Review of Leishmaniasis in the Middle East and North Africa

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Abstract

Background: Cutaneous and visceral forms of leishmaniasis are the most important protozoan infection in the Middle East and North Africa (MENA).

Objectives: Review the current knowledge on leishmaniasis in the MENA.

Methods: The data presented in this review are gathered primarily from WHO reports and from an extensive literature search on PubMed.

Results: There are four cycles of transmission of leishmaniasis: zoonotic cutaneous leishmaniasis (ZCL), induce by *Leishmania* (*L.*) *major*, transmitted by *Phlebotomus* (*P.*) *papatasi*, with rodent species of *Psammomys obesus*, *Meriones libycus*, *Nesokia indica*, and *Rhombomys opimus* are considered as host reservoirs. Zoonotic visceral leishmaniasis (ZVL) is inducing by *L. infantum*, transmitted by several *Phlebotomus spp.* of the sub-genus *Larroussius* and mainly *P. perniciosus* in more than one-half of the MENA countries and the dog species of *Canis familiaris* are considered as the main reservoirs. Anthroponotic cutaneous leishmaniasis (ACL), induce by *L. tropica* and transmitted by *P. sergenti*, without any non-human reservoir in most cases. Anthroponotic visceral leishmaniasis (AVL) induces by *L. donovani* spreads through *P. alexandri*, circulates exclusively in humans.

Conclusion: There are many challenges facing the successful control of leishmaniasis. However, there is continuing research into the treatment of leishmaniasis and potentially vaccinations for the disease.

Keywords: Cutaneous and visceral leishmaniasis, global distribution, Middle East and North Africa.

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Introduction

Leishmaniasis is an important complex of protozoal vector-borne diseases that affects both humans and animals. It is caused by parasites of the *Leishmania* type and spread by the bite of certain types of sandflies. These organisms are mainly maintained and circulate in animals. Indeed, each *Leishmania* species having specific mammal reservoir hosts and vectors[1]. It should be noted that the prevention of leishmaniasis is difficult due to the significant side effects that cause drugsused for treatment and their limited availability outside endemic regions.

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There are several different forms of leishmaniasis in people. It comes mainly in two forms: cutaneous and visceral leishmaniasis, which causes skin sores and affects several internal organs, respectively. It is important to note that a single species can cause both visceral and cutaneous leishmaniasis and can produce lesions with different characteristics in the same person[2-5]. However, generally different species of the *Leishmania* parasite are associated with each form. Further investigations are needed to determine factors that cause different disease manifestations of the same species, but it seems that specific factors are probably influenced by genetic hybrids occurring between *Leishmania* species[6,7], the host immune response[8], and less likely by different sand fly vector species[9-11] since the existence of a vector-parasite specificity although this specificity may be flexible and not completely strict.

Fatality rates for leishmaniasis are the third highest of all the neglected tropical diseases after sleeping sickness and

chagas disease. However, the morbidity due to the disease is often confused and underestimated by clinicians and scientists. This underestimation of the true health burden of leishmaniasis is due to several reasons. First, the mandatory reporting of leishmaniasis cover only 32 of the 88 affected countries. Second, it is known that the disease is embedded in poverty and is typically kept hidden by the affected individuals and their families due to its low mortality rates. Finally, other factors including mainly economic troubles and civil war have participated hugely in the spread and the underestimate of leishmaniasis. Globally, the World Health Organization (WHO) has estimated that 2 million new cases occur yearly (75% for cutaneous leishmaniasis and 25% for visceral leishmaniasis) and that 12 million people are infected globally[12]. About 100,000 cases of leishmaniasis were reported in the MENA region and neighboring countries in 2008. With respect to visceral leishmaniasis, Sudan and Somalia reported 4108 and 583 cases of AVL, respectively. As regards ZVL, 409 cases were reported from five countries: Iran 125; Morocco 163; Saudi Arabia 41; Syria 17 and Tunisia 63. This number should be higher than the recorded one if we take into consideration the underestimation due the reasons cited above.

In the present report, the current status of the prevalence and the distribution of leishmaniasis in the MENA were summarized based on the available and scattered reports. An overview of the Middle East and North Africa was summarized to well understand the aspects particular of the region. Leishmaniasis surveillance and control to prepare the countries of the region for future public health challenges were reviewed based on recent consortium innovation.

