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Research Article

Control of Zoonotic Parasitic Cestode (*Taenia solium*): Sustainability Assessment of Potential Vaccines

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ABSTRACT

Tanenia solium is a zoonotic parasitic cestode that causes taeniasis and cysticercosis in pigs and humans respectively. Taeniasis/cysticercosis is a serious endemic disease in most developing countries and affects both human health and the economy. Different physical and immunodiagnostic techniques developed have been used to reveal the parasite in the host. On the other hand, anthelminthic drugs have been used for many years in controlling the parasite but with less impact. However, vaccines developed from antigen oncospheres named TSOL18, TSOL45-1A and TSOL16 have shown positive results in controlling the parasite under experimental conditions. The recently developed vaccine of TSOL18 antigen has shown nearly complete protection against *T. solium* in pigs. Similarly, the vaccine developed from synthetic peptides (S3Pvac) has shown promising results in the elimination of the parasite. Furthermore, the combination of vaccines and chemotherapy has been used to control the parasite in highly endemic areas. However, despite having the aforementioned interventions, none has been documented to control the parasite at a sustainable level. This calls for further research work to find out the most sustainable means of controlling the parasite. A critical review based on the most recent literature on vaccines that may serve to control *T. solium* in pigs was carried out. The main focus was on an overview of different types of vaccines developed and their impact on controlling *T. solium*. By considering the pros and cons of different interventions developed, we can come up with the most efficient and sustainable method of eradicating *T. solium*.

Keywords: *Taenia solium*; Parasite; Taeniasis; Transmission; Infection

INTRODUCTION

Tanenia solium is a zoonotic parasitic cestode that infects both pigs and humans. The life cycle of *T. solium* involves humans as a definitive host and pigs as an intermediate host (Figure 1). The adult tapeworm lives in the small intestine of humans where they burrow and attach through their scolex. The adult tapeworm may grow up to 7 m in length and produce several proglottids (segments) that are hermaphrodite. The proglottids undergo continuous cell differentiation to become gravid proglottids which detach from the tapeworm after maturation. The gravid proglottids are full of fertilized eggs that are released to the environment after defecation where they can stay for several months. Each egg develops into a hexacanth embryo (oncosphere) followed by the metacestode (larva) stage, a process which takes about 8 weeks. *T. solium* oncosphere has six hooks that enable penetration and attachment to the intestinal mucosa for further development.

Pigs acquire the infection by ingesting *T. solium* eggs or gravid proglottids when exposed to the contaminated environment. Humans may get infected when ingesting either undercooked or raw pork of an infected pig. Also, autoinfection of humans may occur accidentally *via* faecal-oral contamination, when *T. solium* eggs or proglottids enter the body and travel either to the Central Nervous System (CNS), muscles, subcutaneous tissue or eyes. When the parasite's larvae invade the CNS, it may develop Neurocysticercosis (NCC), while infection of the muscles, subcutaneous tissues and eyes may lead to taeniasis [1,2].

Taeniasis/cysticercosis is a serious endemic disease in most developing countries and affects both human health and economy. The infection in humans can be caused by either *T. solium*, Taenia saginata or T. saginata asiatica. But only the infection with adult *T. solium* leads to NCC. NCC is regarded as the most common parasitic infection of the CNS and also the most frequent cause of acquired epilepsy in developing countries. Recent studies carried out showed that successful vaccination of pigs against *T. solium* could be the appropriate way of preventing transmission of the parasite to humans [3,4].

