. In latent infection, TB bacteria can live in the body without any symptoms transmissible. Whereas, people with TB disease have symptoms such as fever, fatigue, and weight loss and they are also able to spread the bacteria to others [1].

Bacillus Calmette-Guérin (BCG), a live attenuated strain derived from an isolate of *Mycobacterium bovis*, is one of the childhood vaccinations widely used against disseminated forms of TB including TB meningitis and miliary TB. BCG is presently one of the most widely used live attenuated vaccines in the world; near 100 million newborn receive it every year. It is also claimed that BCG vaccination has documented

protective effects in improving partial survival in high-TB-burden and low-income countries [2].

However, there is much on against tuberculosis alone [3–5]. In the past four decades, BCG is also used as an adjuvant therapy for patients with non-muscle-invasive bladder tumor [6].

Resistance and tolerance are two key stra-variation (ranges from 0 to 80%) of its efficacy against TB disease in adults. The possible reasons could be geographic variation and previous environmental exposures with endemic mycobacteria [2]. As mixing of cases and controls are unlikely in cases of meningitis and miliary tuberculosis but is more possible in other clinical forms of this infection, it is an important reason for calculation of significantly lower protective effect of BCG vaccination in case-control studies. Interestingly, soon after its introduction in the 1920s, several studies showed that the BCG vaccine reduces infant mortality risk [7,8], and this too big effect could not to be explained by protective strategies employed by the host immune response to defend against helminth parasites. The studies have demonstrated that both T helper cell type 1 (Thl) and Th2 have the role of potential protective immunity against human helminth infections [9,10].

A combination of both Thl and Th2 responses may be important during early parasite infection particularly against tissue invasive larvae such as ascariosis, strongyloidosis, and hookworm as observed for filarial parasite infections [11], while Th2 may provide an defense mechanism for reducing the number of parasites during chronic established parasite infections [12] and in mediating parasite expulsion of adult worms from the intestinal lumen [10].

There is accumulating evidence that BCG vaccination can induce trained immunity-based: monocytes from BCG-vaccinated individuals compared with monocytes from individuals no vaccinated with BCG show expressed higher levels of cell surface markers and release higher levels of inflammatory cytokines, IL-1β, IL-6, IFN-γ and TNF, in immune response to infection with various pathogens [13,14].

The heterologous immune response towards an improved response against other pathogens in addition target microorganism was first reported by Mackaness studies (who called it “non-specific defense”) in the 1960s, demonstrating that BCG is capable to induce heterologous protection against a wide range of organisms, including viruses, bacteria, fungi, and parasites [13–15].

In this study, we are now looking to review the hypothesis that non-specific protection engendered by BCG could provide protection against parasite diseases. A summary of studies evaluating the protection effect of BCG in worm parasites are shown in Table 1.

Human alveolar echinococcosis

Human alveolar echinococcosis (AE) is caused by the larval stage of *Echinococcus multilocularis* (*E. multilocularis*) tapeworm, a dangerous parasitic zoonosis with a wide distribution in the Northern Hemisphere [24,25]. Humans as an accidental dead-end intermediate host for *E. multilocularis* can be infected through close contact with canids, a greater risk factor, or by ingestion of eggs through contaminated water and food [26].

Definitive hosts harbour adult worms in the small intestine, usually without obvious clinical disease, while cyst-like lesions form in the organs of intermediate hosts [25]. Protection against AE is associated with adaptive and innate immune responses. Innate immunity, which is the first line of defense against various pathogens, can help defend against AE [27]. In the next stage, an adaptive immune response comes into action and the direction toward each of the Th1 and Th2 immune responses determines the limitation or progression of the disease [28]. Th2-biased immune response in the chronic stage of AE plays a detrimental role associated with the disease progression, while Th1-dominated immunity induces protective immunity [28,29].

Various studies have shown that BCG has anti-tumor activity and can cause the regression and removal of tumors by stimulating appropriate immune responses [30–33]. Based on these observations, researchers have investigated the effects of BCG on various parasite infections [16–23].

The protective effects of BCG against unrelated infections such as parasite infections can be attributed to the activation of the innate immune system. This non-specific protection forms a memory of previous encounters with pathogens, which trigger an enhanced immune response after reinfection with unrelated pathogens [34–36].