Methodology

The data presented in this review are gathered primarily from WHO reports for each country and from an extensive literature search on PubMed using the term "Leishmaniasis" followed by the name of each endemic country. Similar searches were carried out using the term "global distribution", "incidence", "prevention and control of leishmaniasis", "sandfly", "Leishmaniasis North Afrca". and "Leishmaniasis Middle East".

Particularities of the middle East and North Africa region

The Middle East and North Africa Union is comprised of approximately 20 countries including Morocco, Algeria, Tunisia, Libya, Egypt, Yemen, United Arabes Emirates, Syria, Saudi Arabia, Qatar, Palestinian territory, Oman, Lebanon, Kuwait, Jordan, Israel, Iraq, Iran, Djibouti, and Bahrain[13].

Figure 1: Map of the Middle East and North Africa region, by Adel Rhim

As shown Figure 1, our study was focused on the most important 12 countries, where the situation is serious and data are more or less available. The winds of unrest sweep through the MENA since 2011. It began in Tunisia and spread within weeks to Egypt, Yemen, Libya and Syria[13]. The MENA comprises a small share of the world's population (5%), which is characterized by its youth. Egypt, Iran, Algeria, Morocco and Iraq are the most popular countries[14]. It should be noted that the MENA showed the highest unemployment rate worldwide (24%) associated with a slow down in economic growth (3%). In this context, statistical studies carried out in 2005 confirmed that 3.6% of the MENA population is living on less than US$1.25 per day, while 16.9% is living below US$2 per day[15] hence their vulnerability to the leishmaniasis and other neglected diseases. The highest percentages of people living in poverty are living in Yemen and Egypt compared to other MENA countries[14] without forgetting Algeria, Djibouti, Iran, Iraq, Morocco, and Tunisia where living important percentage of impoverished people[14,16]. Globally, the World Bank classified most of MENA Countries as lower-middle-income countries[17]. Two other factors including modern conflicts ensuing in the geographic and political region and the lack of veterinary and public health were added to poverty factor and enhances the spread of leishmaniasis in the areas[18].

Cutaneous and visceral leishmaniasis

It is important to remember that about two million cases of *Leishmania* are recorded yearly in 88 counrties[19]. Authors suggested that this prevalence was underestimate and not precise due to misdiagnosis and inadequate reporting guidelines and the true numbers was at least five to eight times[12,19] because of the non-declaration of the disease by more than the half of endemic countries. The incidence of the disease is still on the rise in countries with political instability including the MENA[20] although it has reduced by half[21] globally in the past decade.

However the different cycle of transmission and clinical expression, all *Leishmania* species are transmitted to humans via the bite of infected sand flies. Metacyclic promastigotes in the foregut or anterior midgut of the sandfly was regurgitated into the skin of the invertebrate during the blood meal of infected sandflies. Right after and rapidly, the promastigotes are taken up by phagocytic cells, including macrophages and neutrophils. The promastigotes forms differentiate into a dividing, aflagellated amastigotes in the phagolysosome. It is important to note that an infected host is the origin of the parasite that exists in sandflies. After lysing host cells, the amastigotes transform into procyclic promastigotes. They use their flagella to attach to the fly midgut using surface glyconconjugates, a key step in establishment of the infection.

About twenty five *Phlebotomus ssp* are involved in the transmission of *L. major*, *L. tropica*, *L. infantum*, and *L. donovani*, relevant species in the MENA areas among approximately 20 *Leishmania spp*. infect humans worldwide. Cutaneous and visceral forms of leishmaniasis are the most important protozoan infection in the MENA region[22,23]. Visceral leishmaniasis (VL) in the MENA is caused by *L. donovani*, *L. infantum*, and occasionally *L. tropica*. However, the causal agents of cutaneous leishmaniasis (CL) are *L. major*, *L. tropica*, and *L. infantum*, which lesion presentation slightly differs depending on the species. Different nonhumans reservoirs are involved in the transmission of ZL namely rodents, hyraxes, and canids. Globally, ZCL caused by *L. major* is transmitted mainly by *P. papatasi* and *Psammomys* and *Meriones* rodents. Anthroponotic cutaneous leishmaniasis (ACL) caused by *L. tropica* is transmitted by *P. sergenti* and *gundi* and *hyraxes* although the cycle is mainly anthroponotic, as is the VL agent, *L. donovani*. Zoonotic visceral *leishmaniasis* (ZVL) caused by *L. infantum* is mainly zoonotic where candids are considered as the primary reservoir and man as an accidental host; however, anthroponotic cycles also have been characterized.