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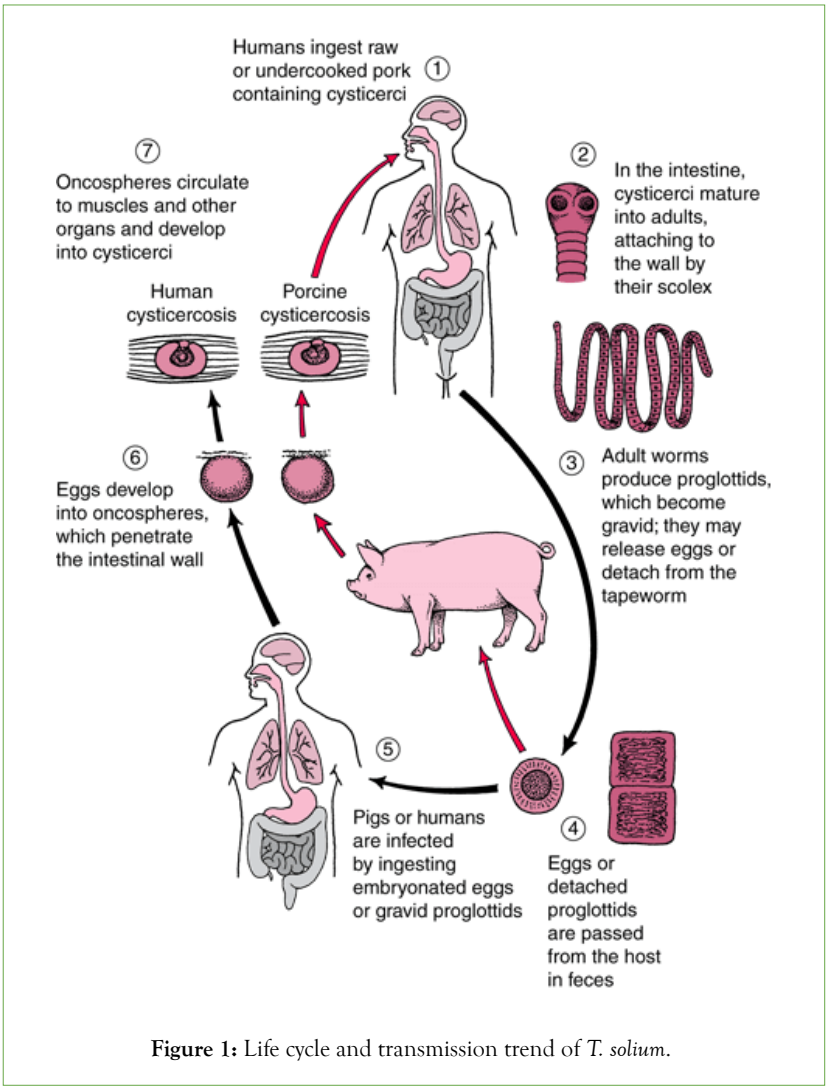

Figure 1: Life cycle and transmission trend of *T. solium*.

Different approaches to developing vaccines against the parasite have been tried but none of these has been documented to control the disease at a sustainable level [5]. This entails that more research should be conducted in order to find out a sustainable means of controlling the parasite.

By definition, a vaccine is a term used to describe an antigenic substance prepared either from the causative agent of a disease or from a synthetic substitutes for the purpose of controlling a single or several diseases. The first vaccine was developed to control smallpox in China and India over the past four centuries [6]. On the other hand, vaccines against *T. solium* transmission began since the last century. These vaccines have been developed from defined proteins, synthetic peptides, recombinant phages and plasmid DNA [7,8]. Two types of potential vaccines for use in pigs were developed, these includes synthetic peptides vaccine (S3Pvac) and protective antigens cloned from *T. solium* [9,10]. The objective of this paper is to review the literature on vaccines that may serve to control *T. solium* in pigs.

METHODOLOGY

A critical literature review that covered the most recent published literature from 2008 onward was conducted. The main focus was on the overview of different types of vaccines developed and their impact in controlling *T. solium*. On the other hand, different diagnostic techniques to reveal the parasite and other control measures were discussed. By considering the pros and cons of different interventions developed we can come up with the most efficient and sustainable method of eradicating *T. solium* in both the definitive and intermediate host.

Taenia solium: A zoonotic parasitic worm of pig and humans

The pork tapeworm (*T. solium*) is a cyclophyllid cestode belonging to the family Taenidae and phylum Platyhelminthes. The adult *T. solium* lives in the intestines of humans, where they attach to the intestinal walls by their scolex and release proglottids and/or thousands of eggs to the environment when the host defecates [11]. Pigs ingest the gravid proglottid or eggs with oncospheres which develops into metacestode, a process which takes about 8 weeks. Humans are considered to be the most important carrier of the parasite from one area/country to another due to immigration and international travelling. This leads to increased incidence of NCC and taeniasis worldwide. NCC contributes to about 30%-40% of the cases of epilepsy and seizures in most endemic regions [12,13]. Based on these findings, *T. solium* cysticercosis is now considered to be among the most important re-emerging zoonotic diseases of public health in the world that needs reliable diagnostic methods and control measures [4,9,10].

Diagnosis

General diagnosis of *Taenia solium*: The most common diagnostic methods in humans involve tracing the clinical history of the patients whether they have observed *T. solium* proglottid released in the faeces. Also, stool microscopy is conducted to reveal the parasite eggs [14]. These diagnostic techniques are insufficient since it is not always possible to differentiate the *T. solium* proglottids from other parasites and also, the discharge of the proglottids from the infected host does not occur daily.