The protection created by an unrelated pathogen could be considered a suitable strategy to improve the treatment and prevention of various parasite

infections, especially AE, but it requires much research in the future to obtain suitable therapy results. Due to the lack of definitive and effective treatment methods for AE, the protective effects observed by BCG could have a very promising perspective.

A study conducted by Reuben et al. [16] indicated the immunoprophylactic effect of BCG in AE. To

Table 1. Summary of studies evaluated the role of BCG in helminthic infections

Parasite	Study design	Methods	Important findings	References
E. multilocularis	Experimental study in a rat model: IP injection of one brood capsule of *E. multilocularis* to cotton rats vaccinated with various doses of BCG (10^1 to 10^7 CFU).	Determination of the level of stimulation of the cellular response by BCG two weeks after treatment. Determination of the minimum effective prophylactic dose of DBCG against *E. multilocularis*. Harvesting and staining of the peritoneal exudate cells	Controlling AE parasite infection with a dose of 10^3 CFU of BCG as a relatively low prophylactic dose providing complete protection without forming macroscopic granulomatous lesions. Protective effect attributed to a significant increase in the number of peritoneal monocytes.	[16]
E. multilocularis	Experimental study in a rat model: inoculation of one brood capsule of *E. multilocularis* to cotton rats vaccinated with nonliving BCG cell walls.	Determination of the level of stimulation of the cellular response by BCG cell walls two weeks after treatment. Determination of the effect of treatment with BCG cell walls on establishment of *E. multilocularis*. Examination of acid phosphatase activity.	Complete protection against AE parasite infection by treatment with nonliving BCG cell walls. Protective effect attributed to a significant increase in the numbers of both peritoneal monocytes and granulocytes.	[17]
T. solium	Experimental study in a pig model: establishment of *T. solium* parasite infection by parasite eggs in pigs vaccinated with rcC1 plus BCG-DNA.	Lymphocyte proliferation assay. Cytokine assays (IFN-γ and IL-4). Antibody assay (IgG1 and IgG2). Protection assessment.	Despite the enhancement of Th1-biased immune responses by coadministration of rcC1 plus BCG-DNA, the level of induced protection did not increase compared to immunization with rcC1 antigen alone. The rcC1 antigen alone induced a Th1-biased immune response, whereas coadministration of rcC1 plus BCG-DNA enhanced levels of IFN-γ, IgG2, the number of CD8+, and peripheral blood mononuclear cells.	[18]
T. taeniaeformis	Experimental study in a mouse model: establishment of *T. taeniaeformis* parasite infection by parasite eggs in mice vaccinated with 0live BCG (IP or SC)	Examining the nature and number of parasite foci in the liver. The viability assessment of strobilocerci. Histological examination of the spleen.	A high level of protection against subsequent parasite infection with *T. taeniaeformis*. Protective effect attributed to the recruitment of T cells in the spleen and the subsequent recruitment and activation of monocytes in the liver. The IP route was more effective than the subcutaneous route in reducing the viability of the established parasite in the liver	[19]

