

Leishmaniasis

MAJ Kris Paolino

March 2014



WRAIR

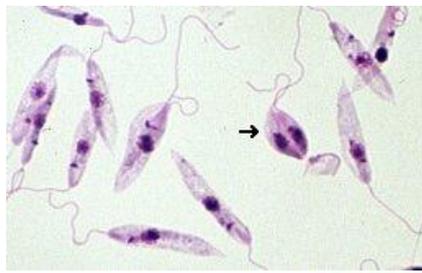
Walter Reed Army
Institute of Research

Soldier Health • World Health

Thanks to

COL (Ret) Kent Kester

MAJ Leyi Lin



Promastigotes divide and migrate to the anterior midgut and foregut.

Sand fly injects promastigotes into the skin during a blood meal. ***infective stage**

Promastigotes are phagocytized by neutrophils that are rapidly recruited to the bite site.

Infected neutrophils release the parasites, which are then consumed by macrophages.

Sand Fly Stages

Human Stages

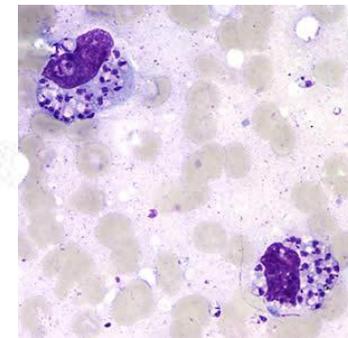
Amastigotes transform into promastigotes in midgut.

Promastigotes transform into amastigotes inside macrophages. ***diagnostic stage**

Ingestion of parasitized cell.

Sand fly ingests infected macrophages when it takes a blood meal.

Amastigotes multiply in cells (including macrophages) of various tissues. ***diagnostic stage**



History

- Sir William Boog Leishman (1865-1926)
- Matriculated at the University of Glasgow at 14.
- Joined British Army Medical Corps and served in India
- Identified the causative parasite of Dum-dum fever (now known as leishmaniasis).
 - From the spleen of a soldier who died in India of kala-azar



Leishmaniasis

- Group of disease caused by infection from one of the obligate intracellular protozoan parasites of the genus *Leishmania*
- Designated one of the five most important diseases worldwide by WHO
- Leishmania threatens 310 million individuals worldwide

Highly Endemic Areas

- 90% of cutaneous leishmaniasis occur in Afghanistan, Algeria, Brazil, Columbia, Iran, Pakistan, Peru, Saudi Arabia, and Syria.
- 90% mucocutaneous leishmaniasis occur in Bolivia, Brazil, and Peru
- 90% of all visceral leishmaniasis cases occur in Bangladesh, Brazil, Ethiopia, India, South Sudan, and Sudan

Question

- Leishmaniasis is acquired through the bite of ...
 - A). *Anopheles* mosquitoes
 - B). *Aedes* mosquitoes
 - C). Sand flies
 - D). Fleas

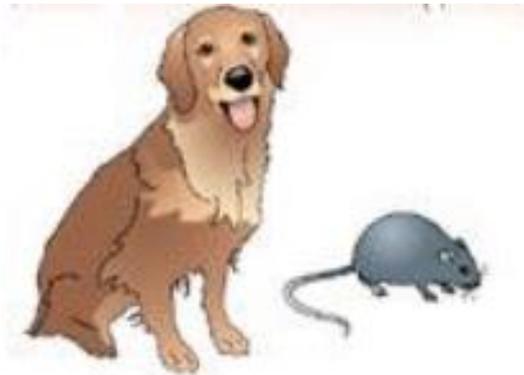
Vectors

- Female Sand fly
 - *Lutzomyia* in the Americas
 - *Phlebotomus* elsewhere
- Poor flyers
- World wide distribution
- Bites at exposed areas and clothing lines



Reservoirs

- Humans
- Dogs
- Rodents



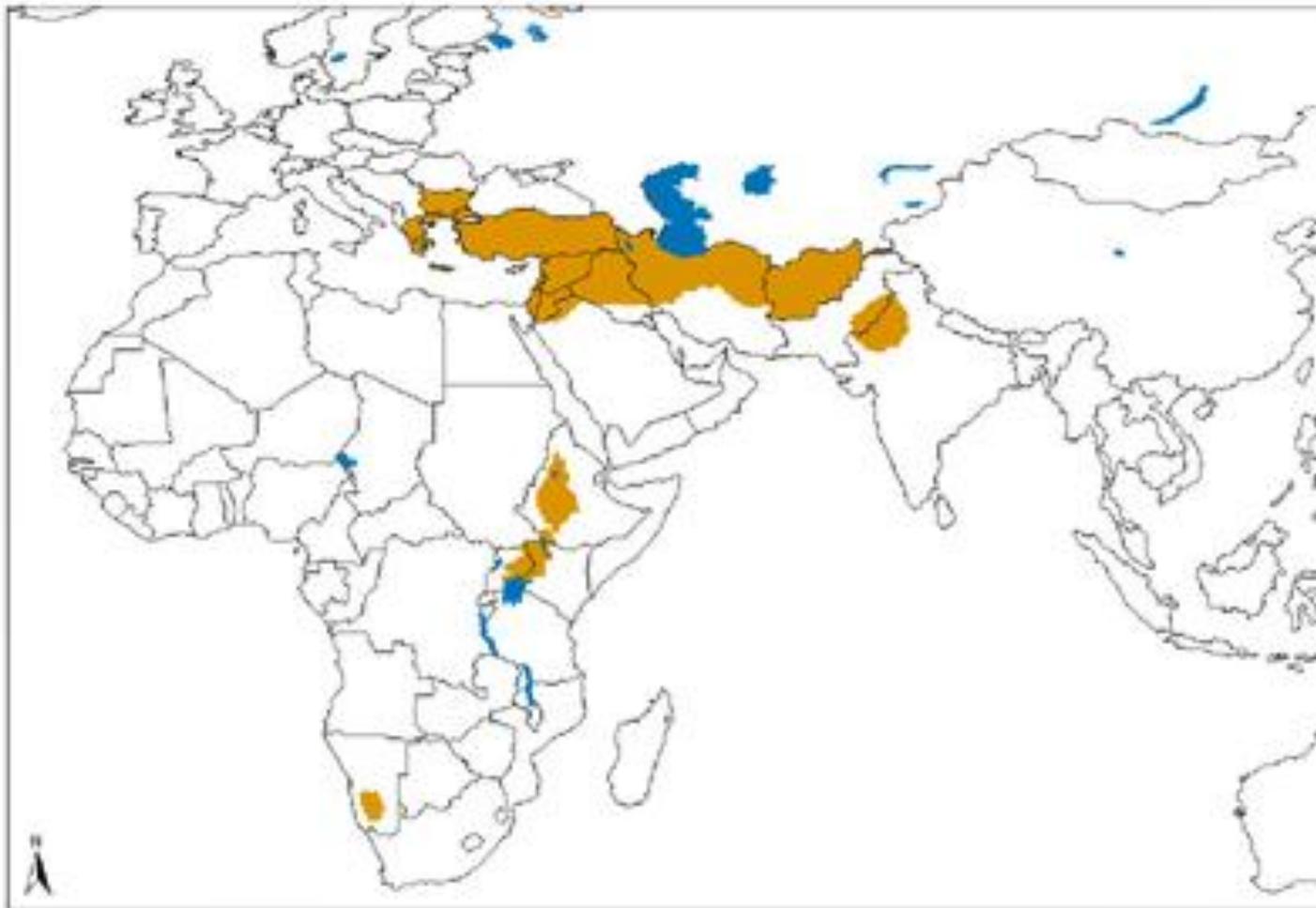
Leishmaniasis

- Same life cycle for all species:
 - Sandfly with promastigote
 - Inoculates human
 - Amastigote replicates in the macrophages
- Three clinical syndromes:
 - Cutaneous (skin)
 - Localized, diffuse, *Leishmania recidivans*, post kala-azar dermal leish
 - Mucocutaneous (mouth, nose, also called Espundia)
 - Visceral (internal organs, also called kala-azar)
 - Determined by species of parasite, location of infected macrophages, and immune response