Another common diagnostic method used for detection of the cysticerci in pigs is by post-mortem examination in the carcass muscles, heart and tongue. However, antemortem diagnosis of the parasite in live pigs is also possible by palpation of the tongue to examine the presence of cysticerci. Also, it involves faecal sample examination and tracing the clinical history of the animal whether they have expelled the *T. solium* proglottids [1,10]. These diagnostic techniques may not be undertaken efficiently in most rural areas due to lack of or insufficient awareness among farmers on the parasite, and lack of animal health practitioners.

Immunodiagnosis of *T. solium* taeniasis/cysticercosis: Immunodiagnosis is based on the antibody-antigen reactions in the blood serum extracted from an infected individual. Immunodiagnosis of taeniasis and cysticercosis is the best alternative when compared to physical examination and stool diagnosis techniques. This is because the immunodiagnosis techniques are highly sensitive even when parasite burden is low [15]. Recent studies show that there are differences in genetic diversity of *T. solium* cysts isolated from naturally infected pigs, either raised from the same or different geographical regions. The differences in genetic diversity have effects on antigenic profiles of vesicular fluids extracted from individual *T. solium* cysts [11]. When *T. solium* infects either a pig or human, the host body releases a specific antibody that can be detected in blood, saliva, tears or Cerebral Spinal Fluid (CSF) in the case of CCN [16]. Currently, different advanced immunodiagnostic techniques are used for detection of the parasite. These techniques include antibody-detection, antigen-detection and copro-antigen detection methods [3,10].

Antibody-detection technique involves the use of Enzyme Immuno Transfer Blot (EITB) assay for detection of anti-parasite antibodies in serum. Antigen-detection technique involves the use of Enzyme Linked Immunosorbent Assays (ELISAs) for detection of the parasite's antigen in body fluids [17]. The monoclonal antibodies based, ELISA is a reliable tool for assessing the response to antiparasitic treatment in pigs as well as for monitoring the efficacy of the antiparasitic treatment of NCC in humans [18]. Another method, coproantigen-detection technique involve detection of antigens found in faeces to diagnose *T. solium* cysticercosis. The technique involves the use of Copro-Antigen Enzyme-Linked Immunosorbent Assay (CoAg-ELISA) for detection of the parasite in faeces. This method is considered to be the best sensitive diagnostic technique for detection of specific *T. solium* antigens in the stool [9]. However, CoAG-ELISA technique has failed to detect brain cysts and thus limits its use to only stool diagnosis [19]. Despite having the above-mentioned diagnostic techniques, eradication of the parasite in most developing countries is still not achieved. Most of the serological diagnostic methods are expensive and not available under field conditions, limiting their use to only research purposes [20].

Advanced diagnostic technics to reveal NCC: Useful advanced diagnostic techniques include Magnetic Resonance Imaging (MRI) and Computerize Tomography (CT) scanning. MRI and a CT scan machines have an ability to create pictures of the internal parts of the body by using medical imaging technologies. These diagnostic techniques are mainly used to detect the parasite in humans. CT scanners and MRI's have exceptional ability in the detection of NCC cases with exceptional small lesions. However, the use of these modern techniques has a minimal contribution in diagnosis of the parasite because they are very expensive and not available in most endemic rural areas [21].

RESULTS AND DISCUSSION

Control and treatment against *T. solium* taeniosis/cysticercosis

The use of chemotherapy: Antiparasitic drugs have been used for many years for treatment and control of *T. solium* taeniasis/cysticercosis. The most effective antiparasitic drugs used include niclosamide and praziquantal. Of these two drugs, niclosamide is mostly preferred because it does not provoke neurological symptoms in individuals with latent NCC. However, severe cases of the NCC require surgery. The use of chemotherapy is limited because the antiparasitic drugs are very scarce in most developing countries [12]. Other common drugs used to treat taeniasis/cysticercosis include Albendazole (ABZ), Oxfendazole (OFZ) and Nitazoxanide (NTZ). A recent study shows that the use of these antiparasitic drugs has successfully killed cysts from the infected pigs. However, clearance of the entire dead cyst from the meat takes a longer time of between 8 to 26 weeks after treatment. This is quite a long time in pig farming since it may interfere the market opportunities available.

