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Prevalence and Distribution of Leishmaniasis, Kingdom of Saudi Arabia, 2010 – 2014

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Prevalence and Distribution of Leishmaniasis, Kingdom of Saudi Arabia, 2010 – 2014

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in the Hubert Department of Global Health
2016

Abstract
Prevalence and Distribution of Leishmaniasis, Kingdom of Saudi Arabia, 2010 – 2014
By ALI A. ALGHAMDI

Background: Leishmaniasis is a vector-born, parasitic disease transmitted to mammals by the bite of an infected phlebotomine sand fly. It affects people in 98 countries and is a major public health concern and endemic in the Middle East, including the Kingdom of Saudi Arabia (KSA). We investigated trends in leishmaniasis prevalence from 2010 – 2014 in KSA to make recommendations for the national control program.

Methods: Leishmaniasis incidence rates (IRs) per 100,000 population in KSA and 95% confidence intervals (CIs) from 2010 – 2014 were stratified by nationality, gender, and 13 administrative provinces.

Results: We observed a decreasing trend in the IRs of leishmaniasis in KSA, by year. This decrease was statistically significant from 2010 (IR=14.97; 95%CI=14.52-15.44) to 2014 (IR=7.11; 95%CI=6.82-7.42). The IR among Saudis was lower than that of non-Saudis and the difference in IRs by nationality was statistically significant for all years of the study. We also observed a significantly decreasing trend in leishmaniasis IRs from 2010 to 2014 for both males and females. For males, the IR was 20.76 (95%CI=20.05 - 21.49) per 100,000 population in 2010 and sharply decreased almost 50% to IR of 9.53 (95%CI=9.08- 10.00) in 2014. A similar trend was observed for females, whose IR was 7.62 (95%CI=7.14 - 8.12) in 2010, decreasing to IR of 4.03 (95%CI=3.71- 4.38) in 2014. We observed higher IRs of leishmaniasis in AL-Madinah, Al-Qasim, and Hail provinces during the study period.

Discussion: Leishmaniasis significantly decreased in KSA from 2010 – 2014. The KSA eradication effort for leishmaniasis has been successful. We recommend active surveillance for early detection and continuous health education for both healthcare professionals and the public.

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ACKNOWLEDGEMENTS

I would like to express my deepest gratitude to my advisor Dr. Scott McNabb for his full support, expert guidance, and encouragement throughout my study and research. Without his wisdom, assistance and counsel my thesis work would never have been completed.

In addition, I express my sincere appreciation to Dr. Abdullah Assiri, Assistant Deputy Minister for Preventive Health, Ministry of Health, for his continuous motivation during my study.

Thanks also go to Dr. Mohammed Alzhrani, Director of Malaria Program and Supervisor of disease Vector Units, Ministry of Health, for facilitating this work during my data collection, and Dr. Adnan Aldahan from the Leishmania program for his kind assistance.

My deepest gratitude goes to the following people:

- Ms. Natalie Schulhofer, for her patience and amazing help in editing my thesis and during my presence in Emory.
- Mr. Prabhjyot Saini, who helped me with the statistical analysis part of my thesis.
- The group of KAF Fellows, for the support and help they have given me during my study.

Finally, I would like to thank my parents, my wife and my kids for their unconditional love and support during the last two years. I would not have been able to complete this journey without their continuous love and encouragement.

Table of Contents

Chapter 1

Background

Leishmaniasis is a vector-borne, parasitic disease transmitted to mammals by the bite of an infected phlebotomine sand fly. It affects people in 98 countries (Salam, Al-Shaqha, & Azzi, 2014), (El-Beshbishy, Al-Ali, & El-Badry, 2013) and is a major public health concern and endemic in the Middle East an infectious disease caused by parasite leishmania, it presents in three clinical forms (de Vries, Reedijk, & Schallig, 2015) (Mansueto, Seidita, Vitale, & Cascio, 2014): visceral leishmaniasis (VL) (also known as *kala-azar*), caused by *L. donovani*, cutaneous leishmaniasis (CL), caused by *L. tropica* and *L. major,* and mucocutaneous leishmaniasis, caused by *L. braziliensis* (Delhi Zoonosis Division, 2005).

Clinical Presentation

CL begins with one or more skin sores; they may vary in size and appearance over time. These sores end up as ulcers that are volcano shaped with raised edges and depressed centers. These ulcers can leave permanent scars and be a source of stigma. Those who have VL usually present with fever and weight loss; the disease can affect bone marrow and result in enlarged inner organs, causing hepatomegaly, splenomegaly, as well as abnormal blood tests (Desjeux, 2004).

Leishmaniasis is transmitted by the bite of an infected female phlebotomine sandfly, whose main hosts are sylvatic mammals like rodents, hyraxes, and canids, including both wild and domestics dogs (Abdalla, 2013). Though all leishmania species are closely similar in their morphology, they produce three clinically different diseases (Delhi

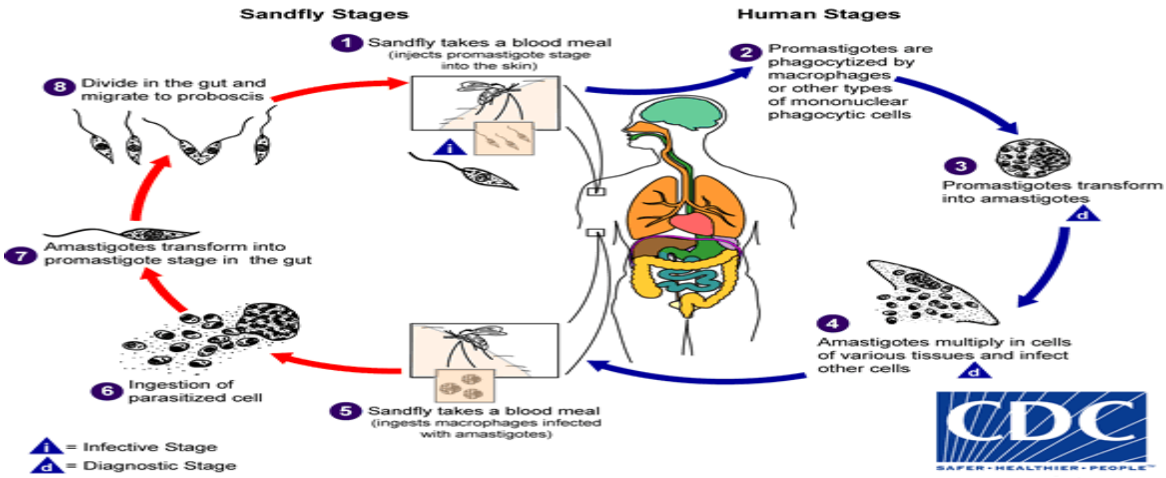
Zoonosis Division, 2005). Human infection is caused by about 21 species that infect mammals: the *L. donovani* complex (*L.donovni, L. infantum*, also known as *L. chagasi* in the New World), *L. tropica, L.major, L.aethiopica, L. Viannia braziliensis, L. viannia Guyanesis*, *L. viannia Panamensis*, and *L. viannia Peruviana*. All of these species have a similar morphology but different genus structures (Cantacessi, Dantas-Torres, Nolan, & Otranto, 2015). The incubation period for *L. major* is from one week to four months, and that for *L. tropica* is from one week to 2 – 8 months.

Photo 1: Child with cutaneous leishmaniasis awaiting treatment in Kabul, Afghanistan
Photo 2: Cutaneous leishmaniasis ulcer on left forearm

Life Cycle of Leishmaniasis

Sandflies inject *promastigotes* while biting humans. Macrophages and other phagocytes then engulf the *promastigotes.* The *promastigotes* transform in the macrophages into the tissue stage of the parasite (*amastigotes*), which multiply and infected other phagocytic cells. The infection will cause cutaneous or visceral leishmaniasis depending on factors such as host immunity and type of parasite.

In sandflies, *amastigotes* transform into *promastigotes*, which develop in the gut.

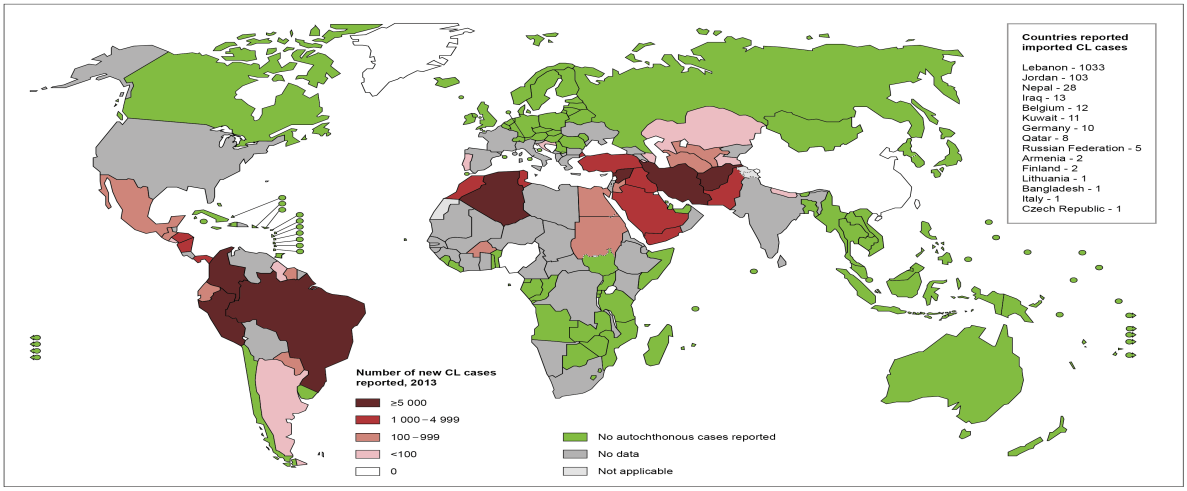


Significance

Leishmaniasis is a parasitic disease found in the topics, subtropics, and southern Europe. It is classified as a Neglected Tropic Disease (NTD). There are two common forms of leishmaniasis: CL, which causes skin ulcers, and VL, which affects the internal organs, mainly the liver, spleen and bone marrow. Leishmaniasis is the most ignored infectious disease when tropical diseases are prioritized, with the ninth largest disease burden. The neglect of leishmaniasis results from the complexity of its epidemiology and ecology and the scarcity of recent data, which obscures its significance.

WHO has taken an important step towards increasing global awareness of leishmaniasis. They convened an Expert Committee on leishmaniasis in March 2010, based on the World Health Assembly (WHA) resolution 2007/60.1. They issued the first updated technical report on leishmaniasis in more than 20 years. The WHA Resolution and Expert Committee report focused on the need to revise the epidemiological evidence base in order to design a long-term strategy for controlling leishmaniasis (Alvar *et al*., 2012).