Table 1. Summary of studies evaluated the role of BCG in helminthic infections

Parasite	Study design	Methods	Important findings	References
M. corti	Experimental study in a mouse model: treatment of one or two therapeutic doses of BCG (4×10^7) in mice infected with *M. corti* by IP route of tetrathyridia.	Using cell transfers to study the specificity of the resistance induced by therapeutic BCG. Determination of parasite burdens.	The reduction of the parasite burden in mice infected with *M. corti* that received two doses of BCG post-infection. These findings probably reflect the vigorous cellular activity developed during secondary responses to BCG.	[20]
S. japonicum	Experimental study in a sheep model: percutaneously challenging with newly shed cercariae of *S. japonicum* to sheep vaccinated with the freeze/thaw schistosomula/BCG.	Counting mean faecal egg per gram 6–10 weeks post-challenge. Counting male and female adult worms after perfusion. Conducting western blotting and enzyme-linked immunosorbent assay (ELISA) for the detection of circulating antibody.	A reduction in the number of adult worms and mean fecal egg counts post-challenge. A specific antibody was also detected in vaccinated groups against the crude antigen of adult worms.	[21]
S. mansoni	Experimental study *in vitro*: the lethal effect of BCG-activated macrophages on *S. mansoni* schistosomula *in vitro.*	Obtaining activated macrophage monolayers from BCG-treated mice. Incubating schistosomula obtained from mice at 37°C with activated macrophage monolayers. Injecting organisms after incubation with activated macrophages IP into groups of normal mice to verify that dye uptake represents actual damage to schistosomula. Evaluating the schistosomicidal effect of the culture supernatants.	A significant effect of mouse-activated macrophages in killing *S. mansoni* schistosomula through soluble mediators.	[22]
T. spiralis	Experimental study in a mouse model: establishment of *T. spiralis* parasite infection by parasite larvae in mice vaccinated with attenuated BCG.	Determination of intestinal worm burdens. Determination of muscle worm burdens. Examination of the pathology of the small bowel.	A delay in the expulsion of adult worms from the intestine, a reduction in the severity of partial villous atrophy induced in the small intestine and an enhancement in non-specific resistance to the systemic larval phase. Directing the immune responses in an orientation that favors the adult worms and delays their elimination	[23]

Explanations: BCG: Bacille (bacillus) Calmette-Guérin, IP: intraperitoneally, CFU: colony forming units, SC: subcutaneous

assay the level of stimulation induced by BCG, 1-ml doses 10^1 to 10^7 colony-forming units (CFU) of BCG in PBS were each injected intraperitoneally (IP) into four cotton rats (treated group); four cotton rats as control group received with IP rout 1 ml of PBS. Two weeks later, half of the animals from both groups

were anesthetized, and a brood capsule was surgically implanted into the peritoneal cavity of each animal. Forty-two days after inoculation of the parasite, the weights of the parasite cysts were obtained for all animals. In addition, differential leukocyte counts were obtained by counting 1,000 leukocytes on each stained cover slip of small incision in the abdominal wall of the exsanguinated animals. A dose of 10^3 CFU of BCG as a relatively low prophylactic dose effectively controlled experimental AE parasite infection in cotton rats and provided complete protection without forming macroscopic granulomatous lesions. The assessment of the cellular response two weeks after treatment with BCG showed that the protective effect can be attributed to a significant increase in the number of peritoneal monocytes [16].

In another study, Reuben et al. [17] assayed protection of cotton rats against experimental *E. multilocularis* infections with BCG cell walls. Treated group (including 12 cotton rats) was treated with a single, 0.1 ml IP injection containing 150 μg of BCGCW, emulsified in mineral oil, Tween-80 and saline, and animals of control group received oil, Tween-80 and saline alone. After two weeks, half of the animals in each group were anesthesized, and a brood capsule was surgically implanted into the peritoneal cavity of each animal. Forty-two days after inoculation of the parasite, all the test and control animals were exsanguinated and followed the weights of the parasite cysts were obtained. A cover-slip smear obtained from the peritoneal exudate of each animal was stained for acid phosphatase activity, followed by 500 monocytes were counted on each stained smear, and the total "active" monocyte population was calculated from the percentage of cells possessing acid phosphatase activity.

The assessment of leukocytes two weeks after treatment with BCG cell walls showed that the protective effect can be attributed to a significant increase in the numbers of both peritoneal monocytes and granulocytes. The findings suggested that protection against AE was associated with an increase in the number and activation of monocytes, as judged by acid phosphatase activity [17].

The results of these studies showed that BCG is effective in protecting cotton rats from infections with *E. multilocularis*, without the concomitant formation of macroscopic granulomatous lesions.

Taeniosis/cysticercosis

Taenia solium

Taenia solium (*T. solium*) is medically one of the most important cestodes because it affects the human nervous system and causes neurocysticercosis. *T. solium* has a complex life cycle with humans as the only definitive host and both humans and pigs as intermediate hosts [37]. Therefore, humans can harbor both adult worms and larval forms (cysticerci) [37]. In humans, parasite infection with adult worms occurs by eating undercooked or raw pork meat containing cysticerci, and cysticercus parasite infection is the result of accidental ingestion of eggs *T. solium* through the oral-faecal route and autoinfection [38,39].