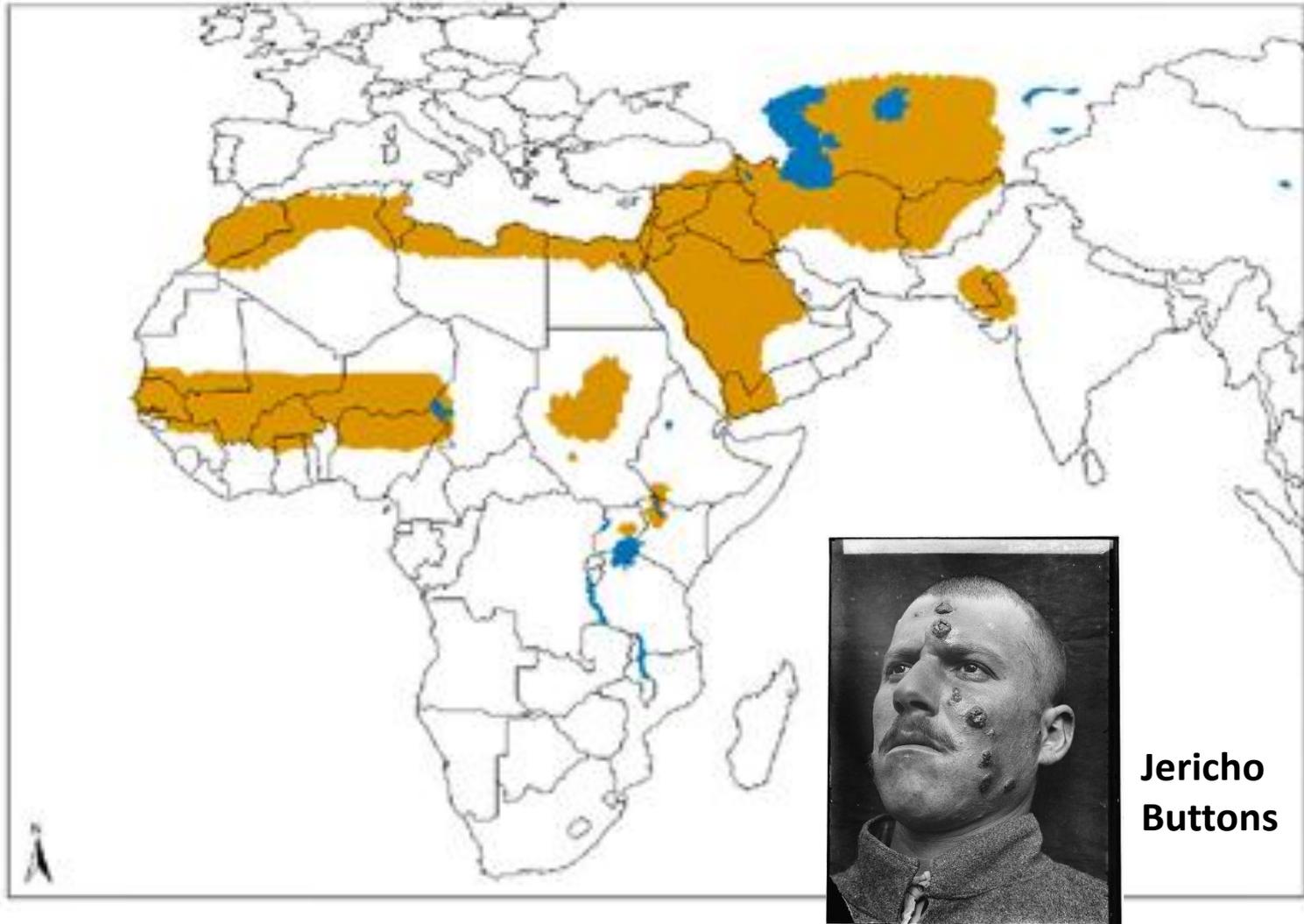
Classification

- *Old World, Cutaneous Disease:*
 - *L. tropica*; *L. major*; *L. aethiopica*
 - *L. tropica* can cause visceral disease
- *Old World, Visceral Disease:*
 - *L. donovani* complex with 3 species (*L. donovani*, *L. infantum*, and *L. chagasi*)
- *New World, Cutaneous disease:*
 - *L. mexicana* complex with 3 main species (*L. mexicana*, *L. amazonensis*, and *L. venezuelensis*)
- *New World, Cutaneous and Mucocutaneous disease*
 - Subgenus *Viannia* with 4 main species (*L. (V.) braziliensis*, *L. (V.) guyanensis*, *L. (V.) panamensis*, and *L. (V.) peruviana*)
- *New World, Visceral Disease*
 - *L. chagasi*

Old World cutaneous leishmaniasis due to *L. tropica* and related species and *L. aethiopica*