Status of endemicity of cutaneous leishmaniasis, worldwide, 2013



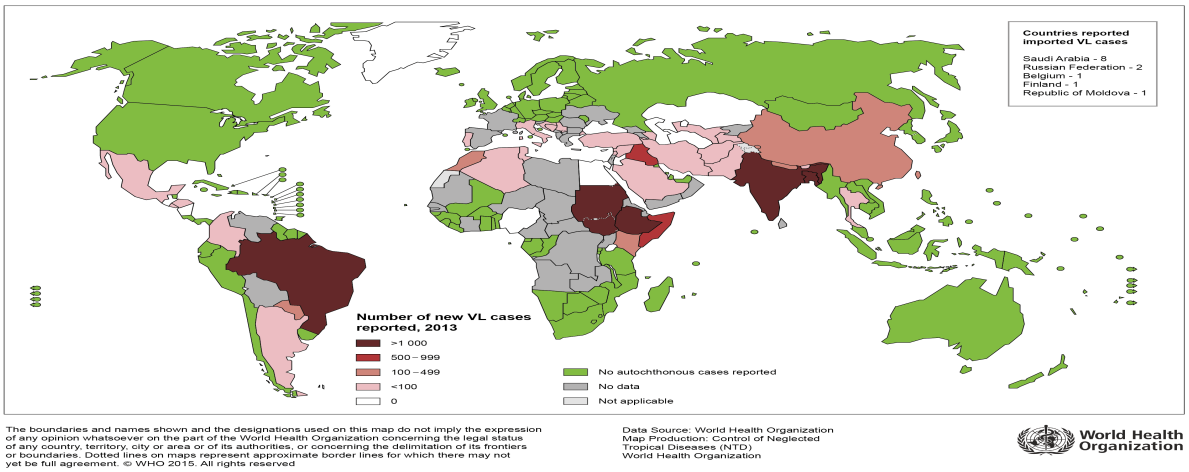
Data Source: World Health Organization
Map Production: Control of Neglected Tropical Diseases (NTD)
World Health Organization

World Health Organization

World : Endemicity of cutaneous leishmaniasis, 2013 (WHO, 2013b)

On World Health Day (2014), the WHO emphasized the significance and growing problem of vector borne diseases including leishmaniasis with the theme “Small bite, big threat.” Cantacessi *et al*. (2015) emphasize exploring the relation of diseases occurring in dogs and whether they can be transmitted to humans, as well as how the One Health concept can open up new approaches of controlling this disease (Cantacessi *et al*., 2015). De Vries *et al*. (2015) points to the necessity for intensified research and control programs for vector control, diagnostic techniques, and the availability of medications in order to address increases in morbidity and mortality due to the disease (de Vries *et al*., 2015). Leishmaniasis occurs in focal clusters mainly in rural areas, which makes it challenging to track accurately and can result in misleading and inaccurate official data, making the evidence base for this disease an issue (Hotez, Savioli, & Fenwick, 2012).

Status of endemicity of visceral leishmaniasis, worldwide, 2013



World : Endemicity of visceral leishmaniasis, 2013 (WHO, 2013a)

Leishmaniasis in the Kingdom of Saudi Arabia

In this study, we highlight the prevalence of leishmaniasis in the Kingdom of Saudi Arabia (KSA) from 2010 to 2014 and describe the epidemiologic trends during these years. KSA has unique experiences in leishmaniasis prevention and control since the establishment of the National Control Program in 1997 (1399 H). The number of cases decreased significantly since the program was established. We focus on successful strategies in leishmaniasis prevention and control and the possibility of achieving eradication in KSA.

Background on the Kingdom of Saudi Arabia

KSA is the largest country in the Arabian Peninsula. Located in western Asia, it is the second-largest country in the Arab world. According to the General Authority for Statistics, KSA's population is 30.7 million, distributed among 13 administrative provinces. Riyadh city is the capital.

KSA's geography is varied, with grasslands, mountain areas, and deserts. The

climate also varies from region to region. Temperatures can reach over 45 degrees Celsius in the desert during the summer, while in the winter, temperatures in the north, high mountain region, and central areas can drop below freezing. KSA has lengthy borders in the north with Jordan and Iraq and in the south with Yemen and Oman. In the east, it is bordered by the Red Sea. The border areas are a major challenge for the Saudi government in terms of controlling refugees and illegal immigration from conflict areas in the north and south. According to the Ministry of Foreign Affairs, KSA has accepted 2.5 millions Syrian citizens (refugees) due to the military conflict in their country, and about one million Yemeni citizens, providing them with health services and other services for free, and granting them the right to work and continue their education in the Kingdom. Healthcare authorities have an additional burden of continuously monitoring, evaluating, and reporting any health emergencies by designing effective strategic control plans.

Study Purpose

In this study, we measure the distribution and prevalence of leishmaniasis in KSA from 2010 to 2014 and focus on the main risk factors in endemic regions to prevent and control this disease. We also discuss the National Control Program and share the strategies. To do this, we calculate the incidence rates (IRs) of leishmaniasis and stratify this by province, type of disease, nationality, and gender.

Terminology

NTD: Neglected Tropical Disease

CL: cutaneous Leishmaniasis

VL: Visceral Leishmaniasis (also called kala-azar)

WHO: World Health Organization

Hepatomegaly: liver enlargement

Splenomegaly: Spleen enlargement

PHC: Primary Healthcare Center

WHA: World Health Assembly

Chapter 2 – Literature Review

Leishmaniasis Case Definition

The 2014 manual for case management of CL in the WHO Eastern Mediterranean Region specifies the case definition for leishmaniasis. A probable case of CL is a patient showing clinical signs (skin or mucosal lesions) without parasitological confirmation of the diagnosis (positive smear or culture) and /or, for mucocutaneous leishmaniasis only, serological diagnosis. A confirmed case of CL is a person showing clinical signs (skin or mucosal lesions) with parasitological confirmation of the diagnosis (positive smear or culture). A cured case has a complete re-epithelialization before day 45. A relapse case has the reappearance of nodule, plaque or ulceration after cure. Parasitological confirmation used only in complex cases. Treatment failure is classified when there is the increase of a nodule, plaque or ulceration within 14 days of treatment, or lack of complete re-epithelialization within 45 days of treatment starting.

The case definition for VL is taken from the indicators for the monitoring and evaluation of the VL elimination program in 2010 (in Bangladesh, India and Nepal).

A case of VL is defined as a person from an endemic area with fever of more than two weeks duration and with splenomegaly, who is confirmed by an Rapid diagnostic test (RDT) or a biopsy. A probable case is a patient from a VL endemic area with multiple hypopigmented macules, papules, plaques or nodules, who is rapid diagnostic test (RDT) positive**.** A confirmed case is a patient from a VL endemic area with multiple hypopigmented macules, papules, plaques or nodules, who is parasite positive in slit-skin smear (SSS) or biopsy. A cured case is a patient is considered clinically cured if he/she has completed full treatment and there are no signs and symptoms of VL. A

relapse is any reappearance of VL signs and symptoms within a period of six months after the end of treatment. Treatment failure is classified when signs and symptoms persist or recur despite satisfactory treatment for more than two weeks (WHO, 2010a).

Emergence of Leishmaniasis

Pavli & Maltezou (2010) performed an extensive and detailed literature review of the emergence of leishmaniasis on non-endemic countries from the years 2000 – 2010. They list of some factors related to the spread of this disease as: international tourism, military operations, and the influx of immigrants from endemic countries. They also name South America as the prime breeding ground for CL. Due to urbanization and deforestation in the past decade, leishmaniasis disease has either expanded its spread or emerged in several countries worldwide. Control of the disease may be quite challenging because of the role of global warming in facilitating the breeding of the sand fly and because of the increased reported resistance to pentavalent antimonials treatment, especially in India, where most cases of VL are reported globally (Pavli & Maltezou, 2010).

The authors stated that at the core of the problem is the travel habit of individuals visiting friends and family and participating in outdoor activities in tropical and sub-tropical locations. This is the most common manner through which they contract and spread leishmaniasis to others. Because this disease has such a lengthy incubation interim, accuracy in diagnosis requires people who have travelled to high-risk areas to be questioned and tested for their travel activities dating back to several months or even years prior.

Pavli & Maltezou (2010) name pentavalent antimonials meglumine antimoniate and sodium stibogluconate as the customary VL treatment. However, recent resistance to this treatment poses a problem. Pentamidine and miltefosine are often utilized in cases of antimonial resistance. Alternate treatments can be used, such as heat, cryotherapy or laser technology. In developed, non-endemic countries, diagnosis and treatment of leishmaniasis can be overlooked because many physicians are not familiar with its main clinical presentation, diagnostic techniques, and proper treatment. A diagnosis of leishmaniasis disease should be considered among travelers with a history of travel to an endemic area, even that travel was years ago, if they have consistent clinical presentation of the disease (Pavli & Maltezou, 2010).

Rahman *et al*. (2014) provide details of a case study of Leishmania tropica in a migrant Bangladeshi worker in KSA. Although it was initially thought to be a case of cutaneous tuberculosis, lab specimens eventually confirmed the diagnosis via a microscopy, which confirmed an abundance of *amastigotes* within macrophages. Migrant workers are known to be one of the primary risk factors for transmission of CL, and this particular worker recalls being bitten by sandflies (common carriers of leishmaniasis) during his stint in KSA. The fact that cutaneous tuberculosis is more common in Bangladesh led doctors to believe that it might be the culprit. The authors describe the range of possible treatments for CL and the degree of difficulty in treating this disease when they state, “Besides oral and parenteral medications (*pentavalent antimonials, liposomal amphotericin B, miltefosine,* and some others), local cryotherapy, intralesional infiltration of *sodium stibogluconate*, local heat therapy, and various topical *paromomycin* preparations are in practice for many many years” (Rahman, 2014). This

thirty-seven year old, male patient was treated with IV SSG at a dose of 20 mg/kg/day for twenty-eight days in addition to intralesional injections at a dose of 30 mg/day/lesion for 10 days.

Abass, Saad & Abd-Elsayed (2009) perform a case study of facial CL and link it to Down syndrome in infants. Down syndrome creates a state of immunodeficiency that makes humans more prone to becoming infected with forms of Leishmaniasis. According to the authors, this is the first documented case of isolated facial cutaneous leishmaniasis that is linked with Down syndrome. The authors highlighted that the parasite may be transmitted by ways other than the bite of the sand fly, either by laboratory accident, direct person-to-person transmission, or blood transfusion. In addition, they mentioned that there is evidence that leishmaniasis may be transmitted either in utero or during the peripartum period. They state as the basis of their study (Abass, Saad, & Abd-Elsayed, 2009). This two-month Saudi Arabian male was admitted in the pediatric ward of maternity and children's hospital, Buraidah, KSA due to numerous facial ulcers, which led to disfigurement. Because of this disfigurement, it was difficult to detect the facial characteristics commonly indicative of Down syndrome. Karyotyping confirmed the Down syndrome, and the child began to improve after two weeks of treatment with IV sodium antimony gluconat plus antibiotics. Unfortunately, the parents stopped and refused additional treatment and were never back again. The authors reported that the child’s proximity to the ground from sleeping in tents may have attracted the sand fly bites to the face. In conclusion, because children with Down Syndrome are immunodeficient and have been reported to have immunological alterations, they are at high risk of infection (Abass *et al*., 2009).

Global Prevalence of Leishmaniasis

Postigo (2010) cites leishmaniasis as being foremost public health concern in the Eastern Mediterranean Region (EMR) WHO. He describes the WHO plan to tackle this problem by supporting ministries of health in setting up a strategic plan by providing training program on case diagnosis and management, establishing surveillance system, connecting and sharing experiences between professionals, and promoting political commitment of national governments (Postigo, 2010). Outbreaks appear to occur in 14/22 of the EMR in ten-year interims. However, there are problems with reported statistics in these countries because the notification process for cases is not mandatory in all countries, there is no distinct reporting format for each type of the disease, and data about vectors and reservoirs of infections are not updated and verified on regular basis. Therefore, these issues would obscure accurate data on the burden of the disease (Postigo, 2010).

Postigo (2010) identifies the main forms of the disease as Zoonotic cutaneous leishmaniasis, anthroponotic cutaneous leishmaniasis, zoonotic visceral leishmaniasis and anthroponotic visceral leishmaniasis. Vector control, when practical, is suggested in addition to treatment for control measures.

Alvar *et al*. (2012) administered surveys to experts and national program managers on the epidemiology and drug access concerning leishmaniasis.