Also, Oxfendazole and albendazole sulphoxide drugs given to the infected pigs have failed to eliminate parenchymal and ventricular brain cysts. This could be due to difficulties in penetrating the blood-brain barrier. The combination of albendazole, praziquantel and oxfendazole have shown the strong results and could be a suitable alternative treatment for human NCC [22]. In a study conducted by Oxfendazole failed to kill cerebral cysticerci in pigs. A similar obstacle was reported by Gilman et al. where antiparasitic drugs have failed to penetrate the blood-brain barrier to kill the parasite.

Generally, the use of antiparasitic drugs has not achieved a sufficient sustainable level in the elimination of *T. solium* in most developing countries. This is because there are insufficient antiparasitic drugs in rural areas and most farmers cannot always afford the costs. Also, the antiparasitic drugs do not provide a permanent cure to the treated pigs. The treated pigs may get a new infection when exposed to an infected environment and thus multiple doses of the drug are required [12]. Also, in most rural areas there is low awareness about the disease, people may consume pork before the recommended waiting period of 26 weeks post treatment, and they may become infected. This shows that combination of vaccines with chemotherapy against the disease could be the best cost-effective methods for eradication of *T. solium*, at a sustainable level [19].

Developing *T. solium* vaccines from protective antigens: Three protective antigens cloned from *T. solium* oncospheres have shown positive results in controlling the parasite under experimental conditions by vaccination. These antigen oncospheres are named TSOL18, TSOL45-1A and TSOL16 [23,24]. The antigens TSOL18 and TSOL45-1A are stage specific antigens occurring only on

the surface of *T. solium* oncosphere. This implies that the antigen oncospheres could be used in developing a high level of protection against *T. solium* cysticercosis in pigs [25].

Recent studies showed that between the three mentioned antigens developed, the antigen TSOL18 leads to nearly complete protection against *T. solium* in pigs. In the high prevalence region of Cameroon, the combination of the TSOL18 vaccine and the anti-parasitic drug oxfendazole has shown greatest potential in controlling the parasite by achieving protection against *T. solium* by almost 100% [26]. Other studies for assessment of the antigen TSOL18 have shown the greatest potential in protecting pigs against the parasite by achieving 99.5%, 99.9% and 99.3% in Mexico, Peru and Honduras respectively [27].

Development of combined vaccine against *T. solium* in pigs: The combination of two or more oncosphere antigens could give the best way of controlling the parasite. In a recent study conducted in Peru, the combination of TSOL16 and TSOL18 oncosphere antigens has reduced the total number of *T. solium* cysts by 99.9% [27]. The results look quite similar to the one reported by Assana et al. in the study undertaken in Cameroon, where they used a combination of TSOL18 and oxfendazole. However, comparing the two methods, the one which involves the combination of TSOL16-TSOL18 antigens seems to be more promising. This method only involves the use of vaccines while the other one combines TSOL18 antigen and an anthelmintic drug Oxfendazole [19].

The development of oncosphere antigens has shown a great potential in the control of transmission of *T. solium* in pigs but requires a higher investment. Currently, the production of TSOL18 vaccine is limited due to relatively higher costs of producing purified recombinant protein. The possible alternative would be to substitute the TSOL18 antigen by either monoclonal antibody or synthetic antigen EG95 or use alternative Synthetic Peptides Vaccines (S3Pvac) [28]. Further research is required in the development of the monoclonal antibody and synthetic antigen EG95. The alternative method should be developed to replace the current techniques that use expensive purified recombinant protein in the development of TSOL18 vaccine.

Development of synthetic peptides vaccines (S3Pvac) against *T. solium*: The development of Synthetic Peptides Vaccines (S3Pvac) was an initiative to reduce the high costs involved in the production of antigenic vaccines. Recently, there are three types of S3Pvac vaccines. These include 3synthetic peptides vaccine (S3Pvac-synthetic), recombinantly expressed filamentous phage M13 (S3Pvac-phage) and three transgenic embryogenic papaya clones (S3Pvac-papaya) anticysticercosis vaccines. The vaccines S3Pvac-synthetic and S3Pvac-phage are parentally administered by injection while S3Pvac-papaya vaccine is administered orally. The vaccine, S3Pvac-synthetic is made of three synthetic peptides named GK1 (amino-acids 69–85 of KETc7 peptide), KETc1 and KETc12 peptides. Similarly, S3Pvac-phage vaccine is composed of recombinant filamentous phages named KETc7, GK1, KETc1 and KETc12. The other vaccine, S3Pvac-papaya is developed by combining three transgenic-embryogenic papaya clones named pKETc126, pKETc19 and pKETc723 peptides. These peptides are expressed in transgenic-embryonic papaya cell suspension and has shown ability to induce the high level of protection against taenia cysticercosis [29-31].