Old World cutaneous leishmaniasis due to *L. major*

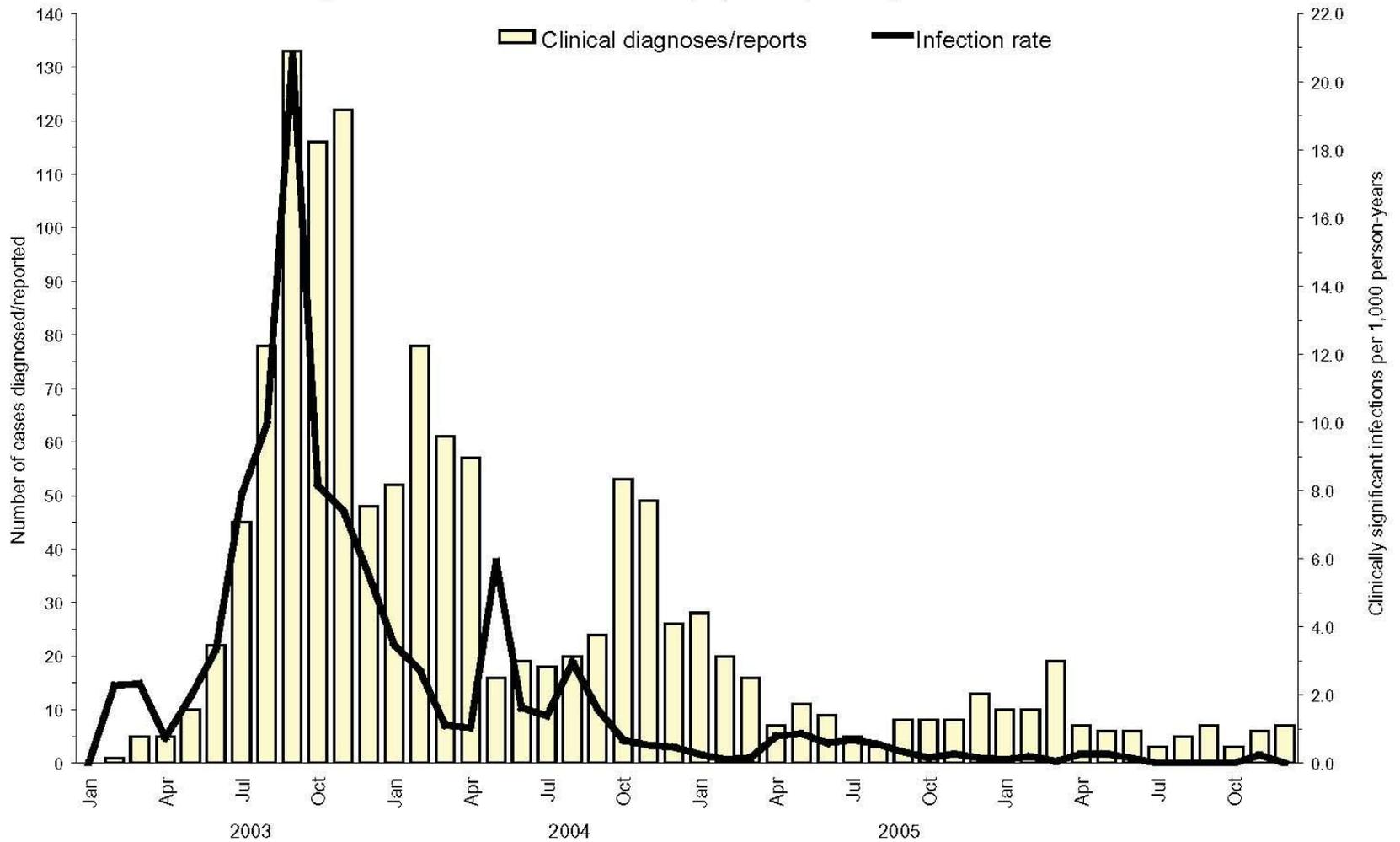


Localized Cutaneous Leishmaniasis

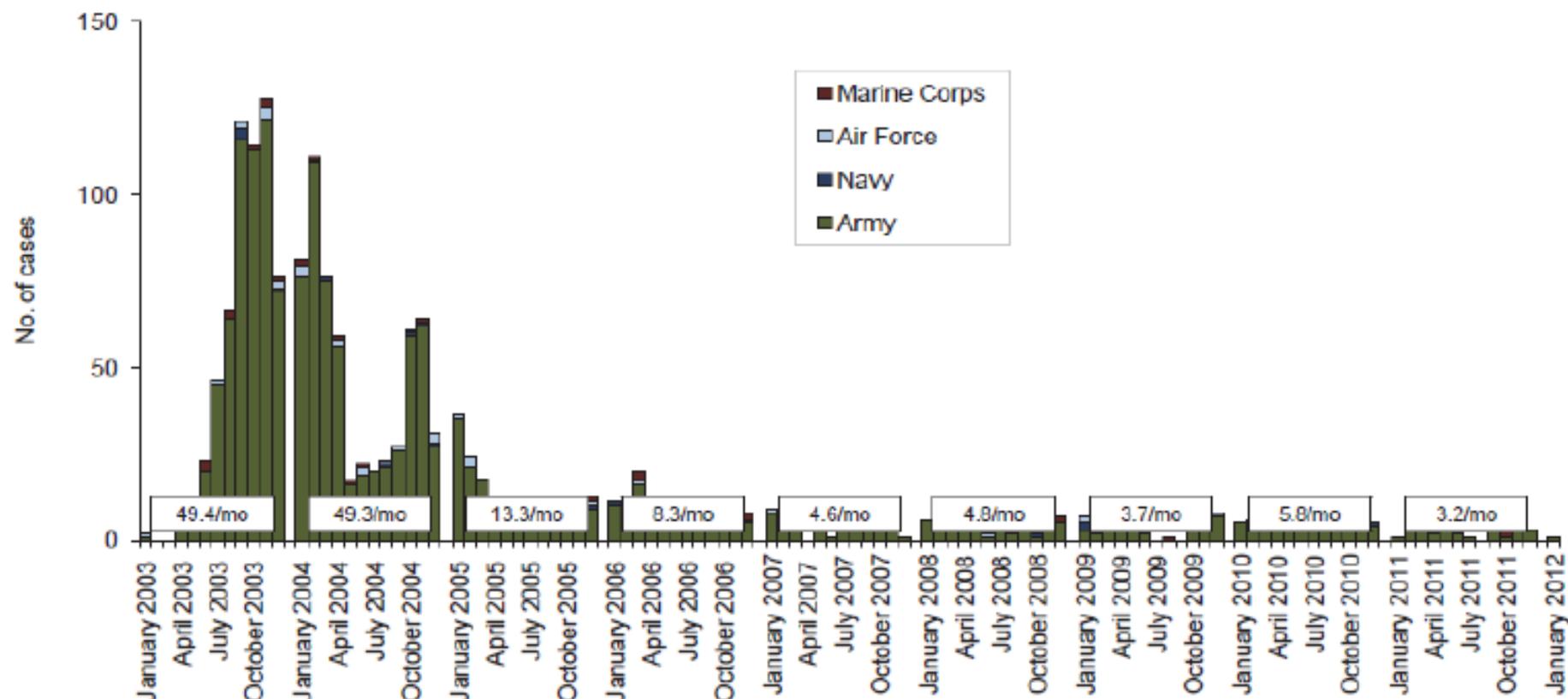
- Jericho buttons, Baghdad boil, Aleppo evil
- Nodules expands → ulcerates over weeks
- Incubation time ~ 40 days (days – one year)
- **Usually painless or minimally painful**
- Single or multiple lesions, appearance varies
- Persists months to years, eventually heals with burnlike scar
- > 2000 cases reported from Operation Iraqi Freedom
 - *L. major* most common species

From MSMR ...

Figure 1. Clinical diagnoses/reports of leishmaniasis at U.S. military medical treatment facilities and estimated leishmaniasis infection incidence rates among U.S. service members in OEF/OIF, by month, January 2003-December 2006



Leishmaniasis (ICD-9: 085.0 to 085.9)^b



Reference: Army Medical Surveillance Activity. Deployment-related condition of special surveillance interest: leishmaniasis. Leishmaniasis among U.S. Armed Forces, January 2003–November 2004. *MSMR*. Nov/Dec 2004;10(6):2-4.

^bIndicator diagnosis (one per individual) during a hospitalization, ambulatory visit, and/or from a notifiable medical event during/after service in OEF/OIF/OND.

“In some cities infection is so common and so inevitable that normal children are expected to have the disease soon after they begin playing outdoors, and visitors seldom escape a sore as a souvenir. Since one attack gives immunity, Oriental sores appearing on an adult person in Baghdad brands him as a new arrival...”