They estimated leishmaniasis to be the ninth most common infectious disease and the most ignored tropical disease. Policymakers usually don't recognize the importance of the disease due to the lack of applied tools for case management and the dearth of current incidence data for the disease (Alvar *et al*., 2012). As a result of the international

collaboration, they concluded that approximately annually 0.2 to 0.4 million VL cases and 0.7 to 1.2 million CL cases. More than 90% of global VL reported in six countries as follow: India, Bangladesh, Sudan, South Sudan, Ethiopia and Brazil. Where CL is more distributed with about one third of cases reported from the Americas, the Mediterranean basin, and western Asia from Middle East to Central Asia. The top countries with the highest incidence rate about 70% – 75% of global reported CL were Afghanistan, Algeria, Colombia, Brazil, Iran, Syria, Ethiopia, North Sudan, Coast Rica and Peru (Postigo, 2010).

Leishmaniasis in the Eastern hemisphere, also called the Old World, is found in some parts of Asia, the Middle East, Africa (mainly in tropical region and North Africa), and Southern Europe. Very importantly, it is not found in Australia or the Pacific Islands (Mansueto *et al*., 2014). Leishmaniasis in the Western Hemisphere (New World) is found in parts of Mexico, Central America, and South America, but not found in Chile or Uruguay (Desjeux, 2004).

WHO studies indicate that priorities must be firmly established in order to control this infection and occurrences of outbreaks. In addition to a literature review, WHO organized a series of regional meetings with the goal of collecting reports for the last five years on CL and VL cases from national officials. A second questionnaire also addressed the state of anti-leishmanial medications in these countries. The results showed that the 10 countries reporting the highest case counts were Afghanistan, Algeria, Colombia, Brazil, Iran, Syria, Ethiopia, North Sudan, Costa Rica and Peru, altogether comprising 70% to 75% of the global estimated CL incidence (Alvar *et al*., 2012). Underreporting of cases and mortality rates also proved to be a major issues.

As a solution to this issue, Alvar *et al*. (2012) highlight the urgent need for reliable surveillance systems, especially for diseases that need intensive control or plans for elimination strategy.

Leishmaniasis Mortality

Alvar *et al*. (2012) draw attention to the mortality rate were the data is extremely insufficient, depending on the case fatality rate of 10%, the temporary estimate of mortality would be between 20,000 and 40,000 deaths /year due leishmaniasis. These data is the most recent estimate of global burden of leishmaniasis although the information is very poor in some countries but at least it can give good estimate of the real impact of leishmaniasis. Good data can help to establish strategic plan to prevent and control the disease (Alvar *et al*., 2012).

Main Features of Clinical Presentation CL and VL

Salam, Al-Shaqha, & Azzi (2014) emphasize the fact that severity of leishmaniasis as a global menace, and they focus on the current epidemiological developments in Iraq, Syria, Saudi Arabia and Jordan. The information included is largely based on WHO reports, and it includes the four modes of zoonotic cutaneous leishmaniasis (ZCL) transmission. Points of interest encompass host–pathogen interaction in leishmaniasis, diagnosis and therapy in leishmaniasis and vector distribution and behavior. Furthermore, leishmaniasis remains a burden on the community due to the emergence of drug resistance and the lack of available vaccines. Additionally, upward trends in human migration increase the chances of infectious disease spread to other areas, introducing diseases like leishmaniasis to new environments and increasing the possibility of mutations that could increase the

virulence of the disease (Salam et al., 2014). A number of cases of leishmaniasis lead to fatalities or permanent disgraces due to bodily scars. The Middle East is known for endemic cutaneous leishmaniasis, and the disease continues to proliferate despite attempts to control the sand fly vector problem and treat burgeoning infections.

A massive effort on reservoir and vector control along with actively pursuing diagnosis in endemic foci will be helpful. Additionally, proper and studious reporting of cases is a necessity for the eradication of this disease, as health care practitioners rely on these data for framing health policies, and there are cases of severe underreporting from some parts of the Middle East. Additionally, drug resistance to pentavalent antimonials and their serious side effects reckons for a greater push towards vaccine research and better therapeutics (Salam *et al*., 2014).

Alvar *et al*. (2008) report, that HIV/ADIS pandemic has changed the natural history of leishmaniasis disease. It increases the risk of having VL by 100 to 2,320 times in endemic areas, decreases response to medication, and increases the likelihood of relapse (Alvar *et al*., 2008). This observation describes the relationship between HIV and the evolution of leishmaniasis, both of which are increasingly attacking parts of Europe as well as underdeveloped countries. The problem remains that most figures of reported cases are deceptive because they omit the multitude of cases in many African and Asian countries on account of sub-par diagnostic facilities and improper reporting systems. Mass migration and wars have exacerbated this situation in parts of Africa.

For example, in Humera (northwest Ethiopia), the proportion of VL patients who were coinfected with HIV increased from 18.5% in 1998–1999 to 40% in 2006. In a retrospective review of 791 cases in Tigray, the case fatality rate among VL-HIV-

coinfected patients was four times higher than that for VL patients not infected with HIV. In Libo, 15 to 18% of all VL patients are HIV positive. The groups at highest risk of coinfection are seasonal migrant laborers, sex workers, young adults in resettlement areas, truck and other public transport drivers, and military personnel deployed in border areas (Alvar *et al*., 2008).

Treatment is also a problem in these areas because of lack of funds for the necessary medications. Recommendations for co-infected individuals include pentavalent antimonials, lipid formulations of AMB, paromomycin, miltefosine, pentamidine and other combinations. Anti-retrovirals are recommended as well to address HIV status.

General Diagnostic and Treatment Methods

Kluger, Girard, Debu & Guillot (2010) discuss Topical photodynamic therapy (PDT) and the possibility of its positive effects on cutaneous leishmaniasis (CL). They describe the logic of heat treatment when they mentioned that, plenty of local and systemic treatments have been offered in order to treat or promote healing with minimal scarring from the disease (Kluger, Girard, Debu, & Guillot, 2010). Unfortunately, the authors anticipate that it is possible that this treatment only achieve cosmetic benefits without properly terminating the actual parasites. However, equivalence in efficacy of a thermosurgery probe with the well-known treatment of a sodium stibogluconate regimen leads the authors to belief that further studies are required. They conclude that any further studies including PDT in CL should take as a negative control light exposure without prophyrin precursors application on CL ulcers to validate whether or not MAL or ALA_PDT is the best treatment for CL (Kluger *et al*., 2010).

Modabber (2010) re-emphasizes the fact that no vaccine currently exists for leishmaniasis. However, he contends that the creation of a vaccine is promising based on the strong immunity resistance that follows the recovery from the disease in humans and animals. Unfortunately, support and funding of a leishmaniasis vaccine is weak within the scientific and medical community due to costs, lack of support from political figures in endemic and impoverished countries, the number of antigens in all species of leishmaniasis and the sub-par cost effectiveness of vaccines. First-generation vaccine attempts include a vaccine cultivated from L. major and immunotherapy. Second-generation vaccines consist of the LEISH-F1 + MPL-SE vaccine, the synthetic vaccine RAPSODI, two DNA vaccines and LEISHDNAVAX (Modabber, 2010).

Van den Berg *et al*. (2012) use surveys conducted in 125 countries with vector control programs as a means to gather information on the usefulness of vector insecticides in an attempt to examine the global use and developments of insecticide use for control of vector-borne diseases between the years of 2000 and 2009. In addition to leishmaniasis, malaria, dengue and Chagas disease were targeted. Data obtained from the surveys included: insecticide type and class, formulation and concentration, method of dispersal, disease targeted or justification of use and the amount of formulation utilized annually.

Van den Berg *et al*. (2012) comments on the efficacy of vector insecticides; since the 1940s, vector control has depended mainly on the action of chemical insecticides like DDT (dichlorodiphenyltrichloroethane) and other organochlorine insecticides, used as a preventive measure against the transmission of the disease to humans.

However, insecticide resistance along with harmful consequences for humans and the environment has recently posed problems. Results incorporated details about country responses, global use, individual diseases and trends. The authors conclude that there should be strategies for insecticide resistance management with coordination with disease-specific programs and donor-supported projects and with the agriculture department. In addition, integrated vector management can offer a long-term approach to ensure that insecticides are used wisely and reasonably. “Insecticide resistance management strategies should be coordinated among disease-specific programs and donor-supported projects and with the agriculture sector. Integrated vector management, as a rational decision-making process, offers a long-term approach to reduce selection pressure for insecticide resistance and to ensure the judicious use of insecticides”(van den Berg *et al*., 2012).

Monge-Maillo & López-Vélez (2013) posit that CL treatment can be accomplished via topical or systemic regimens in their comparison of Old World CL (OWCL), New World CL (NWCL), and oral-nasal mucosa MCL (NWMCL). The goal of this extensive literature review on treatment methods is to offer recommendations stratified according to levels of evidence concerning the specific species of Leishmania identified and the geographical spot of the infection.

Treatment recommendations for CL include the CO2 laser, cryotherapy, thermotherapy and photodynamic therapy. Physical therapy suggestions for NWCL include thermotherapy and topical nitric oxide. Topical drug therapies for OWCL include topical paromomycin, topical imidazole drugs and intra-lesional pentavalent antimonials. Additional options consist of oral drug therapy/treatment as well as parenteral

therapy/treatment. The study concluded that in spite of the lack of evidence, parenteral pentavalent antimonials were the drug of choice to treat OWCL until the 1990s. Recently, evidence has shown that OWCL is self-limiting, and now not intervening is considered the first line of treatment in most cases (Monge-Maillo & Lopez-Velez, 2013).

Leishmaniasis in the Middle East

In the Middle East leishmaniasis is endemic and common reported type of leishmaniasis is CL Leishmaniasis, where Syria reporting the highest incidence. Although some countries established national control programs for preventing and controlling the disease, but the disease still continue to spread and more cases were reported. There is recent factor that contribute to the increased number of cases in the last few years, due to standing military conflicts and civilian revolution in the Middle East, a lot of human migration happened in the region. This factor and other associated factors play a major role in the spread of leishmaniasis because of limited access to healthcare and most cases usually happened among the poor people (Postigo, 2010). Refugees, armed forces and multinational contractors are particularly at risk to get infected with leishmaniasis (Jacobson, 2011).

Jacobson (2011) discusses the endemic state of leishmaniasis in the Middle East in addition to probable and likely phlebotomine sand fly vectors and reservoir hosts of the Leishmaniases species in Afghanistan, Iran, Iraq, Israel, Jordan, Lebanon, Saudi Arabia, Syria, Turkey, and Yemen. The main catalyst of the spread of this disease in this area is the frequent and nomadic traits of entire populations of people that are results of military and civilian discord. Migrants, military personnel and multi-national

contractors pose the highest risk for contraction of this disease. A public health concern exists for new populations of people relocating to these endemic regions as well as emerging sand fly and animal natural reservoirs (Jacobson, 2011).

Hejazi *et al*. (2010) identify CL as a menacing problem in tropical and subtropical regions. Their study focuses on Iran, a country whose climate and risk factors are comparable to those of KSA. It is helpful to create a link between the two through comparison. Again, they stress that an investigation of the knowledge, attitude and performance factors of the affected population are essential to any successful intervention, and program implementation leaders must first gain a firm grasp on these concepts. This particular study involves 166 mothers who have one or more children who suffer from CL. Questionnaires focused on attitude, performance and prevention knowledge. Results revealed that the general performance of the mothers was excellent and instinctual. However, attitude scores were mediocre, and knowledge of prevention scores were abysmal. Due to the high illiteracy rate of these mothers, educational pamphlets were deemed ineffective. In conclusion, the authors recommend
educational programs and other multidisciplinary approaches to promote best health practices in the targeted population, taking in consideration the level of literacy and the lifestyle. Practical instruction or face-to-face educational methods may be effective in this regard (Hejazi, 2010).