Cutaneous leishmaniasis

Two forms of cutanuous leishmaniasis exist in the MENA: anthroponotic and zoonotic caused by *Leishmania* (*L.*) *tropica* and *L. major* parasites, respectively.

Zoonotic cutaneous leishmaniasis

Foci of ZCL occur in all countries of the MENA with higher rates in Iran, Saudi Arabia, Morocco, Tunisia, Syria, Libya, and Iraq[24-29]. Iran and Saudi Arabia have the highest rate of ZCL. The disease is caused by *L. major*, which transmitted through mainly *P. papatasi* and its close relatives, *P. duboscqi* and *P. salehi*. *Phlebotomus caucasicus* has been mentioned as a vector in Iran[30-34]. It is important to note that *P. papatasi* is considered among the most widespread invasive sandflies species in the MENA and worldwide. The close association of these vectors with

human habitation ensures transmission to humans from domestic and other animal reservoirs. Rodent species of *Psammomys obesus*, *Meriones libycus*, *Meriones shawi*, *Nesokia indica*, and *Rhombomys opimus* serving as non-human reservoirs[31]. *Psammomys obesus* occur as reservoir of *L. major* in most foci between Morocco in the West and Syria and Saudi Arabia in the East. The great *gerbil Rhombomys opimus* maintains *L. major* in central and North-Western Iran. This parasite was transmitted through *Meriones shawi* in Southern Morocco and several *Meriones* species in South-Eastern and South-Western Iran where the bandicoot rat *Nesokia indica* was considered as a second reservoir. This disease affects mainly the arid areas of endemic countries which explain the important number of cases (600) in 2004 in US soldiers during the war against Iraq[30]. The breakdowns in public health system and the 8 years of war were the main causes of the emergence of the disease in its both forms in Iraq[30].

Anthroponotic cutaneous leishmaniasis

Anthroponotic leishmaniasis caused by *L. tropica* and its closely related species *Leishmania killicki*[35-37] and spread through *P. sergenti* and related species, circulates exclusively in humans mainly in urban areas. Several previous studies showed that *P. sergenti* is the proven or potential vector of *L. tropica* in many foci of ACL in the MENA[38-39]. This sandfly is known to have an endophilic behavior in rural and urban habitats in semi-arid bioclimates, which explain the transmission of parasites to humans from domestic and other animal reservoirs[36,40-45]. The parasite occurred in high number in Syria, Iran, Morocco, Yemen and Algeria[31,33,34,46]. *Leishmania tropica* is commonly stated to be anthroponotic. However, the relative paucity of CL cases in some countries of the MENA and their spatial distribution suggests that it might be a zoonosis. Infection occurs both in old housing and new suburban settlements and also in peripheral villages. In Tunisia, the North African gundi (*Ctenodactylus gundi*) was suspected to be the *L. killicki* reservoir since the end of the last century[36,47] and recently was considered as a natural host of this parasite after identification of *L. killicki* from infected gundi[49,50]. However, it was the rock hyrax (*Procavia capensis*) in North Israel[51,52]. Indeed, previous studies showed that the rock hyrax is the proven reservoir of *L. tropica*. Its role as reservoir was confirmed by artificial infection and in natura[51,53-55].

Visceral leishmaniasis

There are two different modes of transmission of visceral leishmaniasis in the MENA: Zoonotic visceral leishmaniasis (ZVL) is caused by *L. infantum* and Anthroponotic visceral leishmaniasis (AVL) caused by *L. donovani*.