Experimental studies show that active neurocysticercosis is associated with the stimulation of Th2 immune responses while dying parasites induce granulomatous inflammation and Th1-dominated immunity [40].

An experimental study investigated whether genomic DNA derived from BCG (BCG-DNA) could be used as an effective adjuvant to enhance the immunogenicity against pig cysticercosis when coadministered with recombinant cC1 antigen (rcC1) [18]. Twenty-four 2-month-old piglets were randomly allocated into four groups (each group contains 6 pigs). These pigs were intramuscularly injected twice (3-week interval) with one of the following formulations: (1) rcC1 (100 μg for each); (2) rcC1 plus 2 mg of CpG-ODN; (3) rcC1 plus 2 mg of BCG-DNA; (4) PBS control. Four weeks after the last immunization, animals were infected with *T. solium* eggs. The findings indicated that despite the enhancement of Th1-biased immune responses by coadministration of rcC1 plus BCG-DNA, the level of induced protection did not increase compared to immunization with rcC1 antigen alone. The rcC1 antigen alone induced a Th1-biased immune response, whereas co-administration of rcC1 plus BCG-DNA enhanced levels of IFN-γ, IgG2, the number of CD8+, and peripheral blood mononuclear cells [18].

Thus, the results in this study showed that the BCG-DNA may play a significant role as an effective and economic adjuvant in candidate vaccine against cysticercosis of pigs.

Taenia taeniaeformis

Taenia taeniaeformis (*T. taeniaeformis*) is a common cestode parasite of cats, as the definitive

host, that infects rodents and humans as the intermediate hosts, containing the larval stage of the parasite (*cysticercus fasciolaris*) [41–43]. Transmission to the intermediate host occurs through eating contaminated water or food with eggs of the parasite [44].

In a study by Thompson et al. [19], was assessed the effects of prior treatment of mice with live BCG vaccine on subsequent oral infection with oncopheres of *Taenia taeniaeformis*. They used 10 mice male, 6-week-old inbred C3H/OH, for each experimental group and control group. BCG was inoculated IP or subcutaneously into mice 14 days before eggs challenge and following the effects of two dose levels of BCG were assessed. Fourteen days after BCG inoculation, all mice received 300 eggs of *T. taeniaeformis* orally. Sixty days after parasite challenge were necropsied all mice. Finally, the nature and number of parasite in livers were carefully examined and recorded. The contents of all cystic foci were examined and the contained viability strobilocerci assessed.

BCG does this protection by preventing the initial establishment of the parasite in the liver and killing parasites living in this organ. According to the data of this study, the effective death of parasites living in the liver is influenced by the recruitment of T cells in the spleen and the subsequent recruitment and activation of monocytes in the liver.

According to the data of this study, this protection was dependent on both the route and the dose of BCG administration. The IP route was more effective than the subcutaneous route in reducing the viability of the established parasite in the liver. In addition, the findings showed more dose of BCG generate a high level of neutralizing antibodies for reducing parasite foci in liver of treated groups. For example, with same route, IP, with dose BCG 40×10^6 was reported number of parasite foci in liver 20.7±2.8, in contrast with dose BCG 20×10^6 was observed number of parasite foci in liver 33.4±3.5 [19]. It has been shown that antibodies play an important role in protective immunity against *T. taeniaeformis* and BCG may be involved as an adjuvant in accelerating the production of antibodies [19].

Findings of present showed IP route and high dose of BCG induces protection against *T. taeniaeformis*, *T. solium*. Whereas, further studies are needed to elucidate the nature of the mechanisms involved in protection induced by BCG against *T. taeniaeformis*, *T. solium*, and other parasitic worms.

Mesocestoides corti

Mesocestoides corti (*M. corti*) is a parasitic cestode of mice that is transmitted through the oral-faecal route and involves three subsequent hosts in its life cycle [45,46]. Definitive hosts (e.g. carnivores and humans) harbour adult worms in the small intestine, excreting gravid proglottids with eggs containing oncospheres into the environment [46]. Arthropods, as the first intermediate hosts, develop the cysticercoid in their bodies by ingesting the eggs, which transform into tetrathyridium larvae in the second intermediate hosts (small mammals, birds, amphibians, and reptiles) [46]. In the mammalian host, tetrathyridium proliferates asexually in the peritoneal cavity, liver, and other organs [47,48].