Leishmaniasis in Iraq

Salam *et al*. (2014) mentioned that both forms of leishmaniasis, CL and VL, are present in Iraq, where 23% of the total population live under the national poverty line. Most of cases were reported in 1992 because of war and people migration with 45.5 cases per 100,00 of population. The causes for this increase were poor sanitation, people migration to endemic area, and a rise in vector population. In 2004 cases declined but recent data in 2012 have shown a sudden increase in the past tow years. Underreporting remains major obstacle in acknowledgment of the disease epidemiology. VL found in central Iraq and southeastern parts with 90% of the cases reported in children less than five years of age. There were 1,049 cases of VL reported in 2008 and 1,045 in 2012, which has declined from 3,218 cases in 2004 because of WHO and Iraqi Health Ministry efforts. CL is predominant in the whole country except for the three northeastern provinces. In 2008 there was an outbreak with 300 cases and 400 cases in 2009 (Salam *et al*., 2014).

Leishmaniasis in Syria

In Syria, CL has been endemic for many years. The first documentation of leishmaniasis goes back to 1745 where it was called the “Aleppo boil” (Ashford, Rioux, Jalouk, Khiami, & Dye, 1993). In recent years, there was increase in number of cases being reported since 1990s, with beak of 58,156 cases in 2011 in Idlib, Hamah, and Halab province. Syria is suffering of major political and military disturbances and conflicts since 2011, which has led to massive population migration within Syria and neighboring countries forcing them to lives in refugees’ camps.

In area of conflicts there are many public health concerns such as sanitation, waste disposal, and healthcare infrastructure and sever dearth in healthcare workers.

These factors and other have led to more cases of CL being reported estimated about 52,983 cases in 2012. VL also being reported in Syria with 19 cases in 2010, but these maybe biased because of underreporting and it is an area, which need more research (Salam *et al*., 2014).

Leishmaniasis in Jordan

Salam *et al*. (2014) mentioned the history of the first cases of leishmaniasis goes back to 1929, and being known that CL is endemic in Jordan. Jordon Valley is considered to hyperendemic area with 100% positive Leishmania skin test in individuals over five years of age was reported in 1992. From 2004 to 2008 CL cases being reported were 100-200 cases.

According to Mosleh *et al* (2008), there has been serious underreporting of the cases by an estimated factor of 47 times, which makes it great challenging for health organizations and WHO eager to reach eradication phase. VL is rare in Jordan with about 15 cases being reported since 1960. Point worth mentioning is that Jordan has no national control program for leishmaniasis. Total population of Jordan more than 6 million people, in which 13,3 % are living below the national poverty line, this rises the need for setting strategic plan for more investment in healthcare infrastructures, increase awareness and provide treatment in regions with high incidence (Salam *et al*., 2014).

Leishmaniasis in Saudi Arabia

Salam *et al*. (2014) mentioned that CL is the common form of the disease in Saudi Arabia. The disease is endemic in some region such as Al-Hassa oasis, northeast region, Al-Madinah Al-Monawarah, Al-Quaseem and Assir province. In 1983

leishmaniasis reached epidemic rate with 18,000 cases of CL being reported but after setting up the National Control Program in the same year the incidence decline dramatically (Salam *et al*., 2014)**.**

Zakai (2014) provides a distribution of the leaishmaniasis vectors a cross the Saudi Arabia provinces where L. major which caused CL has been reported from Al-Quaseem, Al-Madinah Al-Monawarah, Al-Hassa, Riyadh and the Eastern Province, whereas CL caused by L. topica found to be restricted in the southwestern part of the country. Moreover, it found that the Phlebotomus papatasi is the transmitting vector of L. major in Al-Hasaa area while Phlebotomus sergenti was the transmitting vector of L. tropica in the southeastern part of the country (Zakai, 2014).

As the statistics of MoH shows the cases prevalence were in 2010 the total cases of CL being reported was 4,129 cases, which declined to 1,988 cases in 2013, but in 2014 there was again mild increase of the cases to reach 2,190 cases where 999 of the total cases were reported among non-Saudi residence (Minisrty).

Zakai (2010) also highlighted on the common risk factors that contributed and may have bestow the raise in leishmaniasis disease in KSA, including urbanization, growing agriculture investment, indigent living conditions for the farmers at farms and the huge immigration from other countries especially those countries with military conflict such as Iraq and Syria in the north and Yemen in South. Most of VL has been reported from Jazan province from 2010 till 2014 (Zakai, 2014).

Amin *et al*. (2012) identify the goals and priorities of the public health sector in relation to management and containment of CL as analyzing links between disease spreading and socio-demographical and environmental risk factors in a furtive attempt

to develop prevention and control protocols. The primary objective of their study is to evaluate baseline comprehension of the existence and dangers of this disease among endemic populations and to provide qualitative data and clarify perceptions in Saudi Arabia. They also strive to relate correlate these views with relevant socio-demographical environments. This cross-sectional descriptive survey of 1824 subjects (15 to 63 years of age) was conducted in the Eastern region of Al Hassa, Saudi Arabia. The authors express the severity of this disease when they highlight the causative agents of CL, which are a group of protozoa transmitted by sand flies to mammals including humans. Also, they mentioned the global estimated incidence of 1.5 – 2 million new cases and that 350 million people are at risk of all forms of the disease (Amin *et al*., 2012).

KSA is at high risk because the main carriers of CL are sand flies and desert rodents. Following a sequence of consultations between educators, public health officials and concerned community leaders, and questionnaire was created and designed to test public knowledge of CL in terms of manner of transmission, epidemiological aspects and prevention methods.

The conclusions revealed that the perceptions and attitudes of the targeted population regarding all aspects of CL including the vector, transmission, and personal protection methods, played a key factor in the success of any community-based intervention (Amin *et al*., 2012).

Amine *et al*. (2012) focused also in this study about public awareness and attitudes towards CL in an endemic regions in Saudi Arabia which concludes that over 76% of the studied population recognized the infectious nature of CL, also the study

found that there were low awareness for important basic epidemiological aspects for the disease such as transmission of the disease, risk factors and prevention. One of the essential findings of this study was about identifying of possible risk factors for CL, which includes presence of farm nearby houses, domestic animal in or nearby houses, nearby water well and springs, presence of pets, sleeping out door with out using sleeping net, camping in the desert or farms, gender male are more than female, living in rural area, low socioeconomic status, low education level (Amin *et al*., 2012).

CL is more common in male than female and this may related to the cultural customs that female in Saudi Arabia are follow, which requires female to cover their faces and extremities, and also because of the main working manpower in the country are male (Haouas, Amer, Ishankyty, Alazmi, & Ishankyty, 2015).

Desjeux (2004) differentiates between types of Leishmaniasis according to clinical presentation: visceral leishmaniasis (VL), which is usually fatal if untreated, muco-cutaneous (MCL), diffuse cutaneous leishmaniasis (DCL), which is a chronic disease due to a defect in cellular immune system, and cutaneous leishmaniasis (CL), which can lead to disability if there are many lesions (Desjeux, 2004).

This review of literature and studies cites leishmaniasis as a dire public health threat that is only worsening over time. It is spread via sandfly bites, which have a parasitic effect on the human hosts as they multiply in the intestinal tract and do not become full-blown infections for between eight and twenty days. This disease, which plagues 88 countries, is especially prevalent in 13 countries, one of them being Saudi Arabia. 1-1.5 million CL cases and an upwards of half a million VL cases cause human suffering and despair every year. Desjeux (2004) asserts that numerous other cases

exist, but figures are difficult to determine due to patchwork distribution in endemic regions, a multitude of undiagnosed, misdiagnosed and unreported cases, and finally, the difficulty in detecting leshmaniasis early in many cases. Other risk factors include migration of seasonal workers, new project development and land cultivation, malnutrition, crumbling of socio-economic conditions in low-income, urban suburbs and an intersection of VL/AIDS infections. The author also discusses disease burden, current control tactics and obstacles for disease control. In conclusion, Desjeux (2004) suggests that there is a need to translate new knowledge into cost effective tools and provide better access for patients so they receive the best diagnosis, treatment and vaccines.

Khan & Zakai (2014) study endemic occurences of CL in the endemic Taif region of Saudi Arabia. Additional endemic areas of Saudi Arabia include Al-Hassa, Al-Gaseem, Madina, Hail, Riyadh, Asir, Tabooq, Al-Baha, Jazan, Najran and Bisha**.** Their objective was to test the efficacy of fluconazole and itraconazole in patients with CL and to measure the end result of these drugs on liver and kidney functions (Khan & Zakai, 2014). Due to developing drug resistance, combination therapy is often necessary. Methods of detection included microscopic smear analyses as well as nested polymerase chain reactions. Turbah, Al-Garya, Missan and Hadad were included as regions of interest as well in this study due to their diverse ecological conditions. In addition to sandfly hiding places that protect them from fogging, lack of awareness of this disease is a major problem. Results and conclusions indicated that fluconazole and itraconazole may be used for the treatment of CL with favorable recovery rates and a smaller number of side effects. In conclusion, the authors emphasize the importance of

promoting proper awareness programs about the sand fly life cycle and breeding places and how the public can take preventive and protective measures against this insect (Khan & Zakai, 2014).

Abdalla, Abdelgani, Osman & Sarhan (2013) analyze a case report of a twenty-five year old Egyptian male who stayed in Utama, near the El-Madina Manowra region of Saudi Arabia and developed suspicious skin lesions on his upper extremities over a period of one to three months. The man was a farmer who lived amongst rodents and other domesticated animals that could have been animal reservoirs. They divide CL transmission into two major categories: arthropods (ACL) and animal reservoirs (ZCL). As mentioned in the study, according to WHO report on neglected tropical diseases in 2009, leishmaniasis is endemic in 88 countries, with about 350 million people at risk of having the disease. It is estimated that 12 million people are affected by leishmaniasis worldwide with about one person infected every 20 seconds; 90% of cases being reported are from Afghanistan, Algeria, Iran, Iraq, Saudi Arabia, Syria, Brazil and Peru. (Abdalla, 2013). Diagnosis methods included skin smear using Giemsa stain, leishmanin test (LST), polymerase chain reaction (PCR), sequencing and phylogenitic analysis BLAST (NCBI). They also introduce post Kala-azar Dermal Leishmaniasis (PKDL), which can occur after remission from VL. They recommend drug treatment due to the absence of a vaccine, and they contend that L. major is a prevalent species leading to CL in this region. In conclusion, the author emphasizes the importance of diagnosing each type of leishmania species in order to be able to prescribe appropriate therapeutic treatment for that specific species (Abdalla, 2013).

Global Leishmaniasis Control and Prevention Programs

As international effort to minimized the impact of the disease the WHO in their first report on neglected tropical disease titled with the global impact of neglected tropical diseases mentioned that more than 70 years, the first line of treatment in most countries was by using injectable pentavalent antimonials which need long time to cure , toxic and painful. Recently drug resistance has been reported in part of India and Nepal. The medication is too expensive to be used by developing countries. The second line of treatment is more toxic such as amphotericin B or pentamidine. New medicine has been developed called liposomal amphotericin B, which considered being highly effective, and with no side effects yet reported, now it is the first line of treatment against visceral disease.

Developing and improving control measures of leishmaniasis would have a great impact on the rate of morbidity and mortality. The disease affects humans; implementing of active case detection and early treatment can decrease transmission. A great example of international collaboration against leishmaniasis was the signing of a memorandum of understanding in 2005 by Bangladesh, India and Nepal to eliminate visceral leishmaniasis by reducing the incidence of the disease to less than 1 case/ 10000 individuals by 2015.

There is an urgent need to continuously improve active case detection of both CL and VL, and to provide the diagnostic techniques in peripheral health center where majority of patients are usually treated based on clinical symptoms. Establishing strategic program in order to control both vectors and reservoir are important part in leishmaniasis disease control. Using combined campaigns targeting mosquitoes and sand flies are more cost effective in vector control program (WHO, 2010b).