- Chandler A., in “Introduction to Parasitology” 1944



Coleman, et al. J Med Entomol 2006



Photos from Dr. Glenn Wortmann

Leishmaniasis Recidivans Recurrence after 43 Years: A Clinical and Immunologic Report after Successful Treatment

**Mary A. Marovich,^{1,2} Rosalia Lira,¹ Marc Shepard,² Glenn H. Fuchs,³
Richard Kruetzer,⁴ Thomas B. Nutman,¹ and Franklin A. Neva¹**

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Cutaneous and Mucocutaneous Leishmaniasis in the New World



Leishmaniasis is Endemic in Texas

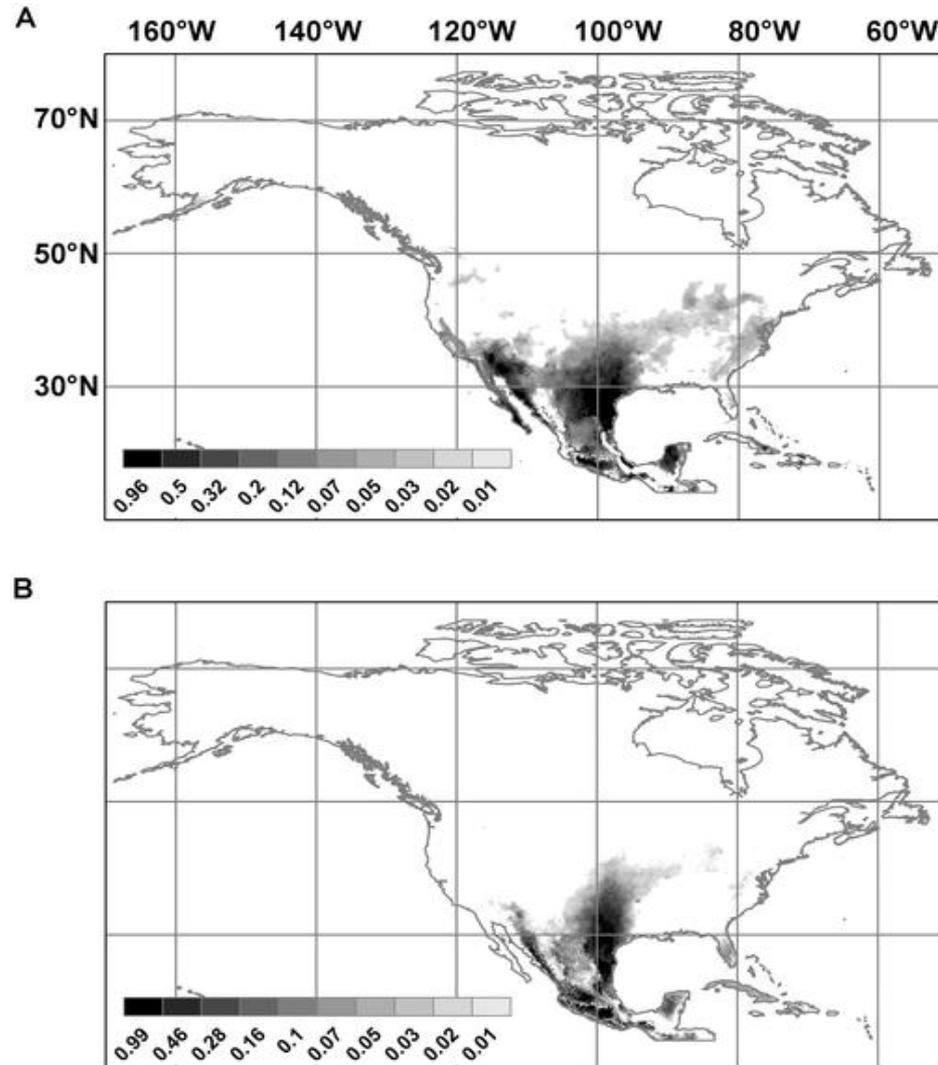
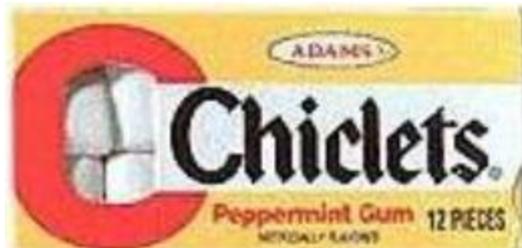


Figure 2. Predicted current distributions for leishmaniasis vector species.

González C, Wang O, Strutz SE, González-Salazar C, et al. (2010) Climate Change and Risk of Leishmaniasis in North America: Predictions from Ecological Niche Models of Vector and Reservoir Species. *PLoS Negl Trop Dis* 4(1): e585. doi:10.1371/journal.pntd.0000585
<http://www.plosntd.org/article/info:doi/10.1371/journal.pntd.0000585>

Chiclero's Ulcer

- Localized cutaneous leishmaniasis
- Majority of cases caused by *L. Mexicana*
- Chicleros – men who collect the chicle latex from which chiclets chewing gum is made



Can Med Assoc J 1986; 134: 216



Photo: Dr. Jason Blaylock



South American Leishmaniasis Associated with Mucocutaneous Disease

- Subgenus *Viannia* with 4 main species
 - 1). *L. (V.) braziliensis*
 - 2). *L. (V.) guyanensis*
 - 3). *L. (V.) panamensis*
 - 4). *L. (V.) peruviana*
- True incidence of mucus membrane involvement is well documented, estimated at least 5% - 25 %
- Destructive lesions, possibly immune-mediated
- Delay in diagnosis

ML in British travelers

- 5.1% of CL patient concurrently dx with ML
- 2 cases of ML without CL



New world mucosal and cutaneous leishmaniasis: an emerging health problem among British travellers

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From the ¹The Hospital for Tropical Diseases, London, ²Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, and ³Royal National Throat, Nose & Ear Hospital, London, UK