In a recent study conducted in the endemic region of Mexico, synthetic S3Pvac vaccines have shown a significant damage of *T. solium* cysticerci in vaccinated pigs. The examination of vaccinated pigs after 5 months to27 months post vaccination has shown reduced number of cysticerci, and incidences of tongue and muscle cysticercosis by 87%, 70% and 54% respectively [30]. The results of a recent experimental research conducted by Betancourt et al., shows that the use of S3Pvac-papaya (oral) and S3Pvac-phage (injectable) vaccines could be the best cost efficient alternatives to control *T. solium* cysticercosis. The method allows the production of antigens at low cost since it does not include the expensive steps of antigen purification and artificial antigen encapsulation. However, the use of the S3Pvac-papaya is limited due to logistical difficulties in the oral application of the vaccine under field condition. Further research work is required for the development of the parental S3Pvac that is sufficient and sustainable for global use [32].

Can we develop a vaccine against *T. solium* for humans?: *T. solium* cysts may survive for many years in human brain before being detected and the infection could be recognized in the critical condition [18]. Theoretically, we can develop a vaccine to prevent NCC in humans by considering two major options. First, humans could be vaccinated directly against taeniasis, and secondly, vaccination against metacestode stage of the *T. solium* (NCC when the cysticerci lodge in nervous tissue). Based on the availability of the common diagnostic methods in endemic areas, the infection of *T. solium* in pigs could be notified earlier as compared to NCC in humans. Similarly, the predominance of muscles cysticercosis is seen more prominent in pigs than in humans. The development of the human vaccine against Taenia cysticercosis would provide a direct benefit, but the prevalence of the disease is mainly occurring among the poorest people in the world and requires higher investments. For this reason, the development and implementation of a human vaccine have yet to be considered seriously [8]. This suggests that development of desirable control measures for the parasite in pigs could be a more sustainable alternative. The basis for developing vaccines against porcine *T. solium* transmission stands on elimination or reducing the number of metacestodes and cysticerci in pigs. Certainly, this might reduce the transmission of the parasite to humans.

CONCLUSION AND RECOMMENDATIONS

Elimination of *T. solium* in both definitive and intermediate hosts requires a combination of effective interventional practices. The local communities in the endemic regions should be involved in designing and implementation of different control programs. Furthermore, the sustainable control programs require a political support as well as farmer's awareness on the importance of the disease. Thus, long a term intervention programs that include public health education, improved sanitary conditions, the use of latrines, regular mass deworming of humans are essential for reducing the incidences of *T. solium* taeniasis and NCC.

Also, in-depth research is required to find out more specific and sensitive diagnostic methods that are sustainable and cost effective under field conditions. Most of the available immunodiagnostic methods have been successfully used under restricted experimental conditions. The use of ELISA has to be promoted based on outstanding diagnostic results observed in different experiments. This method is a reliable tool for assessing the response to antiparasitic treatment in pigs, as well as monitoring treatment of NCC in humans. The combination of simple diagnostic methods that involves tongue palpation, meat inspection, and stool

microscopy could be reliable, and are the only directly available methods under field condition where there are no/insufficient immunodiagnostic techniques.

A vaccine developed of TSOL18 antigen could be the best one since it leads to nearly complete protection against *T. solium* in pigs. The mprovements in the strength of TSOL18 vaccine could be the best alternative in developing vaccines against the parasite. There are possibilities of using TSOL18 vaccine as a standalone vaccine, as well as combining with other vaccines (i.e., TSOL16) or with effective antiparasitic drugs to obtain efficient results. However, alternative methods should be developed to replace the current techniques that use expensive purified recombinant protein in the development of TSOL18 vaccine. Further research is required to develop monoclonal antibody and synthetic antigen EG95 to replace/minimize the use of the purified recombinant protein.

On the other hand, the development of synthetic Peptides Vaccines (S3Pvac) could be the best alternative for high costs involved in the production of antigenic vaccines. The development of S3Pvac does not require the expensive steps of antigen purification and artificial antigen encapsulation. However, between the three S3Pvac vaccines developed, S3Pvac-papaya vaccine was cheaper and shows the best results in controlling *T. solium* in pigs. Thus, further research work is required to develop the most efficient and sustainable papaya based-S3Pvac that could be given parentally.

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