Global Best Practices for Controlling and Preventing Leishmaniasis

Stockdale & Newton (2013) in this literature review aims to identify and evaluate the current evidence base for the use of various preventative methods against leishmaniasis. This review focuses on the absence of research measuring human specific outcomes (35%of the total) across all intervention categories. The study highlights the shortage of generalized finding for all of the different geographic areas and the lack of knowledge about the mechanism of transmission of leishmania in various setting. More study and research is needed for vaccine development and to investigates human infection as main outcome.

A conclusion from this review raises the necessity to develop a cheap, rapid, sensitive and specific diagnostic test that can provide evidence of infection this will accelerate the early detection and containment of the infection. Applying the right diagnostic techniques to measures human outcomes in future studies. Intervention studies should accomplish the intervention purpose either different species of lieshmania or the mode of transmission.

There is need of conducting survey prior applying the prevention and control intervention studies to help determine the vector specific behavior or habits relating to transmission (i.e., where and when the sand fly bite), reservoir specific behavior or habits relating to infected animal with the disease and clinical presentation, finally, human at risk behaviors and habits would they accepts the interventions and are they having the enough knowledge about the disease and its symptoms (Stockdale & Newton, 2013).

Role of Active and Passive Surveillance in Controlling Disease

A strong surveillance system is a fundamental component of control or elimination program. Surveillance in public health field should provide true scientific information to high authorities and stakeholder about appropriate public health action. One of the important objectives of surveillance is to provide essential information in order to guide the intervention.

Nsubuga *et al*. (2006) pointed the substantial rule of surveillance in public health is to design and fulfill valid and reliable information to the decision makers with cost effective and in regular basis. Nsubuga *et al*., explained that in public health surveillance precision can be oversight to improve timeliness and save resources that can be spent on the intervention instead, " what is worth doing is worth doing right" (Nsubuga *et al*., 2006).

Active and Passive Surveillance

Active surveillance is a system employing staff members to regularly contact heath care providers or the population to seek information about health conditions. Active surveillance provides the most accurate and timely information, but it is also expensive. Passive surveillance is a system by which a health jurisdiction receives reports submitted from hospitals, clinics, public health units, or other sources. Passive surveillance is a relatively inexpensive strategy to cover large areas, and it provides critical information for monitoring a community's health. However, because passive surveillance depends on people in different institutions to provide data, data quality and timeliness are difficult to control (Nsubuga *et al*., 2006).

Leishmaniasis Elimination Programs in Bangladesh, India and Nepal

Das *et al*. (2014) study was done to analyze the effectiveness of active case detection (ACD) for new VL cases (active surveillance). The percent of newly diagnosed VL cases has been increased in all the three countries significantly compared to passive case detection (PCD), which considered as (passive surveillance). And the cost varies between these countries depends on the type of working staff, transportation and training. As result of using active case detection further effort and cost rises when incidence of the cases falls or passive case detection improves.

In this study they conclude to achieve VL elimination goals, designed programs need to be more flexible and could be modify based on epidemiologic and implementation needs in the country. One of the study suggestion about ACD that could be a cost effective when using as complementary approach to PCD especially in endemic areas with indigent access. As result of the study the active surveillance is the best methods used in endemic situations and elimination programs. It is important to consider combination of approaches that are cost effective, sustainable, and flexible to the epidemiological condition (Das *et al*., 2014).

Leishmaniasis Control and Prevention in KSA

KSA has a successful story in prevention and controlling of leishmaniasis disease when the Ministry of Health established the National Control Program of both CL and VL leishmaniasis in 1979. Leishmanisis infection was decreased significantly since the last outbreak was reported 1983 till recent years. National Control Program is under the umbrella of Communicable Disease Control General Department in the

Ministry of health. Furthermore, this program focus also on both vector control and reservoir control in order to reach the maximum level of controlling leishmaniasis.

Thee main objectives of the National Control program for leishmaniasis are:

- Prevention of leishmaniasis in endemic area to reach level of non public health concern.
- Monitor and maintained zero incidence in area with no leishamniasis cases.
- Treat and follow up cases.
- Continuous epidemiological surveillance to detect the cases when reported from healthcare providers such as Hospitals or Primary Healthcare Center (PHC), and sending responds team accordingly.
- Comprehensive vector control (Sand fly) in area where cases were reported.
- Comprehensive reservoir (desert rodent) in area where cases were reported.
- Continuous training for all workers in the program.
- Health education to the community.

Leishmaniasis Surveillance in KSA

Surveillance system is a gold standard to establish reliable data and indicators about leishmaniasis impact to that led to early detect and assist efforts for prevent and control of the disease. As WHO released the recommendation for surveillance standards in the second edition in 1999 the recommended type of surveillance has different approaches. At first, at peripheral level patient records must be saved for further investigation and case management. Second, monthly reporting of total cases from periphery to intermediate and central level. Third, active case surveys can be performed as standards or periodical of certain population is an alternative way to

obtain an estimate about CL prevalence. Fourth step, annual reporting from central level to WHO. This what have been used in nation control program in the country.

National Control Program

The main structure for the national control program plan is listed as follow

First: Epidemiology Screening and case reporting.

1- Case Reporting: All hospitals (governmental or private) and PHCs are monthly reporting all diagnosed Leishmaniasis cases to the Vector control department in Health affair in that region. Also, continuous evolution and monitoring of reporting process done by healthcare facilities and make sure they following the appropriate steps. Monthly report must be submitted to the Ministry of health, leishmaniasis department.

2- Epidemiology Screening: Upon receipt of any reported cases of CL, vector control department in health affair in the region will send responding team. The Mission of responding team includes: complete description of the area of cases (location, nature of the area, and confirmation of the presence of the vector and reservoir). Identify the behavior and way of living and habits of citizens in the study area and make them aware of the seriousness of the disease and conduct periodic follow-up to verify the implementation of the protective recommendation of the population in that region with collaboration with control centers, Municipal branches and health education department.

Leishmaniasis Control Strategies in KSA

Secondary: Control of the reservoir

- Control of desert rodent (CL reservoir) in areas where cases were reported.

- Control of dogs (VL reservoir) in area where cases were reported.
- Cleaning farms and fields in the surrounding environment and demolition for desert rodents burrows.
- Remove (RAMTH) plants, which is the main source for nutrition to the rodent.
- Setting control measures for both rodent and dogs in affected areas.
- Educate farms works about the precautions measures.
- Prevention and control measures will started in area where CL was reported.

Third: Control of sand fly

- Assigned a special team to control sand fly.
- Arranging home visits of control team to the cases.
- Spraying pesticide with specific instructions in affected area.
- Follow spraying indications and instructions in sand-fly control.

Fourth: Health education

- Determine the number of primary health centers in each region and estimate the number of patients in each center, and then provide them with education posters and pamphlets targeted the public about the leishmaniasis diseases and ways of prevention and protection.
- Provide all healthcare workers in all healthcare facilities with educational material about leishmanaiasis including clinical presentation, diagnosis technique, treatment and reporting process.
- Provide Seminars and workshops for all healthcare providers about leishmaniasis update in diagnosis methods and vector control.

Fifth: Continuous training for all technician personnel working in the program.

Sixth: Continuous evaluation of the program;

During the implementation of the program there is a continuous assessment of all the stages of implementation in order to identify the difficulties and obstacles facing the program plan and to discover weaknesses to avoid them in the future.

Achievements National Control Program

The program has Indicators of achievement, which includes:

- Annual incidence rate of cutaneous leishmaniasis.
- Monthly and annually Prevalence of visceral leishmaniasis.
- Mortality rate of visceral leishmaniasis.
- Density of the vector in area of cases.
- Density of reservoir in area of cases.

I. Achievements in terms of the epidemiological situation:

- Cutaneous Leishmaniasis (CL):
  - CL infection rate in 2014 was 7.1 cases per 100,000 of the population, down from what is planned under the Ninth Development Plan for the same year, which was (8.3) per 100,000 of the population.
  - Maintain the infection free areas of CL in the year 2014 by activation of epidemiological surveillance systems in all regions.
- Visceral Leishmaniasis (VL):
  - VL infection rate in 2014 was (0.036) cases per 100,000 of the population, down from what is planned under the Ninth Development Plan for the same year, which was (0.05) per 100,000 of the population.

- Maintaining the infection free areas of VL in the year 2014 by activation of epidemiological surveillance systems in all regions.

II. National program provides Training courses annually targeting all healthcare works and providers as well as technicians who works in the control program in order to keep them updated about leishmaniasis disease from comprehensive view such as diagnosis, treatment, management, education. Also provides laboratory courses and general educational courses.

III. Achievements on the level of support control programs in regions;

Maintaining adequate infrastructure and recourses for all regional program and facilitate any obstacles the control team may face.

IV. The program has recently edit DRUG POLICY manual following the WHO standers.

V. For the first time Rapid Diagnosis test was licensed, as it is time-consuming test done to diagnose VL.

Obstacles and challenges of Leishmaniasis Control Program in Saudi Arabia

- Lack of cooperation with the relevant government agencies:

  - The Ministry of Agriculture in the fight against (sand fly) the vector of the disease

  - The Ministry of Municipal and Rural Affairs in the fight against (rodent) the reservoir of CL.

- Shortage in some specialized categories of manpower in the program (insect specialist, insects technicians).
- Shortage of seasonal manpower force to work in control team in regions.

Recently, one of the major factor is the regional instability due conflict in Syria and Yemen with the huge number of human displacement been accepted in the country has great challenges to the health system including the prevalence of leishmaniasis.

Chapter 3 - Manuscript

Prevalence and Distribution of Leishmaniasis in Saudi Arabia, 2010-2014

Abstract

Background: Leishmaniasis is a vector-born, parasitic disease transmitted to mammals by the bite of an infected phlebotomine sand fly. It affects people in 98 countries and is a major public health concern and endemic in the Middle East, including the Kingdom of Saudi Arabia (KSA). We investigated trends in leishmaniasis prevalence from 2010 – 2014 in KSA to make recommendations for the national control program.

Methods: Leishmaniasis incidence rates (IRs) per 100,000 population in KSA and 95% confidence intervals (CIs) from 2010 – 2014 were stratified by nationality, gender, and 13 administrative provinces.

Results: We observed a decreasing trend in the IRs of leishmaniasis in KSA, by year. This decrease was statistically significant from 2010 (IR=14.97; 95%CI=14.52-15.44) to 2014 (IR=7.11; 95%CI=6.82-7.42). The IRs among Saudis was lower than that of non-Saudis and the difference in IRs by nationality was statistically significant for all years of the study. We also observed a significantly decreasing trend in leishmaniasis IRs from 2010 to 2014 for both males and females. For males, the IR was 20.76 (95%CI=20.05 - 21.49) per 100,000 population in 2010 and sharply decreased almost 50% to IR of 9.53 (95%CI=9.08- 10.00) in 2014. A similar trend was observed for females, whose IR was 7.62 (95%CI=7.14 - 8.12) in 2010, decreasing to IR of 4.03 (95%CI=3.71- 4.38) in 2014. We observed higher IRs of leishmaniasis in AL-Madinah, Al-Qasim, and Hail provinces during the study period.

Discussion: Leishmaniasis significantly decreased in KSA from 2010 – 2014. The KSA eradication effort for leishmaniasis has been successful. We recommend active surveillance for early detection and continuous health education for both healthcare professionals and the public.