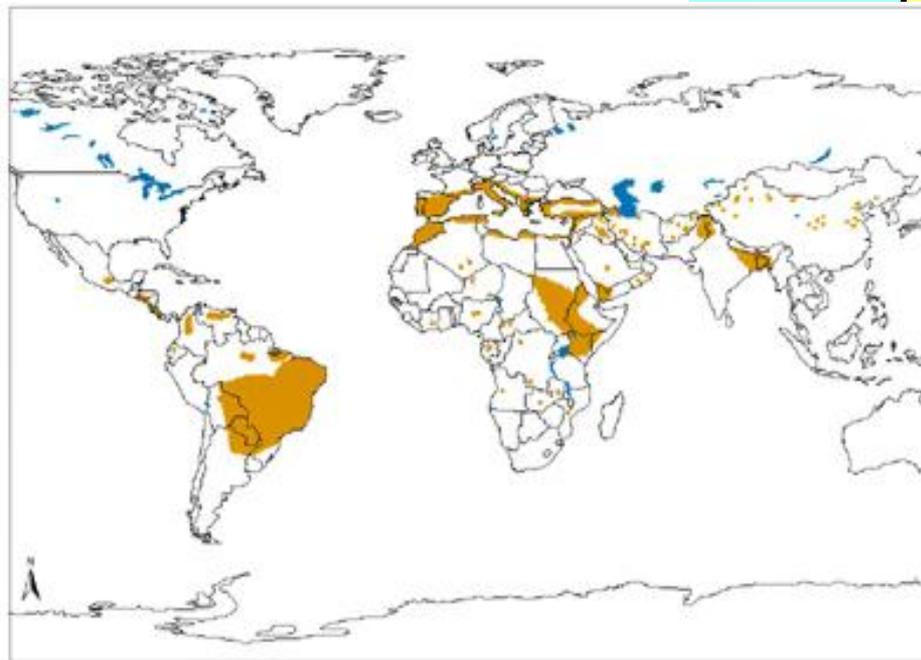
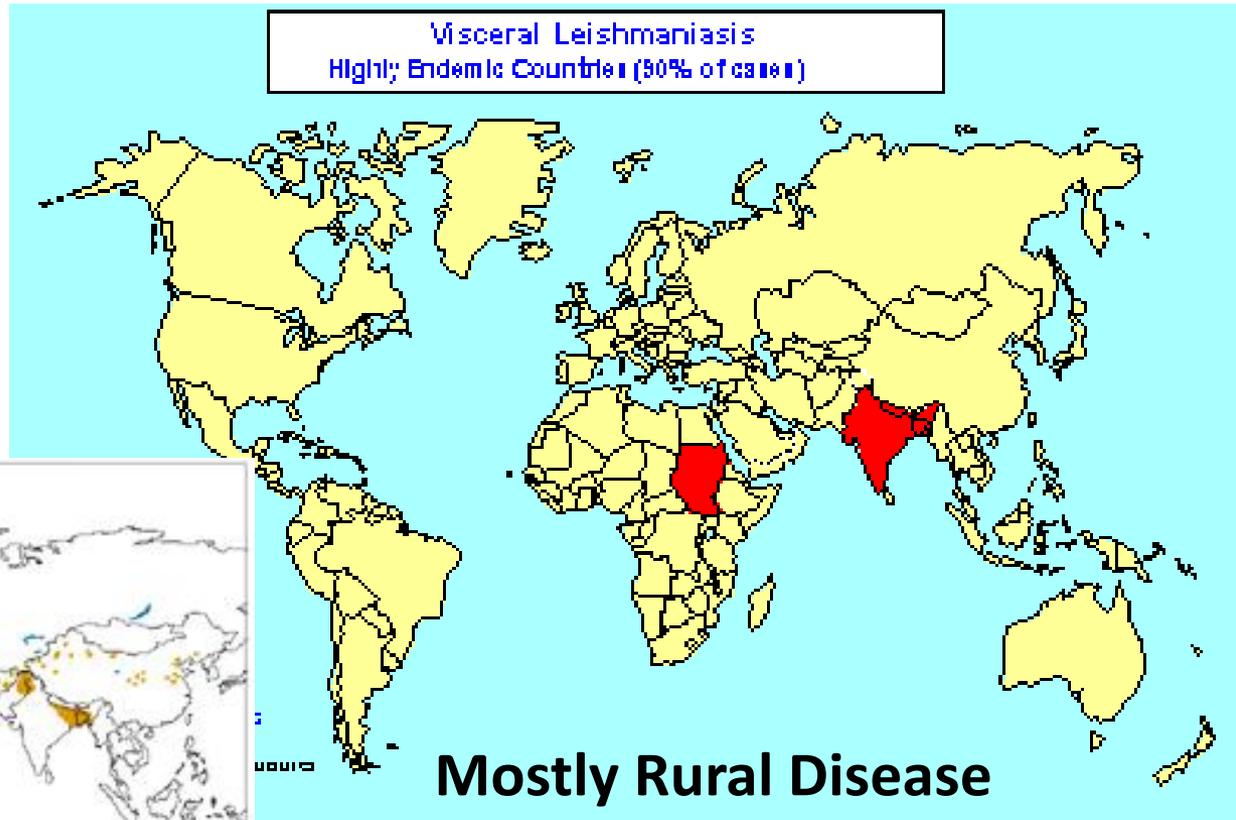


T. Evans © 1996



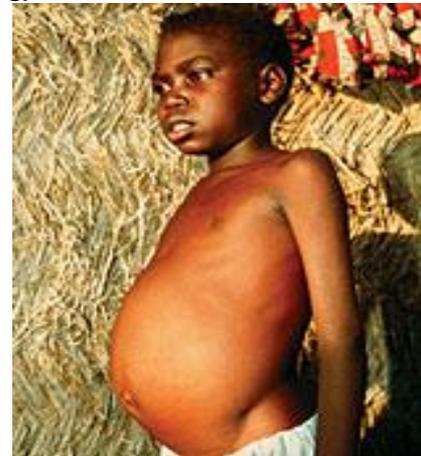
Prof. Luis A. Leon
LAB. LEON Quito-Ecuador
Manson-Bahr, 1972

Visceral Leishmaniasis in the Old and New world



Visceral Leishmaniasis (kala-azar)

- *L. donovani*, *L. infantum*, *L. chagasi*, *L. tropica*
 - Most infected individuals do not have symptoms (30:1)
- Progressive disease caused by parasite dissemination throughout the reticuloendothelial system
 - spleen, liver, bone marrow, other organs
- Symptoms:
 - Fever, weight loss, organomegaly, dark skin, anemia, hypergammaglobulinemia, thrombocytopenia
- > 90% mortality within first two years
- VL can be an **opportunistic infection**
 - Southern Europe
 - HIV / AIDS
 - Weakened T-cell mediated immunity



Post-Kala Azar Dermal Leishmanoid (PKDL)



- Skin lesions develop months or years after treatment
- In PKDL, the amastigotes of *L. donovani* leave the viscera and enter macrophages in the skin and multiply
- Macular lesions or nodules
- Sandflies can transmit organisms from skin lesions

Viscerotropic Leishmaniasis from Desert Storm (*L. tropica*)

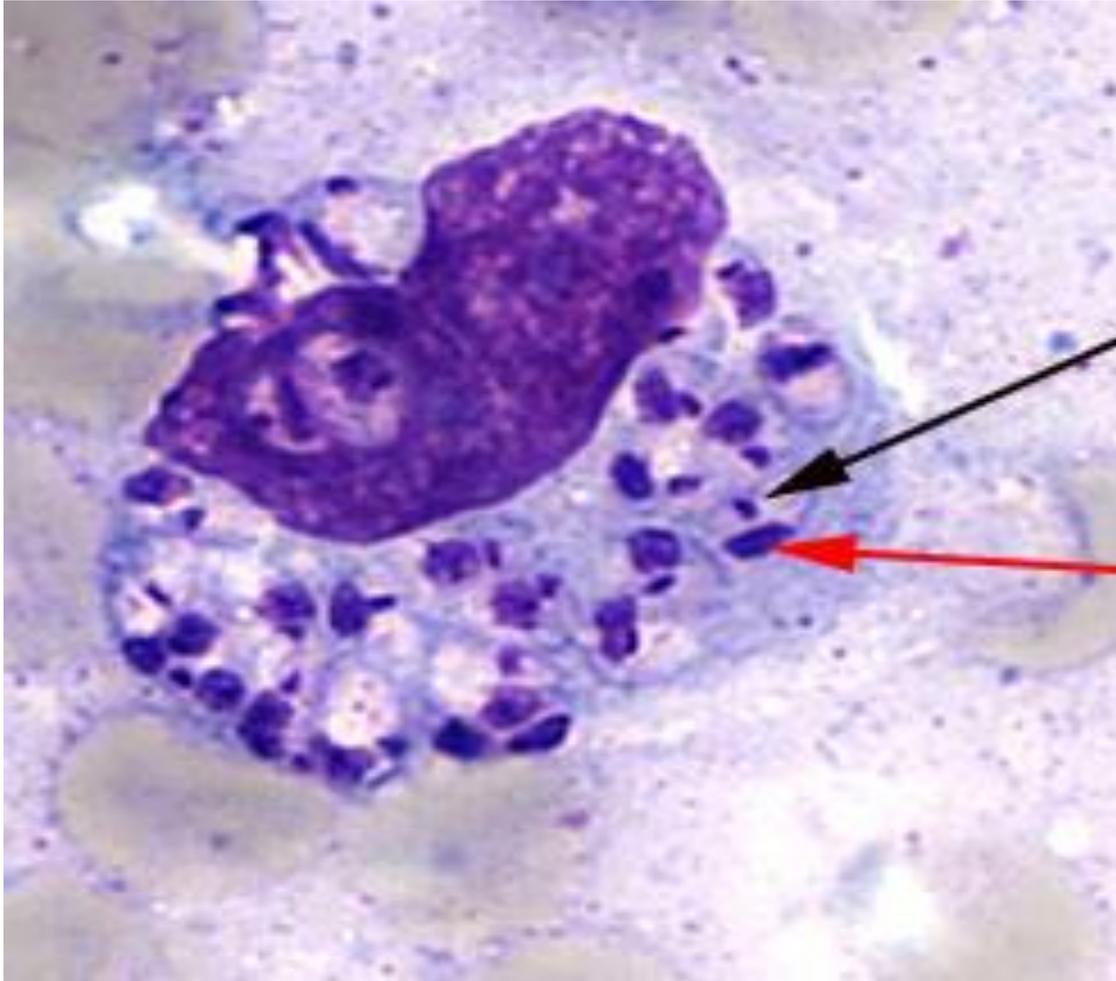
- 8 visceral leishmaniasis patients returning from Desert Storm
 - Fevers: 6 of 8
 - Weight loss: 2 of 8
 - Nausea, vomiting, low-grade watery diarrhea: 2 of 8
 - Lymphadenopathy: 2 of 8
 - Hepatosplenomegaly: 2 of 8
 - Anemia: 3 of 8
 - Leukopenia or thrombocytopenia: 0 of 8
 - Elevated liver enzymes: 6 of 8
 - No symptoms: 1 of 8