M. corti tetrathyridium, like many parasitic worms, induces Th2-biased immune responses that play a protective role and prevent parasite colonization [46,49].

In a study conducted by White et al. [20], male CBA/H mice 6-8 weeks of age were used as animal model (each group contains 9 or 10 mouse) and mice infected with *T. crassiceps* (20 cysticerci) or *M. corti* (50 tetrathyridia) by the IP route. These infections were left untreated (control group) or treated with one dose BCG (4×10^7 CFU on days I4 post-infection) and two dose BCG (each of 4×10^7 CFU on days I4 and 28 post-infection). Two doses BCG reduced significantly lower parasite burdens in total the liver and peritoneal cavity of mice (362±69) compared with untreated controls (1725±160) and mice treated with one dose BCG (1348±174) [20]. These findings probably reflect the vigorous cellular activity developed during secondary responses to BCG.

Considering the use of *M. corti* as an ideal laboratory model for studying medically important cestodes, the protection provided by BCG could be considered a landmark for future therapeutic research of these cestode parasite infections. In conclusion, findings observed in the present study suggest that the effector cell populations induced following BCG immunotherapy might be candidates for protection against *M. corti*.

Schistosomes

Schistosomosis is a common tropical intravascular disease caused by trematode worms of the genus *Schistosoma* [50,51]. In the life cycle of the parasite, surface waters are contaminated by faeces

or urine containing eggs, and the presence of specific freshwater snails as an intermediate host causes the production of cercariae that are infectious for humans [50]. Symptoms of acute parasite infection commonly seen in people traveling to endemic areas for the first time include fever, malaise, fatigue, myalgia, diarrhea, cough, haematuria (*S. haematobium*), and right upper quadrant pain [52]. In the chronic stage of parasite infection, due to the persistent responses of the immune system to the eggs trapped in tissues, symptoms such as hepatosplenic inflammation, intestinal disease, and liver fibrosis (*S. mansoni* and *S. japonicum*) or inflammatory and obstructive disease in the urinary system (*S. haematobium*) may be observed [53,54].

In the acute stage of parasite infection, the levels of TNF, IL-1, and IL-6 cytokines increase, which reflects a dominant Th1 immune response [55,56]. As the course of the disease progresses, the Th2-biased immunity is enhanced and reduces the production and functions of the pro-inflammatory mediators with the effective role of IL-10 [55,57]. Unregulated production of the cytokine IL-13 (related to Th2 immune responses) can result in extensive liver fibrosis [58,59]. On the other hand, the reduction of Th2 immune responses, especially IL-4, leads to tissue damage and host mortality due to the predominance of Th1 proinflammatory responses [60,61]. Therefore, the effective protection of the host depends on a suitable balanced Th response that can prevent fatal acute disease and minimize intense complications during the chronic stage of parasite infection.

Xu et al. [21] investigated the protective potential of the freeze/thaw schistosomula/BCG vaccine against *S. japonicum* in sheep. Groups of ten sheep in each group were studied as follows: Group I: 2×F/T 30 000 schistosomula + BCG 3×10^8 organisms, with a 2-week interval between vaccinations; Group II: 3 X F/T 20 000 schistosomula + BCG$\times10^8$, with 4-week interval; Group III: control (not vaccinated). All sheep were challenged percutaneously with 500 normal, newly cercariae. Mean faecal egg counts per gram were assayed 6–10 weeks post-challenge. One week after the last faecal egg count, sheep of groups were killed and perfused and following adult worms were collected and counted. Tissue samples such as liver and large intestine were taken from identical sites of equivalent sizes from the animals for egg count. Mean faecal egg counts reduced statistically significant 83.38% ($P<0.005$) in Group II in contrast control group. One week after the last faecal count, adult worm reductions were obtained 40.36% ($P<0.05$) in Group I and 37.26% ($P<0.025$) in Group II. A specific antibody was also detected in vaccinated groups against the crude antigen of adult worms [21]. The findings presented that resistance to *S. japonicum* infection in the sheep was induced specifically by a variety of immunostimulants such as BCG. Thus, the observed favorable protective effects of the BCG vaccine show that it could have the perspective of becoming a practically effective vaccine.

