

Cutaneous Leishmaniasis and the Strategies for Its Prevention and Control

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Despite zoonotic leishmaniasis is considered as a public health problem worldwide, it is one of the most neglected diseases [1,2]. This disease is identified by an annual incidence of about 2 million cases and a prevalence of 12 million cases globally [3]. Leishmaniasis is the third most important vector-borne disease after malaria and filariasis [4]. The disease is caused by the intracellular protozoa of the genus *Leishmania*, is common in tropical and subtropical regions of the world and transmitted by phlebotomine sand flies [5]. The numbers of the leishmaniasis cases are increasing throughout because of some factors such as the lack of vaccines, the increased parasites resistance to chemotherapy and inability to controlling vectors. Depending on the tropism, leishmaniasis can be divided into at least four forms namely cutaneous leishmaniasis (CL), muco-cutaneous leishmaniosis (MCL) or mucosal leishmaniasis (ML), visceral leishmaniosis (VL) also known as kala-azar, and post kala-azar dermal leishmaniasis (PKAL) [6,7]. Approximately three-quarters of incidence cases of leishmaniasis are related to CL [6]. Leishmaniasis can vary from a self-limiting cutaneous disease to a fatal visceral disease depending on the effecting species [8]. CL is characterized by the presence of one or more ulcers which may heal spontaneously or persist for period of some months [4]. Rarely, CL may be transformed into ML at the advanced stages, if untreated [9]. In the Old World, CL is caused by primarily *Leishmania major*, and then *L. tropica*, *L. infantum*, and *L. aethiopica* [1,10,11], while in the New World, it is caused by *L. Mexicana*, *L. braziliensis*, and *L. guyanensis* species [6,12]. The parasite *Leishmania* exists in the extracellular promastigote form, inside the midgut of the vector and culture media, and in the intracellular amastigote form, in the mammalian host [2,13]. Diagnosis of the disease is made based on demonstration of the parasite by methods such as fine-needle biopsy of lymph nodes, bone marrow aspiration, splenic puncture, skin scraping cytology and culture [3,10]. Cytology including touch smear and needle aspiration is cheap and performed with high sensitivity for the typical cases, but it may be unable to detect the atypical cases of leishmaniasis [14,15]. The serology tests are limited because of the probable cross reaction of antibodies with some diseases like toxoplasmosis and trypanosomiasis [15]. Other methodologies such as immunohistochemistry (ICH) and polymerase chain reaction (PCR) are preferably applied for supplementary diagnosis of the disease in particularly CL form [1,15-17]. Treatment of CL may be topical or systemic, on the basis of several factors such as *Leishmania* species, geographic regions and clinical manifestations [18]. For focal therapy, thermotherapy, cryotherapy, paromomycin ointment, local infiltration with antimonials may be promising options with less systemic toxicity. Systemic treatment is provided by using azole drugs, miltefosine, pentavalent antimonials, pentamidine and amphotericin B and its liposomal formulation [18,19].

Early diagnosis and appropriate treatment are important for the management and control of CL and due to the risk of developing the ML or MCL [4]. Since, the control and prevention of leishmaniasis based on chemotherapeutic treatments is expensive, toxic, and associated with high recurrence and resistance rate therefore, it is performed based on vector and reservoir control and vaccines [8]. However sand flies possess the biomechanical defensive mechanisms, they are suspected to

insecticides [4,20]. Indeed, the application of insecticide-impregnated clothing and curtains and also implementing training programs for early diagnosis are promising and cost-effective preventive strategies for reducing leishmaniasis transmission [4]. Disease control and prevention are difficult and challenging because of the complexity of the control of the vectors and the reservoir hosts especially rodents and asymptomatic dogs [13,20-22]. Meanwhile, the protection of canine populations as an important reservoir of *Leishmania* species is crucial. Therefore, considerable attempts should be made towards monitoring of the prevalence and incidence of canine leishmaniasis and developing cost-effective control strategies against this disease [20].

Development of a safe, efficient and cost-effective vaccine is the critical global public-health propriety [8]. An ideal vaccine developed against the disease should be efficient, safe, reproducible, and cost-effective and used for effective therapeutic and anaphylactic indications. Moreover, it must contain antigens sharing among several species, protect against infection and disease, and induce relevant T helper 1 and 2 cell responses [7,8]. Vaccine antigens should be maintained between species and thus cross-protective against different *Leishmania* parasite species [7]. Vaccines based on live *Leishmania* promastigotes harvested from cultures or leishmanization have adverse side effects including persistent lesions, psoriasis, as well as concerns of standardization and quality control, and immunosuppression [8]. The live-attenuated antileishmanial vaccines are still at their early stages of development [8] and the advances in the development of these live attenuated parasites may make a promising vaccine approach [7]. These vaccines offer a new approach to immunization against leishmaniasis, while there are concerns that the parasite may revert to a virulent form, and the destruction of the parasite due to deletion of essential virulence genes [7,8]. So, these may make the use of killed parasites more attractive for vaccine options [8]. Formulation of the first generation vaccines against leishmaniasis include whole killed or fractions of the *Leishmania* parasites is difficult to standardize [6,8]. These vaccines are inadequate to produce long lasting and relevant immune responses required for protection [6]. Second-generation vaccines composed of vaccines using recombinant viruses and bacteria as delivery vehicles expressing *Leishmania* parasite antigens [6,8]. These vaccines are safe because of they do not contain any pathogenic organism [8]. Third-generation vaccines or DNA vaccines have some advantages such

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as stability, standardization, large-scale of manufacturing, and the possibility of combining different genes in one construct [6,8]. Some vaccines composed of sand fly saliva and salivary proteins alone or in combination with *Leishmania* antigens are under development. These vaccines have been designed on the basis of adverse impacts of the salivary proteins-induced immunity [12]. It seems that combined vaccines include multiple antigens and well-developed adjuvants have the most chances to succeed [6,8]. The selection of adjuvant and induction of Th1 response to protect against leishmaniasis are critical [8]. Therefore, the future researches should include appropriate adjuvants in order to design and fabricate an effective vaccine against leishmaniasis. Nevertheless, vaccination remains the most promising strategy for control of all forms of the disease.

Finally, collaboration among medical physicians, veterinarians, researchers, and public health authorities is critical to find a suitable platform and strategy for the control and prevention of leishmaniasis.

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