Zoonotic visceral leishmaniasis

Zoonotic visceral leishmaniasis (ZVL) is caused by *L. infantum*, spread through several *Phlebotomus* spp. of the subgenus *Larroussius* and mainly *P. perniciosusin* more than one-half of the MENA countries, including Egypt, Iran, Iraq, Jordan, Lebanon, Libya, Morocco, Saudi Arabia, Syria, Tunisia, and Yemen3[0,31,56]. According to the concerned countries and areas, *P. perniciosus, P. longicupis, P. langeroni, P. perfiliewi, P. ariasi, P. galilaeus, P. syriacus, P. tobbi*, and *P. halepensis* acts as proven and potential vectors and the dog species of *Canisfamiliaris* acts as the main nonhuman reservoirs. However, other wild and domestic animals including Canidae and rodents were considered as secondary reservoirs after found them naturally infected[57]. Nevertheless, their own role as reservoirs in the transmission life cycle is not proven. *Phlebotomus* (*P.*) *perniciosusis* the most widespread vector of *L.infantum* (Protozoa, Trypanosomatidae) to humans and dogs in the MENA and is characterized by its endophilic behavior[58-60].This disease is strongly related to low socio-economical levels and houses with deteriorated bad quality walls[61].These conditions are suitable for *L. infantum* transmission[59,62,63]. Indeed, dogs have an important role in these agricultural areas including guarding houses and tending flocks. Furthermore, sandflies are strongly related to these biotopes by its different blood sources and by its suitable biotope for rest and egg-laying[38,64].The number of cases of ZVL has risen in the MENA because global warming and land degradation, which together affect the epidemiology of leishmaniasis. As an example, hundreds of patients have been diagnosed yearly in NA countries since the 90's in comparison with just few cases registered before the 80's in the same countries[59,65-67].

Anthroponotic visceral leishmaniasis

Anthroponotic visceral leishmaniasis (AVL) caused by *L. donovani* spreads through probably *P. alexandri* and *P. orientalis* occurs in Yemen and Saudi Arabia, where no accurate data are available[31] without any nonhuman reservoir[68-70].

Strategic framework for leishmaniaisis in the MENA

The main goal of the World Health Organization[71] network for leishmaniasis surveillance and control is to reduce the prevalence of disease. To reach this goal, each country's health development activities should integrate these surveillance and control measures. Early diagnosis and treatment, control of sand fly populations, reservoir control, especially for zoonotic forms, health education and training, intersectoral collaboration, and partnership action are the global goals of this network[31].

Here, the different goals of this network will be detailed as following: firstly, each country's health development activities should implement health education, community participation and risk assessment with special attention to program management, case detection and management, disease surveillance. Secondly, the detection of new emerging foci is of great importance to well conduct preventive measures, case diagnostic and management. The monitoring system should learn from already existing systems (strengths, weaknesses, failures and successes) and ameliorate them. Data should be collected correctly as maximum possible by professional staffs. Thirdly, each country's health development activities should create a regional network to share information and experiences, make medicines available to more patients who need them and extend the collaboration at the sub-regional scale. Fourthly and finally, each country's health development activities should encourage and develop cross-border cooperation, multisectoral and intersectoral collaboration to prepare the country for future and international public health challenges.

Since leishmaniasis has been a major public health problem in the MENA for many years, considerable scientific efforts and infrastructures have been allocated to control this severe yet neglected health problem. Recently, McDowell et al (2011) suggested an international research agenda for leishmaniasis in the MENA[22]. In fact, the collaboration between the USA and endemic countries of the MENA was improved in 2009 during a *Leishmania* research and policy conference held in Tunisia[22]. The possibility of the globalization of this disease by importation through immigrants, travelers, non-governmental organization workers, and even tourists raise the interest of the USA and other developed countries in *Leishmania*. In November 2016, scientists of member countries of the Institute Pasteur International Network including Morocco, Algeria, Tunisia, and Iran, which have similar characteristics and elements of CL diseases (parasites, vectors, and reservoir animals) meet in Tehran with scientists of Institute Pasteur in Paris and suggested a new consortium to develop an integrative research approach to better understand this disease[22,72]. *Leishmania* genetics, host immune response, and vector transmission were the three main thematics, which need more investigations according to different participants. In this context, scientists insist that essential discoveries will be reported thanks to the dynamic interaction among these factors[73]. Indeed, the first thematic (*Leishmania* genetics) can engender novel vaccine candidates and drug-target against CL using *Leishmania* genetics and evolvability. The second thematic (host immune response) can engender the development of novel biomarkers for vaccine development and immunotherapy elucidating the host immune response to infections. The third thematic (vector transmission) can engender new insight into entomological risk assessment and vector control, and risk anticipation as a part of tasks dedicated to vector biology and transmission dynamics. However, health education and training at both the national and international levels will be of great importance of this consortium.

In summary, there are many challenges facing the successful control of cutaneous and visceral leishmaniasis. Leishmaniasis is still endemic in many poverty stricken and war torn areas, which complicate such efforts[70]. However, there is continuing research into the treatment of leishmaniasis and potentially vaccinations for the disease.

Conflict of interest

The author declare that there is no conflict of interest.

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