In another study, the lethal effect of BCG-activated macrophages on *S. mansoni* schistosomula was investigated *in vitro*. The findings indicated a significant effect of mouse-activated macrophages in killing *S. mansoni* schistosomula through soluble mediators [22].

Considering the above, there are still many uncertainties about how BCG works and how it causes a protective effect, which should be focused on in the future.

Trichinella spiralis

Trichinella spiralis (*T. spiralis*), the most common cause of human trichinellosis, is a food-borne zoonotic nematode that infects a wide range of mammalian hosts [62,63] .*T. spiralis* completes its life cycle in a single host and its larvae establish chronic parasite infections in the skeletal muscle cells of immunocompetent hosts [62,64]. The parasite's life cycle begins when a new host eats meat containing first-stage muscle larvae. The severity of disease symptoms depends on the number of parasites ingested and includes myositis, myocarditis, and encephalitis [62,65].

It has been shown, mainly in a mouse model, that during intestinal phase of *T. spiralis* infection, Th1 immune response dominates and contributes to the elimination of the parasites [66]. During the muscle phase, Th2 response is induced, which alleviates tissue damage and may enhance tissue repair [67]. Mice experimentally infected with *T. spiralis* also induce a strong response from T-regulatory (Treg), characterized by increase in $CD4^+CD25^+Foxp3^+$ cells and which, in fact, is accompanied by high levels of IL-10 and TGF-β [68]. There are also available data from other experiments, with pigs as an animal model. In pigs experimentally infected with *T. spiralis*, an increase of B lymphocytes,

$TCD3^+$, $CD4^+$, T regs and Th17, and a decrease of $TCD8^+$ are usually observed. Some experiments also shown that in pigs experimentally infected with *T. spiralis*, Th2 response is mainly induced and Treg which suppresses Th1 response. It was also shown that in pigs infected with *T. spiralis*, an increase of the expression of IL-10 and IFN-γ in the intestinal mucosa and IL-6 and IL12 in the spleen is observed, and this may indicate a mixed Th1/Th2 response, with a predominance of type two [69].

In an experimental study to investigate the protective effects of BCG, 2×10^7 CFU of attenuated BCG were given one week before *T. spiralis* parasite infection [23]. One week after immunization, treated and un-treated mice (8 mice in each group) were infected with 300 larvae of *T. spiralis*. Then, intestinal worm burdens and the numbers of muscle larvae were measured 14 days and 4–6 weeks after challenge, respectively. In addition, one week and 4 days after challenge respectively, adult worm's fecundity and crypt ratio of intestinal biopsies from both mice treated and un-treated groups were examined.

The immunization of BCG produced a number of changes in the host-parasite relationship in murine trichinellosis. The most striking alterations were a delay in the expulsion of adult worms from the intestine, reduced numbers of muscle larvae and a reduction in the severity of partial villous atrophy induced in the small intestine [23].

Prior exposure to *T. spiralis*, either by infection or immunization with using antigenic fractions, facilitates the expulsion of worms from the gut [23] and reduces their fecundity [70]. In contrast, the injection of BCG in nonspecific delays the expulsion of worms and has no effect on their fecundity. Since the persisting adult worms in BCG-treated mice were fecund but the numbers of larvae recovered from the muscles did not increase despite more persistence of adult worms.

This is suggested that the systemic migration of these larvae or their maturation in the muscles was impaired in BCG-treated mice. This increased resistance to the systemic phase of trichinosis was confirmed after directly into the veins injection of newborn larvae in mice.

This study, like other research, confirms the protective effects of BCG against parasitic infectious agents, but obtaining more practical findings requires more focus in the future.

In conclusion, this review summarizes the pathophysiology of helminth infections and considers the possible protective role of BCG and the mechanisms involved. It is hoped that this review will motivate further research into the effects of BCG against parasite infections, which affect hundreds of millions of people in developing countries every year.

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