Introduction

Leishmaniasis is a vector-born, parasitic disease transmitted to mammals by the bite of an infected Phlebotomine sand fly, where the main hosts are sylvatic mammals like rodents, hyraxes, wild canids, and dogs (Abdalla, 2013). Though all leishmania species are closely similar in their morphology, they produce three clinically different diseases (Delhi Zoonosis Division, 2005). Human infection is caused about 21 species that infect mammals, that include the *L. donovani* complex (*L.donovni, L. infantum* (which also known as *L.Chagasi* in the New world); *L. tropica; L.major; L.aethiopica*; and the *L. Viannia braziliensis*, *L. viannia. Guyanesis, L. viannia. Panamensis and L. viannia*. Peruviana.

All species have similar morphology, but with different genus structures. (Cantacessi et al., 2015) A parasitic disease found in the topics, subtropics, and southern Europe, leishmaniasis is classified under Neglected Tropic Disease (NTD). There are two common forms of leishmaniasis: cutaneous leishmaniasis (CL), which causes skin ulcers, and visceral leishmaniasis (VL) and affects the internal organs (mainly the liver, spleen, and bone marrow).

Leishmaniasis ranks ninth in disease burden. And the neglect of this disease comes from a complexity of epidemiology and ecology, scarcity of recent data, and high authorities who could not perceive its importance. We investigated trends in leishmaniasis prevalence from 2010 – 2014 in KSA to make recommendations for the national control program.

Methods

We conducted a retrospective analysis of all cases of cutaneous and visceral leishmaniasis reported through the Ministry of Health (MoH) Registry between 2010 and

2014 to estimate the IRs at 95% confidence intervals (CI) of leishmaniasis in KSA from 2010 – 2014. IRs were stratified by nationality, gender, and the 13 administrative provinces. Leishmaniasis IRs were estimated using the number of cases per year over the total population per 100,000 individuals.

We used the chi-square test to determine the statistical difference between the IRs of male and female and Saudi and Non-Saudi cases. Corresponding p-values were reported. The source of population data was the General Authority for Statistics for Kingdom of Saudi Arabia, which released their mid-annual population estimates from 2010 – 2025 using a model estimate from the population distribution in the provinces and regions based on the 2010 annual census. The population dataset contained estimates for the total population per province and total population by nationality per province.

This dataset was used to estimate the IR for the total population and by nationality. To investigate the trend of IR by gender, population data for men and women were only available in the 2010 census. In order to estimate the population data for other years, we first estimated the growth factor in each province per year based on the population data as reported by the Central Department of Statistics and Information (CDSI) from 2007 – 2012. We also estimated the gender proportion of the population for each province. Assuming the same growth factor for both men and women, and maintaining the average proportion in the population from 2007 – 2012, we estimated the size of the population by gender in other years. The overlap between the CDSI population data per province from 2010 – 2012 matched the General Authority of Statistics data from 2010 – 2012.

A p-value of less than 0.05 was considered statistically significant. Descriptive and analytic statistics were performed using Microsoft Excel 2016 (Microsoft, Seattle, WA).

Results

We observed a downward trend in the IR of CL in KSA over the course of the study period (Table 1). This decrease was statistically significant from 2010 (IR=14.97; 95% CI = 14.52 - 15.44) to 2014 (IR=7.11; 95% CI = 6.82 - 7.42). The CL IRs of Saudis were slightly lower than those of non-Saudis (Table 2). Among Saudis, we observed a significant decrease in IR from 2010 (IR=11.48; 95% CI = 11.00 - 11.97) to 2014 (IR=5.75; 95% CI = 5.43 - 6.08). A similar trend was observed for non-Saudis from 2010 (IR=22.70; 95% CI = 21.71 - 23.72) to 2014 (IR=9.92; 95% CI = 9.32 - 10.55). The difference in IRs by nationality was statistically significant from 2010 to 2014.

Table 1. Reported Cases of Cutaneous Leishmaniasis and Incidence Rates, by Year, Kingdom of Saudi Arabia, 2010 – 2014

Year	#	IR°	95% CI*
2010	4129	14.97	14.52- 15.44
2011	1951	6.87	6.57- 7.18
2012	1464	5.01	4.76- 5.27
2013	1988	6.62	6.34- 6.92
2014	2190	7.11	6.82 - 7.42

°IR = incidence rate per 100,000 population
*CI = confidence interval

Table 2. Reported Cases of Cutaneous Leishmaniasis and Incidence Rates, by Year and Nationality, Kingdom of Saudi Arabia, 2010 – 2014

Year	Saudi			Non-Saudi			P-value
	#	IR°	95% CI*	#	IR°	95% CI*	
2010	2179	11.48	11.00 - 11.9	1950	22.70	21.71- 23.72	0.0001
2011	1015	5.23	4.91 - 5.55	936	10.43	9.78 - 11.11	0.0001
2012	761	3.83	3.57 - 4.11	703	7.51	6.97- 8.08	0.0001
2013	1028	5.18	4.87- 5.50	960	9.87	9.26 - 10.51	0.0001
2014	1191	5.75	5.43 - 6.08	999	9.92	9.32- 10.55	0.0001

°IR = incidence rate per 100,000 population
*CI = confidence interval

We observed a statistically significant decrease in CL IRs from 2010 to 2014 among both males and females (Table 3). Among males, the IR was 20.76 (95% CI = 20.05 - 21.49) in 2010, sharply decreasing by 50% to 9.53 (95% CI = 9.08 - 10.00) in 2014. A similar trend was observed among females; their IR was 7.62 (95% CI = 7.14 - 8.12) in 2010, decreasing to 4.03 (95%CI = 3.71 - 4.38) in 2014. The difference in IR by gender was generally statistically significant during the study period (Table 5). Over the course of the study period, we observed a high and fluctuating CL IR above that of the general population in the provinces of Al-Madinah, Al-Qasim, and Hail.

Table 3. Reported Cases of Cutaneous Leishmaniasis and Incidence Rates, by Year and Gender, Kingdom of Saudi Arabia, 2010 – 2014

Year	Male			Female			P-value
	#	IR°	95% CI*	#	IR°	95% CI*	
2010	3204	20.76	20.05 -21.49	925	7.62	7.14 - 8.12	0.0001
2011	1538	9.68	9.20 - 10.17	413	3.30	2.99- 3.63	0.0001
2012	1163	7.11	6.71- 7.53	301	2.34	2.08- 2.61	0.0001
2013	1615	9.61	9.15- 10.09	373	2.82	2.54- 3.12	0.0001
2014	1643	9.53	9.08- 10.00	547	4.03	3.71- 4.38	0.0001

°IR = incidence rate per 100,000 population
*CI = confidence interval

Table 4. Incidence Rates of Cutaneous Leishmaniasis, by Year in Al-Madinah, Al-Qasim and Hail provinces, Kingdom of Saudi Arabia, 2010 – 2014

Male IR

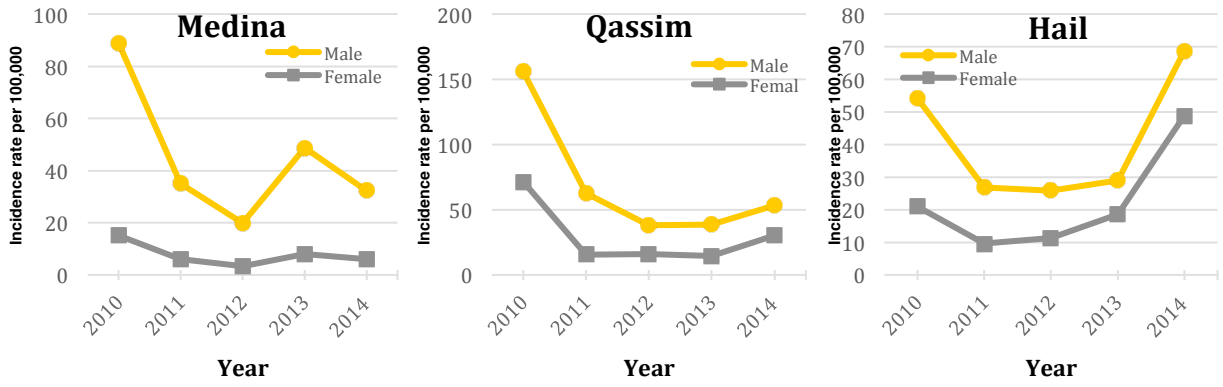
	Year				
Province	**2010**	**2011**	**2012**	**2013**	**2014**
Al-Madinah	88.94	34.96	19.88	48.63	32.18
Al-Qasim	155.82	62.83	37.85	38.62	53.08
Hail	54.14	26.81	25.84	28.93	68.53

Female IR

	Year				
Province	**2010**	**2011**	**2012**	**2013**	**2014**
Al-Madinah	15.20	6.03	3.33	7.94	6.00
Al-Qasim	71.32	15.73	16.01	14.42	30.46
Hail	20.85	9.63	11.40	18.64	48.88

In 2010, the IR in Al-Madinah was 55.38 (95% CI = 52.02 - 58.89), which decreased to 12.35 (95% CI = 10.84 - 14.00) in 2012, increased to 30.11(95% CI = 27.76- 32.61) in 2013, and fell again in 2014 to 20.27 (95%CI= 18.37- 22.31). This fluctuation was seen among males but not among females over that period (Figure 1).

Figure 1. Incidence Rates of Reported Cases of Cutaneous Leishmaniasis, by Year and Provinces, Kingdom of Saudi Arabia, 2010 – 2014



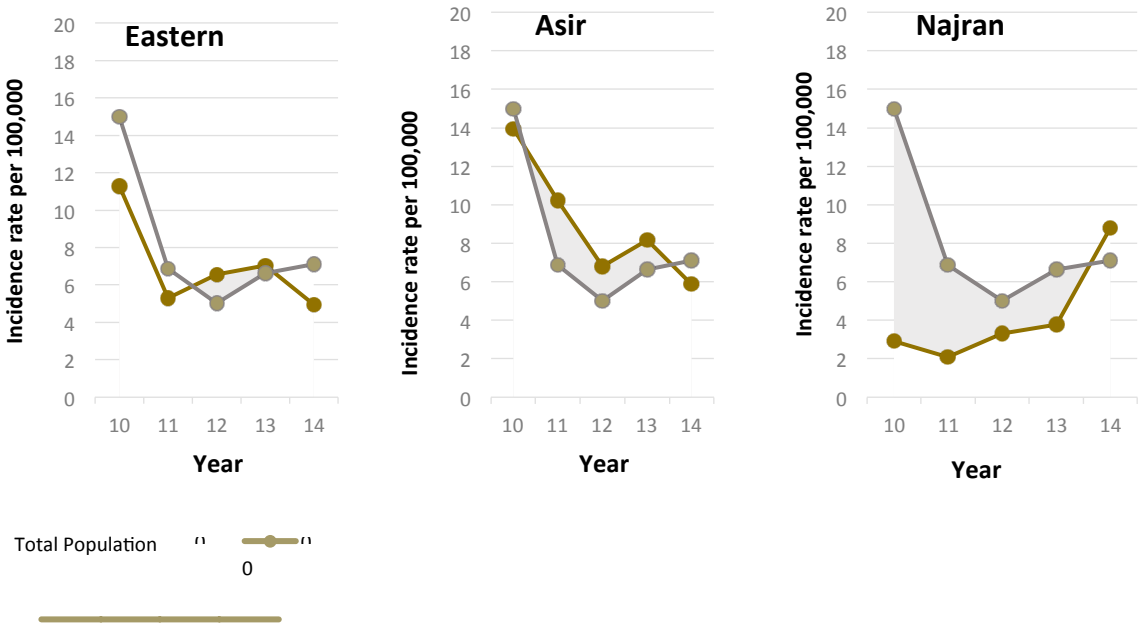
In Al-Qasim, the IR was 118.58 (95% CI = 112.63 - 124.78) in 2010, decreasing to 27.96 (95% CI = 25.23 - 30.90) in 2013, then rising in 2014 to 43.12 (95% CI = 39.74 - 46.69). Unlike in Al-Madinah, the IRs among males and females in Al-Qasim exhibited similar trajectories over the years (Figure 1).