Diagnosis

- Clinical Diagnosis
- Cutaneous Leishmaniasis
 - Biopsy/Aspiration/Scraping
 - Amastigotes in a smear
 - Promastigotes in culture
 - PCR of sample
- Visceral Leishmaniasis
 - Biopsy of Bone Marrow or Spleen
 - Touch Prep, PCR, Culture
 - Immunologic
 - rK39 leish. antigen direct agglutination test



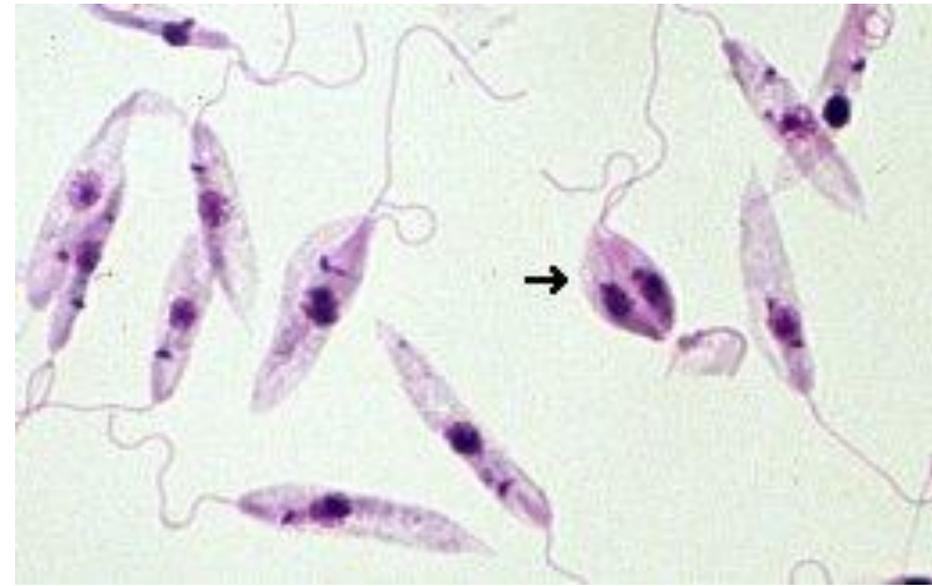
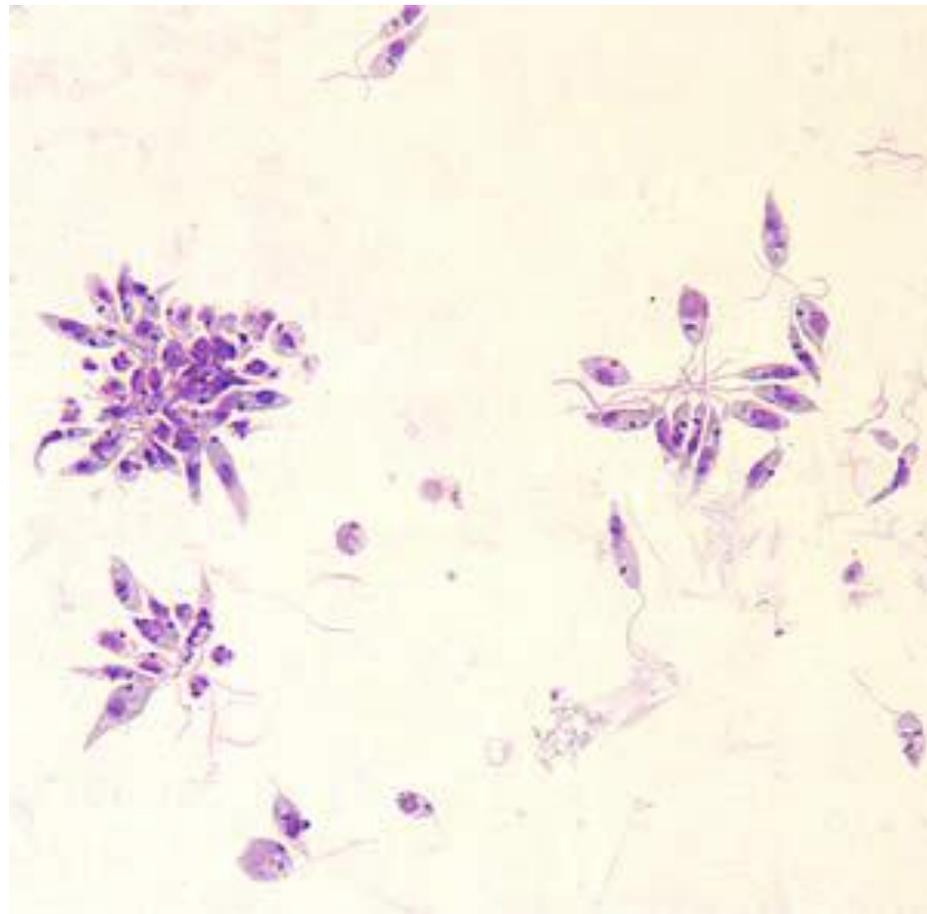
Tissue Diagnosis –skin, spleen, bone marrow



- **Infected macrophage with amastigotes**
 - a nucleus (red arrow)
 - a rod-shaped kinetoplast (black arrow)

(CDC Slide)

Diagnosis - culture



Promastigotes

Photo: CDC

Photo: www.msu.edu

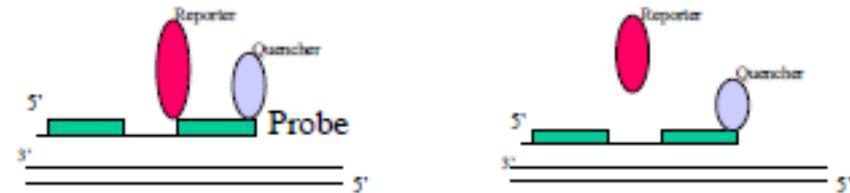
Diagnosis

Montenegro Skin Test

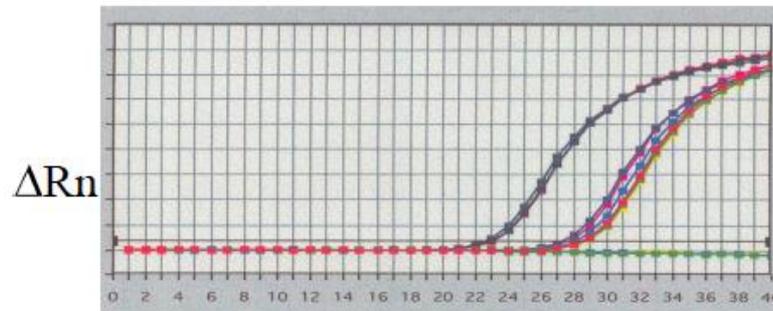
- Injection of dead promastigotes into skin
- Not licensed in U.S