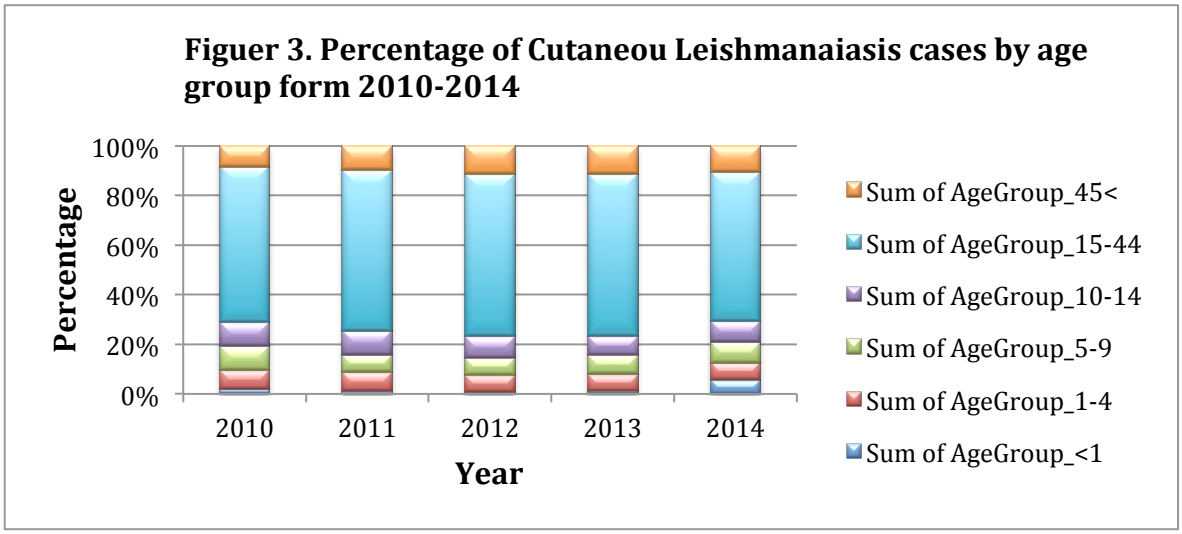
In Hail, the IR was 38.60 (95% CI = 33.89 - 43.79) in 2010, decreasing to 19.10 (95% CI = 15.93 - 22.72) in 2012, then increasing to 24.13 (95% CI = 20.58 - 28.12) in 2013, and to 59.36 (95% CI = 53.74 - 65.41) in 2014. In general, we observed decreases during the period from 2010 to 2012, after which we observed a sharp increase in IR among males, more so than that among females (Figure 1).

The male to female ratio CL IR is 7 to 1 in Al-Madinah, 3 to 1 in Al-Qasim, and 2 to 1 in Hail. Assir's IR was below that of the general population through the entire study period. Najran's IR was below that of the general population rate until a sharp increase in

2014, resembling that seen in Hail. Eastern Province's IR fluctuated to above and below the IR of the general population, which could be an area of further investigation (Figure 2). The proportion of cases was much higher among those aged 14-44 years old (Figure 3).

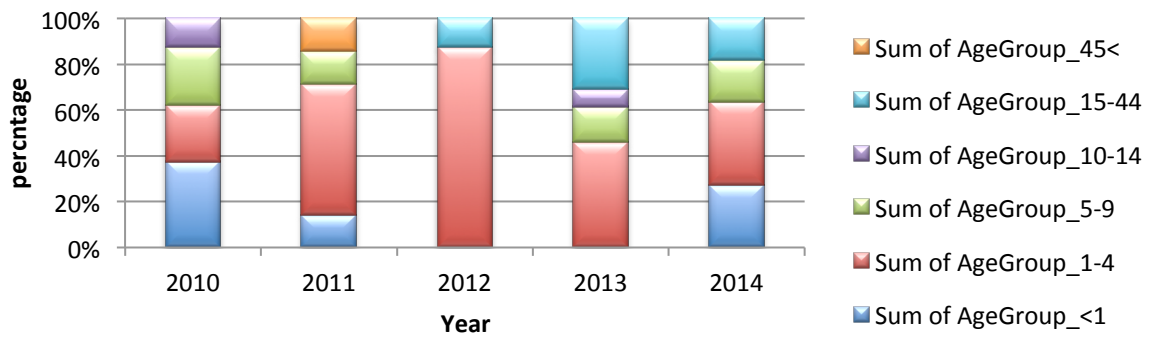
Figure 2. Incidence Rates of Reported Cases of Cutaneous Leishmaniasis, by Year and Provinces, Kingdom of Saudi Arabia, 2010 – 2014





In general, VL cases were low among the total population, but we observed an increase in the total number of reported VL cases from 2010 to 2014. In 2010, there was a total of eight reported VL cases, which increased to 11 cases in 2014 (Table 4). Over the study period, the greatest number of VL cases was reported from Jazan (36 cases), followed by Assir (8 cases), and Makkah (3 cases). Of the 47 reported cases, 48.9% occurred among those aged 1 - 4 (Figure 4). Among males, there were 34 reported cases; among females, there were 13 cases. Among Saudi nationals, there were 28 cases, and among non-Saudis, there were 19 cases over the study period.

Figuer 4. Percentage of Viseral Leishmaniasis cases by age group from 2010-2014



Discussion

The number of CL cases and IR decreased significantly from 2010 to 2012, then increased slightly the following two years. The downward trend was observed by both nationality and gender. The CL IR among non-Saudis was greater than that among Saudis, and males had a greater IR than females. The CL IRs in Al-Madinah, Al-Qassim, and Hail provinces were greater than that of the total population, and the proportion of CL cases was much greater in those 14-44 years of age.

Higher CL IRs among non-Saudis (in comparison to Saudis) could be due to the fact that the majority of those working in agriculture and farming are non-Saudi. Non-Saudis working in agriculture, construction, and with livestock are at high risk of exposure to the sand fly, as many in these jobs engage in behaviors that make them prone to being bitten, including sleeping out in the open near desert rodent burrows. In addition, underreporting could be a factor. Some non-Saudis do not have proper health insurance, may be afraid of deportation, or may prefer to receive treatment in their home country. Underreporting might be a factor among Saudis as well, as they may seek herbal treatment and traditional healers in lieu of medical treatment.

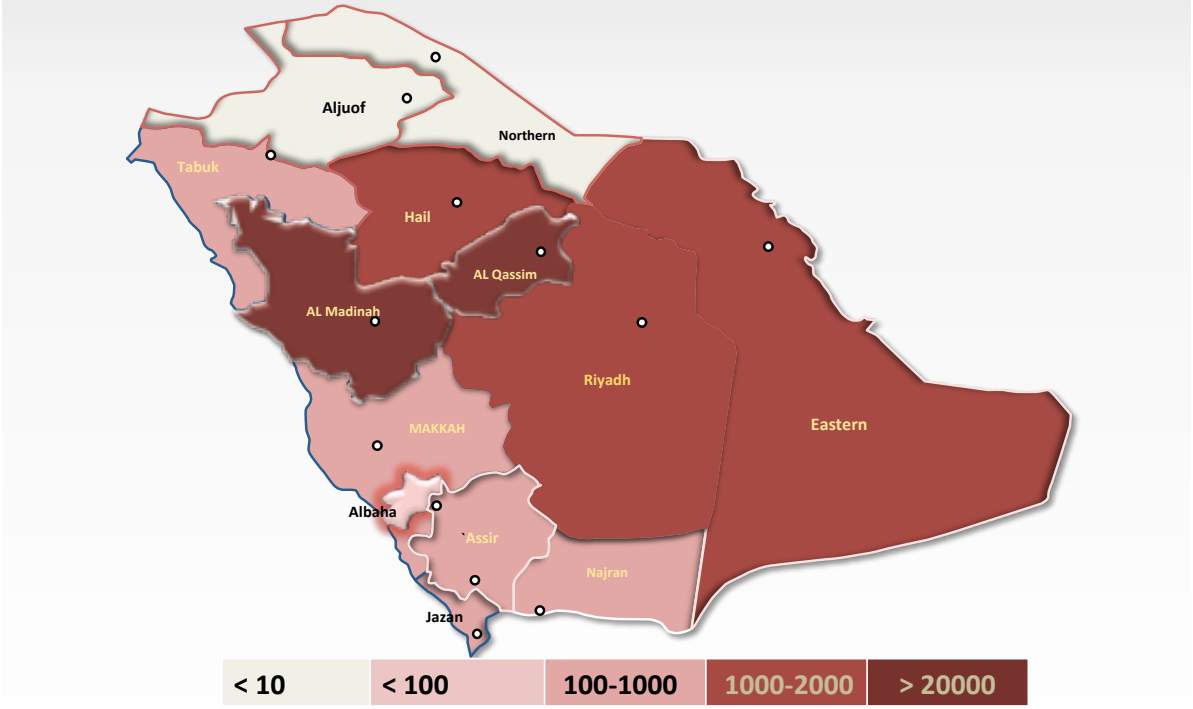
Our findings revealed that CL IRs were much higher among men than women; this should be a crucial aspect for future research. Higher IRs in Al-Madinah, Al-Qassim and Hail provinces might be attributed to agriculture's being the main industry there. The majority of farms produce dates, and the question of whether palm trees may play a role in the lifecycle of the vector or be a reservoir warrants further investigation. We observed that IRs among both males and females were high in those provinces, which contributed to the high IR among the population overall.

Assir's IR was below that of the general population through 2014, in contrast to Najran's, which saw a sharp increase in its IR in 2014, similar to that of Hail. Eastern Province's fluctuation in IR (shifting above and below the general population's IR) could be an area of further investigation and assessment.

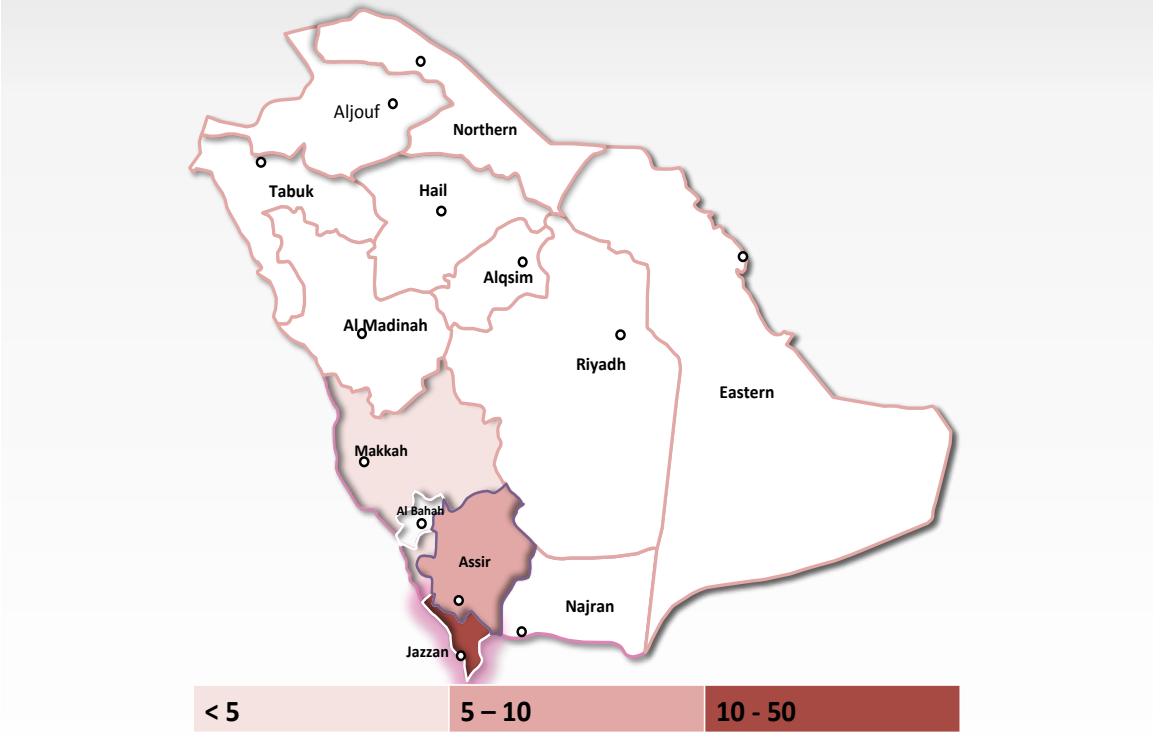
We observed a very low number of VL cases during the study period, with a total of 47 cases among the total population. Reported cases came mainly from the southern provinces of Assir and Jazan. Makkah province reported 3 cases from 2013 to 2014. We do not have information explaining why there was an increase in reported VL cases during the study period; it could be due to an improvement in the reporting system or the

wider availability of diagnostic tools. VL was more common among males, who represented 34 cases; 13 of the cases were female. The proportion of VL cases was much greater among those who were 1-4 years of age. This might be due to the type of leishmaniasis occurring in the south, which is called anthroponotic, by which humans act as the reservoir (sand fly bites someone who is infected and transmits it to another person). This warrants further investigation and discussion.

Saudi Arabia map with provinces shows estimated reported cases of CL, 2010-2014



Saudi Arabia map with provinces shows estimated reported cases of VL, 2010 - 2014.



This study had limitations. The first was our inability to trace the georgraphical origin of each case. The MoH records did not capture reported cases by sector and region; they are listed by province only. Having more specific location data could guide researchers to a better understanding and evalution of the risk factors in those areas where cases are reported. Inclusion of these data in future studies may very well provide important answers. In addition, we were unable to pinpoint the specific age group most affected by leishmaniasis. In the national reporting structure, the age intervals for adults range from 14-44 and 45 and over; these broad ranges make it difficult to identify the specific age group most at risk. The data collection form could be reevaluated and updated to include province, region, and sector. Also, some terminology could be clarified to improve the accuracy of its interpretation (e.g., the Residency variable).

The results of our study strongly suggest that continuous surveillance should be maintained for the early detection and treatment of leishmaniasis in all sectors, regions, and provinces of KSA. The reporting system should be reevaluated in all regions, especially those not reporting any cases that have a climate and geography similar to regions that did report cases over the study period. Further investigation into the presence of risk factors in these regions is needed.

We recommend implementing an active surveillance system in the highly endemic provinces. Health education about leishmaniasis and the importance of early detection and treatment for reducing its prevalence should also be promoted, especially in provinces with higher IRs. The need for strong and continuous collaboration between the Ministry of Municipal and Rural Affairs, the Ministry of Agriculture, and the MoH should be emphasized in order to strengthen the national control program and lead the country to leishmaniasis eradication. We recommend that the national control program publish a guidance manual, as it is considered a pioneer program in Middle East region. We strongly recommend that provinces along the borders receive more support and incentives to continuously monitor the prevalence of leishmaniasis, as they receive the majority of refugees from conflict areas in Syria and Yemen. Finally, keeping accurate records of patients, the areas in which cases originated and were reported, and the medical histories will provide more reliable data and allow researchers to better identify areas that could be improved in the fight against this disease.

Chapter 4

Conclusion

The main purpose of this study was to analyze the CL IRs for the period from 2010 – 2014 to determine the distribution of the disease by nationality, gender, and province. CL IRs decreased in KSA over the study period. There were specific demographic factors such as province, age, nationality, and gender that seemed to impact IRs.

The scientific literature indicates that the variation by province is probably linked to the two types of species causing leishmaniasis, as well as to the presence of the vector and reservoirs near populated areas in endemic provinces. Also, the main industry in certain provinces is agriculture, which can contribute to the risk of exposure to the disease. The National Control Program uses a passive survillance system for tracking cases from each province. Active surveillance could be considered as an approach to improving the reporting system; this would improve early detection and treatment of the disease and evantually decrease its prevalence.

The leishmaniasis IR decreased from 2010 to 2012, then it increased slightly through 2014. This trend was reflected in stratifications by nationality and gender. Lack of data showing exactly which sector and region the cases were reported from made it difficult to make a more precise assessment of IR within provinces. The IRs in the provinces of Asir, Eastern, and Najran require further investigation and evaluation.

Recommendations

The results of our study strongly suggest that continuous surveillance should be maintained for the early detection and treatment of leishmaniasis in all sectors, regions, and provinces of KSA. The reporting system should be reevaluated in all regions, especially those not reporting any cases that have a climate and geography similar to regions that did report cases over the study period. Further investigation into the presence of risk factors in these regions is needed.

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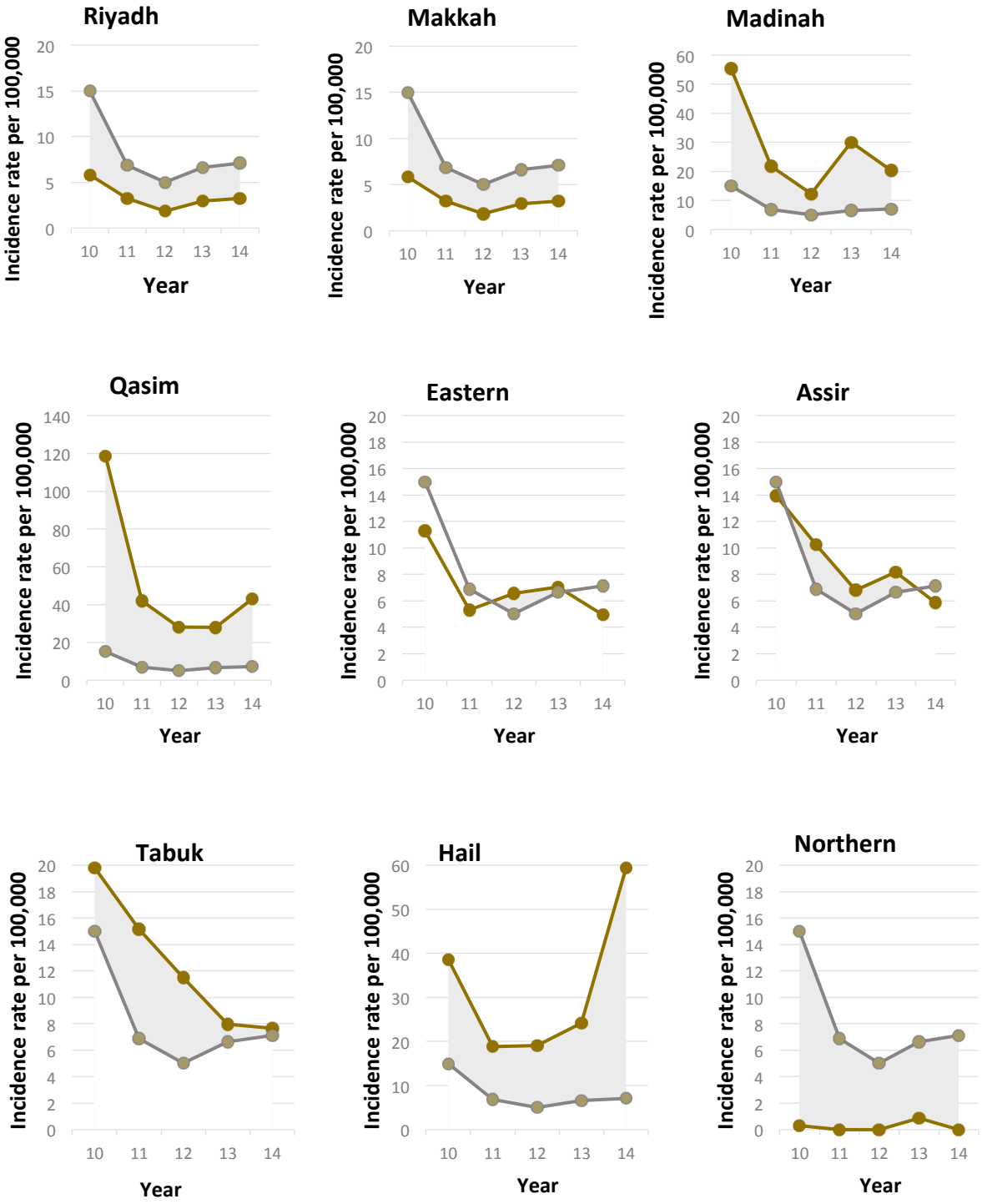
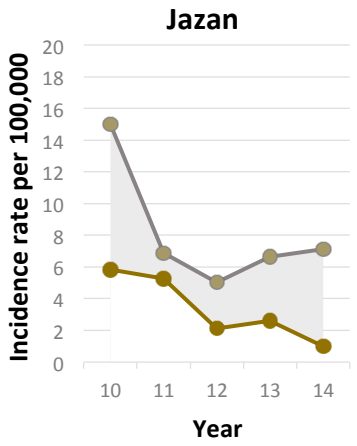
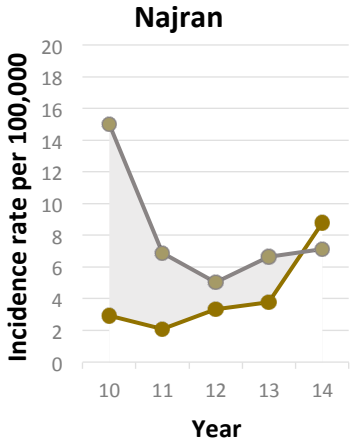
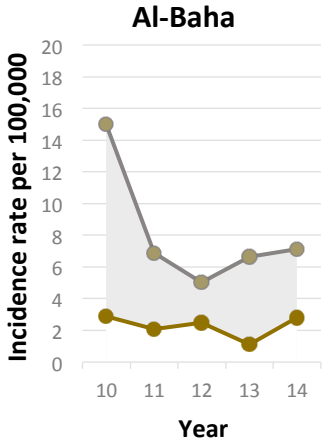
Appendix

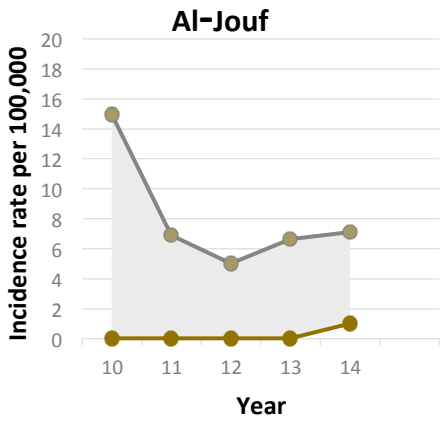
Figure 5. Incidence Rates of Reported Cases of Cutaneous Leishmaniasis, by Year and Provinces, Kingdom of Saudi Arabia, 2010 – 2014

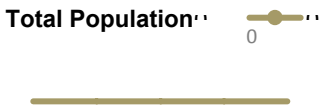



Jazan
Incidence rate per 100,000
20
18
16
14
12
10
8
6
4
2
0
10
11
12
13
14
Year


Najran
Incidence rate per 100,000
20
18
16
14
12
10
8
6
4
2
0
10
11
12
13
14
Year


Al-Baha
Incidence rate per 100,000
20
18
16
14
12
10
8
6
4
2
0
10
11
12
13
14
Year


Al-Jouf
Incidence rate per 100,000
20
18
16
14
12
10
8
6
4
2
0
10
11
12
13
14
Year


Total Population
0