Real-Time PCR



During each extension cycle, the Taq DNA polymerase cleaves the reporter dye from the probe



L. major

L. major

L. V. panamensis

Negative control

Cycle



InBios

Kalazar Detect

Lot #: DC1015 Exp: 08/2004

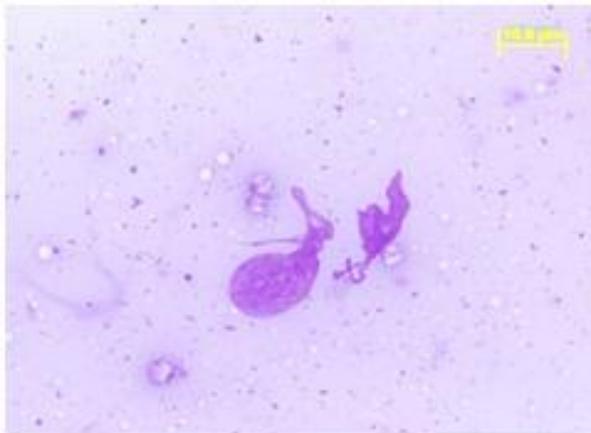
Store at Room Temperature

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Seattle, Washington 98104



- **Leishmania Diagnostics Laboratory**
- http://wrair-www.army.mil/OtherServices_LDLD.aspx
- usarmy.detrick.medcom-wrair.mbx.leishmania-diagnostic@mail.mil
- 240-595-7353
- **ID or Dermatology Electronic Consult Service**



Question

- What's the best way to treat Leishmaniasis ?
 - 1). Amphotericin
 - 2). Watch it
 - 3). Pentostam
 - 4). We don't know
 - 5). Surgery

Treatment

- CL
 - Watchful waiting
 - Local destructive therapies
 - Liquid NO₂
 - Thermo-Med device
 - Topical creams
 - Paromomycin
 - Systemic treatment
 - Sodium stibogluconate (Pentostam)
 - Fluconazole
 - Amphotericins
 - Pentamidine
 - Miltefosin
- MCL, VL
 - Systemic therapy, usually Pentostam or amphotericin

Interventions for Old World cutaneous leishmaniasis (Review)

Authors' conclusions

Most trials have been designed and reported poorly, resulting in a lack of evidence for potentially beneficial treatments. There is a desperate need for large well conducted studies that evaluate long-term effects of current therapies. We suggest the creation of an international platform to improve quality and standardization of future trials in order to inform clinical practice.

In *Leishmania major* infections, there was good RCT evidence of benefit of cure around 3 months after treatment when compared to placebo for 200 mg oral fluconazole (1 RCT n = 200, RR 2.78; 95% CI 1.86, 4.16), topical 15% paromomycin + 12% methylbenzethonium chloride (PR-MBCL) (1 RCT n = 60, RR 3.09; 95% CI 1.14, 8.37) and photodynamic therapy (1 RCT n = 60, RR 7.02; 95% CI 3.80, 17.55). Topical PR-MBCL was less efficacious than photodynamic therapy (1 RCT n = 65, RR 0.44; 95% CI 0.29, 0.66). Oral pentoxifylline was a good adjuvant therapy to intramuscular meglumine antimoniate (IMMA) when compared to IMMA plus placebo (1 RCT n = 64, RR 1.63; 95% CI 1.11, 2.39)

In *Leishmania tropica* infections, there was good evidence of benefit for the use of 200 mg oral itraconazole for 6 weeks compared with placebo (1 RCT n = 20, RR 7.00; 95% CI 1.04, 46.95), for intralesional sodium stibogluconate (1 RCT n = 292, RR 2.62; 95% CI 1.78, 3.86), and for thermotherapy compared with intramuscular sodium stibogluconate (1 RCT n = 283, RR 2.99; 95% CI 2.04, 4.37).



This record should be cited as: González U, Pinart M, Reveiz L, Alvar J. Interventions for Old World cutaneous leishmaniasis. *Cochrane Database of Systematic Reviews* 2008, Issue 4. Art. No.: CD005067. DOI: 10.1002/14651858.CD005067.pub3.

Treatments to consider

- Cutaneous Leishmania
 - Pentostam – 20 mg/kg IV x 10 -20 days
 - Ambisome (liposomal amphotericin B) 3 mg/kg on days 1-5, 14, & 21
 - Fluconazole – 8 mg/kg per day (4 – 12 weeks)
- Visceral Leishmania
 - Ambisome (liposomal amphotericin B) 3 mg/kg on days 1-5, 14, & 21
 - or
 - Pentostam – 20 mg/kg IV x 28 days

Watchful Waiting

- CL due to *L. major* (MON-26) in Saudi Arabia
 - Healing time (after study enrollment)
 - Six weeks: 6%
 - Three months: 34%
 - Alrajhi, et al. NEJM 2002;346
- CL in Guatemala
 - *L. mexicana* 68%
 - *L. braziliensis* 6%
 - Herwaldt, et al. J Infect Dis 1992;165

No Treatment

- CL acquired in Afghanistan
- Evaluated in Nov 2008 with 3 cm ulcer
- No treatment
- Follow-up in Jun 2009



Photo courtesy of Dr. Julie Ake

Locally Destructive Therapies

LNO2

- May cause hypopigmentation
- Not standardized
 - Cyroprobe suggested
- Painful / blister formation

Thermomed

- Heats lesions to kill parasites
- ~ 70 % efficacy in CL caused by *L. major* in Iraq and *L. tropica* in Afghanistan

Reithinger, et al CID 2005

Aronson, et al PloS Negl Trop Dis 2010

Photo: Dr. Glenn Wortmann





Day 4



Day 6



Day 8

Systemic Treatment

- Sodium stibogluconate (Pentostam[®])
 - Investigational New Drug
 - Available from the CDC for civilians
 - Available at Walter Reed for military
 - Intravenous administration once a day for 10-20 doses at 20 mg/kg/d
 - Outside the U.S., often given intra-lesionally



0302 pre (4/21/03)



0302 post therapy 5/10/03



Photos: Dr. Glenn Wortmann



Pentostam[®]

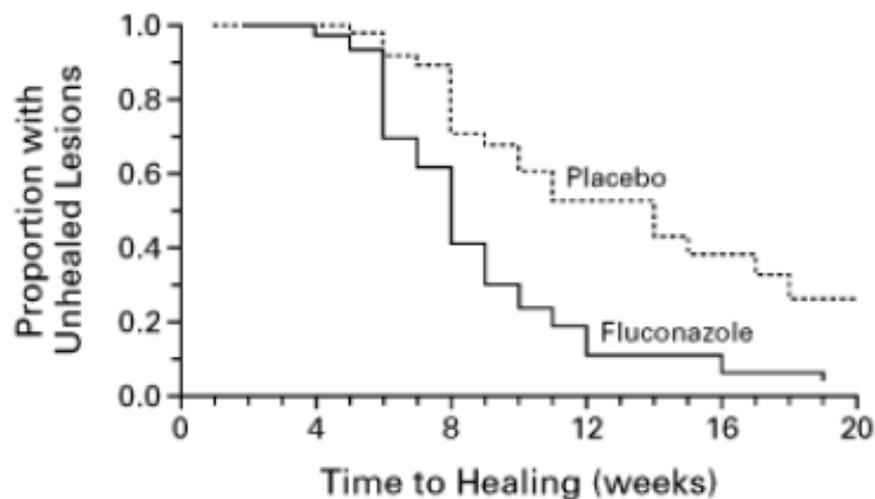
- Toxicities
 - Elevated amylase/lipase ~95%
 - Elevated liver-associated enzymes ~50%
 - Arthralgias/myalgias ~65%
 - Rare significant EKG changes/cytopenias
 - Dermatological (~10%)
 - Wide range of presentations
 - Herpes zoster (shingles)



L. guyanensis—Fr Guiana—
Ambisome for 7 doses

Fluconazole

- Prospective study
 - 200mg daily for 42 days
 - 6 weeks: 29% vs 6% placebo
 - 3 months: 79% vs 34% placebo



Prevention

- Sandflies bite and are active **at night during warmer months**
- Stay indoors **between dusk and dawn**
- Keep dogs and susceptible animals indoors at night
- Sandflies are **poor fliers** and are deterred by wind; fans are helpful
- Sandflies are small and can get through mesh netting if not extremely fine
- House construction and modification; sandflies breed in cracks of houses
- Insecticides for people and animals
- Help from entomologists
- Dog vaccine available in Brazil

Sandfly Habitat

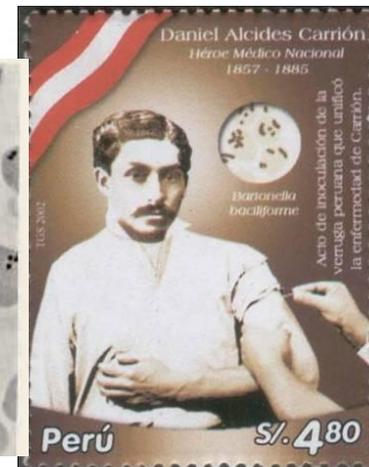
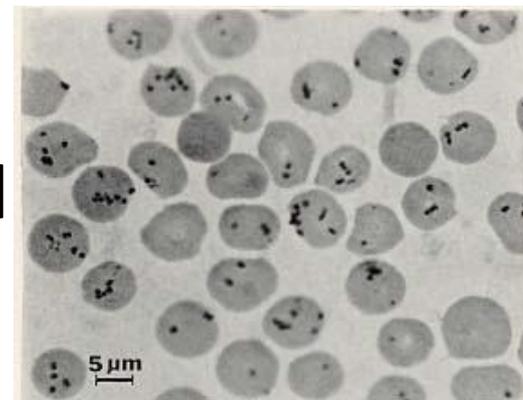


- [Volume 28, Issue 12](#), December 2012, Pages 531–538

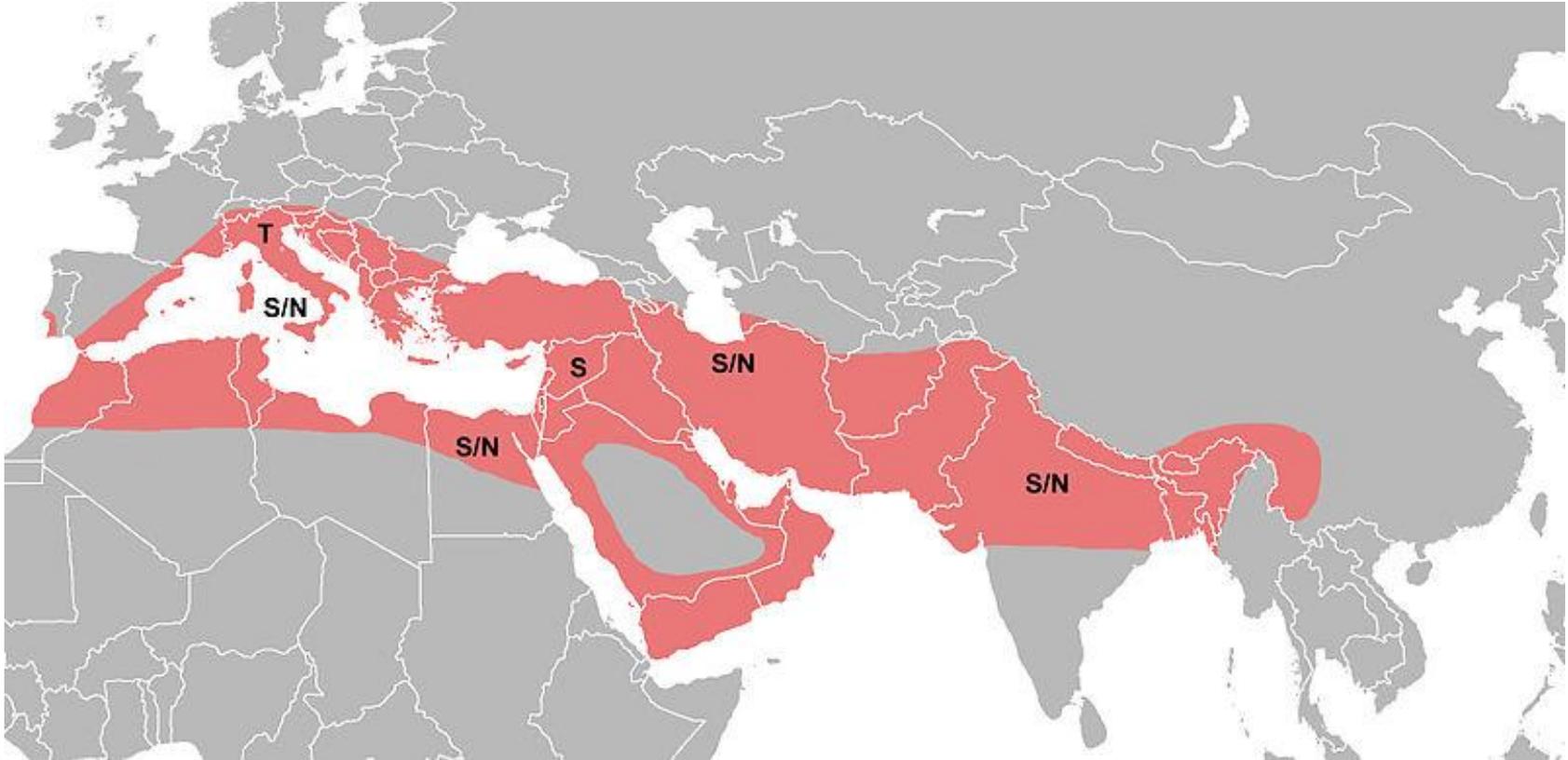
What South American disease is transmitted by sandflies ?

What South American tropical disease is transmitted by sandflies ?

- Bartonellosis (Carrión's disease)
 - Also called Oroya Fever or Peruvian warts
 - Peru, Andes mountains
 - *Bartonella bacilliformis*
- Traveler infection is not common
- Fever, myalgia, headache, and anemia
- High mortality – 40%
- Chronic infection
- Rifampin, chloramphenicol
TMP/SMX, Streptomycin



Sand Fly Fever Viruses



- Toscana
- Sicilian
- Naples
- Most People are NOT symptomatic

Summary – Leishmaniasis

- World wide distribution
- Many species with different disease presentations
- Cutaneous form may be self-limited
- Think about mucocutaneous disease, especially in South America
- Resources available for diagnosis
- Treatment response varies with species and host

Thank You

